ONCOMPASS™ REPORT

POWERED BY

Realtime Oncology
Molecular Treatment Calculator™

Oncompass Report

A Realtime Oncology Molecular Treatment Calculator számításaival

AZONOSÍTÓ	431898
NÉV	Anonymous

BETEG ADATAI

Oncompass™ ID:
Név: Anonymous
Születési dátum: 1965

Primer daganat lokalizációja: endometrium
Szövettani típus: adenocarcinoma
Metasztázis lokalizációja: Ismeretlen

SZAKÉRTŐK

Kezelőorvos:
Molekuláris Farmakológus: Dr. Peták István
Genetikai Tanácsadó: Déri Júlia, MSc
Molekuláris Biológus: Várkondi Edit, PhD
Konzulens Orvos: Dr. Pajkos Gábor
Szakértő: Dr. Rácz Anna
Betegút Koordinátor: Czető Réka
Molekuláris Bionikus Mérnök: Dirner Anna, MSc
Molekuláris Biológus: Dóczi Róbert, PhD

PATOLÓGIAI ÉS MOLEKULÁRIS DIAGNOSZTIKAI VIZSGÁLATOK

Az Oncompass vizsgálatot a XXX azonosítójú, primer tumorból származó szövettani, valamint a YYY azonosítójú, metasztázisból származó szövettani mintákból végeztük.
Tumorarány: 90% (XXX), 80% (YYY)
Tumortípus és szövettan: endometrium adenocarcinoma

Elvégzett vizsgálatok

NGS – 591 gén
IHC – ER pozitív (80%), PD-L1 negatív
MSI – instabil (MSI-H)
TMB – magas (TMB-H): 32,19 mut/Mb

KORÁBBI KEZELÉSEK

Einsiedlerstrasse 23, 8834 Schindellegi, SWITZERLAND
E-mail: info@realtimeoncology.com **Web:** www.realtimeoncology.com

Oncompass Report

A Realtime Oncology Molecular Treatment Calculator számításaival

AZONOSÍTÓ	431898
NÉV	Anonymous

ÖSSZEFOGLALÁS

Az endometrium szöveti mintát (XXX) vizsgáltuk 90 % tumorarány mellett.

Az 591 génes NGS vizsgálat sikeresen lefutott.

Az **immunterápia** hatékonyságára utaló biomarkerek közül:

MSI-High (instabil)

Tumor mutational burden (TMB) roppant magas (32,2: 100 %-ban kaptunk ennél alacsonyabb értéket).

PD-L1 negatív.

A mutációs mintázat (mutational signature) az immunterápiákra érzékeny daganatokra jellemző (20-as mintázat).

IHC – **ER pozitív** (80%)

A magas Tumor Mutational Burden mellett, ilyenkor jellemző módon sok egyéb, célzott terápia esetén fontos mutációkat detektáltunk:

PTEN-R130Q, FBXW7-R479Q, CTNNB1-T41A, PIK3CA-E81K, ATM-S214fs*16, CDH1-I594fs*19, RECQL4-L339fs*20, MRE11-R364*, IL2RG-R226C, PMS1-G417fs*

Immunterápia negatív biomarkerei lehetnek: PTEN mutáció; NSD1, TET2 frameshift mutációk.

Összefoglalva:

Az adjuváns kezelést javasoljuk felvenni.

Az első vonalas kemoterápia után igen fontos célpont az MSI-High (instabilitás) és a rendkívül magas tumor mutational burden, ami a szakirodalom szerint korrelál az immunterápia iránt mutatott érzékenységgel. Az immunterápiák közül a PEMBROLIZUMABot hozza magasabb AEL értékkel a Calculator. A **PEMBROLIZUMAB a TMB-High és az MSI-High esetén is törzskönyvezett** daganat típustól függetlenül az első vonal kemoterápiás kezelés után. Olyan sok génhibát látunk, hogy nem váratlan, hogy látunk olyat is, ami okozhat rezisztenciát immunterápiára: a PTEN mutációi biztosan (esetleg még: NSD1-, TET2 frameshift mutációk és a JAK2 ismeretlen variáns). A PTEN PI3K vagy PARP-gátlókkal vehető célba, az mTOR-gátlás hatékonyságát megkérdőjelezik, de a METFORMIN könnyen biztosítható az immunterápia mellett. Az ideális lehetőség a **PEMBROLIZUMAB + OLAPARIB** lenne (a PARP-gátlás hatékony még az ATM, ARID1A, RECQL4, CDK12, PPP2R2A mutációk ellen is), ha annak finanszírozása nem várható, akkor a **PEMBROLIZUMAB + METFORMIN**.

Az endokrin terápiára több génhiba is rezisztenciát okoz, így a PTEN és a PIK3CA mutációk, amennyiben mégis szükséges lenne, érdemes lehet mTOR-gátlással, legalább **METFORMIN**nal kiegészíteni.

Magyarországon egy klinikai vizsgálatban lehet első vonalban immunterápiához hozzájutni 50% eséllyel kemoterápia mellett (Dr. Bagaméri):

A Study to Evaluate Dostarlimab Plus Carboplatin-paclitaxel Versus Placebo Plus Carboplatin-paclitaxel in Participants With Recurrent or Primary Advanced Endometrial Cancer (RUBY)

Az alábbi vizsgálatról azt írják, hogy fog futni Mo.-on is több helyen, de még nem indult, itt a vizsgálat keretében adnak 1L kemoterápiát, és után fenntartó kezelést: Durvalumab With or Without Olaparib as Maintenance Therapy After First-Line Treatment of Advanced and Recurrent Endometrial Cancer (DUO-E)

MMR vizsgálatot végzünk, érdemes lenni genetikai tanácsadás keretében vérből is vizsgálatokat végezni Lynch szindróma irányában.

MOLEKULÁRIS CÉLPONT ELEMZÉS

MOLEKULÁRIS ALTERÁCIÓK

MSI-H driver (AEL: 8467,85, AF/TR: NA/90%, NA/80%),
TMB-H driver (AEL: 796,72, AF/TR: NA/90%),
ER protein overexpression driver (AEL: 578,13, AF/TR: NA/80%),
PTEN-R130Q driver (AEL: 71,70, AF/TR: 68.98%/90%),
FBXW7-R479Q driver (AEL: 64,84, AF/TR: 30.4%/90%),
CTNNB1-T41A driver (AEL: 41,88, AF/TR: 24.8%/90%),
PIK3CA-E81K driver (AEL: 37,22, AF/TR: 5.64%/90%),
ATM-S214fs*16 driver (AEL: 15,61, AF/TR: 6.3%/90%),
CDH1-I594fs*19 driver (AEL: 13,12, AF/TR: 6.14%/90%),
RECQL4-L339fs*20 driver (AEL: 10,28, AF/TR: 8.7%/90%),
MRE11-R364* driver (AEL: 10,07, AF/TR: 21.43%/90%),
IL2RG-R226C driver (AEL: 10,00, AF/TR: 4.57%/90%),
PIK3CB-L1049R driver (AEL: 8,87, AF/TR: 18.24%/90%),
ATM-I1581fs*20 driver (AEL: 5,61, AF/TR: 3.28%/90%),
CIC-R507C VUS, driver gén (AEL: 2,69, AF/TR: 5.32%/90%),
TSC2-I475T VUS, driver gén (AEL: 2,68, AF/TR: 34.48%/90%),
CTNNB1-Q26* VUS, driver gén (AEL: 2,67, AF/TR: 3.35%/90%),
CTNNB1-496-1G>T VUS, driver gén (AEL: 2,67, AF/TR: 3.88%/90%),
ALK-M830L VUS, driver gén (AEL: 2,50, AF/TR: 3.32%/90%),
ARID1A-F2141fs*59 driver (AEL: 2,48, AF/TR: 4.43%/90%),
ARID1A-Q1519fs*8 driver (AEL: 2,46, AF/TR: 4.36%/90%),
ARID1A-Y551fs*68 driver (AEL: 2,45, AF/TR: 10.56%/90%),
RAD51D-P65L VUS, driver gén (AEL: 1,91, AF/TR: 6.6%/90%),
KMT2C-L4419P VUS, driver gén (AEL: 1,72, AF/TR: 29.12%/90%),
TET2-L1276fs*24 VUS, driver gén (AEL: 1,71, AF/TR: 12.38%/90%),

INDIREKT CÉLPONT GÉNEK

PD-1 vad típus (AEL: 9342,33),
- MSI-H driver (AEL: 8467,85) ;
- TMB-H driver (AEL: 796,72) ;
- JAK2-C68R driver (AEL: -0,27) ;
- PTEN-R130Q driver (AEL: -71,70) ;
- EPHA7-I473V driver (AEL: 0,55)

CD274 vad típus (AEL: 9236,18),
- ARID1A-Y551fs*68 driver (AEL: 2,45) ;
- ARID1A-Q1519fs*8 driver (AEL: 2,46) ;
- ARID1A-F2141fs*59 driver (AEL: 2,49) ;
- TET2-L1276fs*24 driver (AEL: -1,71) ;
- CTNNB1-496-1G>T driver (AEL: -2,67) ;
- EPHA7-I473V driver (AEL: 0,55) ;
- TMB-H driver (AEL: 796,72) ;
- CTNNB1-T41A driver (AEL: -41,88) ;
- CTNNB1-Q26* driver (AEL: -2,67) ;
- MSI-H driver (AEL: 8467,85)

CTLA4 vad típus (AEL: 9223,61),
- EPHA7-I473V driver (AEL: 0,55) ;
- CTNNB1-T41A driver (AEL: -41,88) ;
- TMB-H driver (AEL: 796,72) ;
- CTNNB1-Q26* driver (AEL: -2,67) ;
- CTNNB1-496-1G>T driver (AEL: -2,67) ;

Oncompass Report

A Realtime Oncology Molecular Treatment Calculator számításaival

AZONOSÍTÓ	431898
NÉV	Anonymous

MOLEKULÁRIS CÉLPONT ELEMZÉS

FAT1-S1782N VUS, driver gén (AEL: 1,46, AF/TR: 3.97%/90%),
FAT1-L3946P VUS, driver gén (AEL: 1,46, AF/TR: 6.35%/90%),
FAT1-M3869T VUS, driver gén (AEL: 1,46, AF/TR: 5.84%/90%),
SOX9-L60V VUS, driver gén (AEL: 1,12, AF/TR: 48.82%/90%),
DNMT3A-Q110fs*14 driver (AEL: 1,08, AF/TR: 23.53%/90%),
PTPN11-R386K VUS, driver gén (AEL: 1,03, AF/TR: 3.87%/90%),
GNAS-A36V VUS, driver gén (AEL: 0,83, AF/TR: 3.58%/90%),
CBL-E196fs*16 driver (AEL: 0,72, AF/TR: 25.24%/90%),
SMARCA4-Q1195H driver (AEL: 0,66, AF/TR: 4.5%/90%),
FH-A104T driver (AEL: 0,64, AF/TR: 6.76%/90%),
MED12-R431L VUS, driver gén (AEL: 0,60, AF/TR: 4.64%/90%),
EPHA7-I473V VUS, driver gén (AEL: 0,54, AF/TR: 5.51%/90%),
TGFBR2-Q334H VUS, driver gén (AEL: 0,50, AF/TR: 5.74%/90%),
KDM5C-R68fs*5 VUS, driver gén (AEL: 0,50, AF/TR: 3.12%/90%),
CARD11-R555fs*45 driver (AEL: 0,46, AF/TR: 7.38%/90%),
NSD1-M1531fs*43 driver (AEL: 0,46, AF/TR: 4.37%/90%),
NSD1-F1799fs*22 driver (AEL: 0,45, AF/TR: 3.05%/90%),
XRCC2-K267fs*? driver (AEL: 0,45, AF/TR: 6.13%/90%),
CARD11-R404M VUS, driver gén (AEL: 0,41, AF/TR: 3.84%/90%),
ARID2-D1758G VUS, driver gén (AEL: 0,41, AF/TR: 6.79%/90%),
CDK12-G1271fs*23 driver (AEL: 0,35, AF/TR: 4.78%/90%),
CDK12-A1174S VUS, driver gén (AEL: 0,34, AF/TR: 3.78%/90%),
ARAF-S157N VUS, driver gén (AEL: 0,33, AF/TR: 4.09%/90%),
TP53BP1-H964R VUS, driver gén (AEL: 0,30, AF/TR: 49.19%/90%),
IGF2R-D1317fs*5 driver (AEL: 0,28, AF/TR: 5.18%/90%),
JAK2-C68R VUS, driver gén (AEL: 0,27, AF/TR: 3.07%/90%),
IGF2R-W53R VUS, driver gén (AEL: 0,26, AF/TR: 6.97%/90%),
PAX5-A322fs*11 driver (AEL: 0,23, AF/TR: 3.21%/90%),
FANCF-G357D VUS, driver gén (AEL: 0,18, AF/TR: 4.98%/90%),
CTCF-E691fs*30 driver (AEL: 0,14, AF/TR: 6.95%/90%),
ESRP1-S625G VUS, driver gén (AEL: 0,13, AF/TR: 4.24%/90%),
EPHA3-T115N VUS, driver gén (AEL: 0,12, AF/TR: 32.69%/90%),
PPP2R2A-Y189* VUS, driver gén (AEL: 0,12, AF/TR: 3.23%/90%),
ERBB4-G1109S VUS, driver gén (AEL: 0,11, AF/TR: 42.02%/90%),
WNK2-P1381fs*11 VUS, driver gén (AEL: 0,11, AF/TR: 3.01%/90%),
LAMA2-R185C VUS, driver gén (AEL: 0,10, AF/TR: 5.17%/90%),
DMD-S3343fs*34 driver (AEL: 0,10, AF/TR: 6.36%/90%),
DMD-R1957Q VUS, driver gén (AEL: 0,10, AF/TR: 3%/90%),
PMS1-N489I VUS, driver gén (AEL: 0,10, AF/TR: 48.43%/90%),
PMS1-G417fs*6 VUS, driver gén (AEL: 0,10, AF/TR: 27.58%/90%),
ZRSR2-P383A driver (AEL: 0,10, AF/TR: 47.59%/90%),
ZMYM3-C723F VUS, driver gén (AEL: 0,09, AF/TR: 29.17%/90%),
SLX4-P1004L VUS, driver gén (AEL: 0,08, AF/TR: 7.06%/90%),
CSMD3-S3630Y VUS, driver gén (AEL: 0,03, AF/TR: 5.43%/90%),
SCN11A-K491fs*5 driver (AEL: 0,03, AF/TR: 7.23%/90%),
SAMD9L-K21fs*3 driver (AEL: 0,02, AF/TR: 5.68%/90%),
TAF1-R855C VUS, driver gén (AEL: 0,02, AF/TR: 33.72%/90%),
SLIT2-K904fs*13 VUS, driver gén (AEL: 0,01, AF/TR: 3.43%/90%),
CDC27-K319fs*24 VUS, driver gén (AEL: 0,01, AF/TR: 7.52%/90%),
DDX11-S407R ellentmondásos driver (AEL: 0,00, AF/TR: 5.76%/90%),
BAZ2B-N2000S ellentmondásos driver (AEL: 0,00, AF/TR: 46.73%/90%),
THSD7B-P642A ellentmondásos driver (AEL: 0,00, AF/TR: 6.64%/90%),
GLI1-G162D ellentmondásos driver (AEL: 0,00, AF/TR: 5.54%/90%),
ADGRB3-E227A ellentmondásos driver (AEL: 0,00, AF/TR: 5.26%/90%),
ZBED4-V241I ellentmondásos driver (AEL: 0,00, AF/TR: 48.75%/90%),
RPTOR-V1192I ellentmondásos driver (AEL: 0,00, AF/TR: 6.16%/90%),
SMAD2-R410G ellentmondásos driver (AEL: 0,00, AF/TR: 6.6%/90%),
SEC16A-P9L ellentmondásos driver (AEL: 0,00, AF/TR: 10.95%/90%),
GATA2-G273fs*53 ellentmondásos driver (AEL: 0,00, AF/TR: 3.59%/90%),
TRIO-L2277* ellentmondásos driver (AEL: 0,00, AF/TR: 3.86%/90%),
AKAP9-P1381L ellentmondásos driver (AEL: 0,00, AF/TR: 8.82%/90%),
AKAP9-R434W ellentmondásos driver (AEL: 0,00, AF/TR: 11.13%/90%),
OTOP1-L104M ismeretlen jelentőségű variáns (AEL: 0,00, AF/TR: 33.9%/90%),
ELMO1-N65S ismeretlen jelentőségű variáns (AEL: 0,00, AF/TR: 3.39%/90%),
FAT3-Q2328K ismeretlen jelentőségű variáns (AEL: 0,00, AF/TR: 3.17%/90%),
TRIO-I957T ismeretlen jelentőségű variáns (AEL: 0,00, AF/TR: 6.64%/90%),
GATA4-P290S ismeretlen jelentőségű variáns (AEL: 0,00, AF/TR: 11.31%/90%),
PAX3-P300T ismeretlen jelentőségű variáns (AEL: 0,00, AF/TR: 5.29%/90%),
IGSF10-N579D ismeretlen jelentőségű variáns (AEL: 0,00, AF/TR: 46.82%/90%),
SYNE3-P559T ismeretlen jelentőségű variáns (AEL: 0,00, AF/TR: 46.3%/90%),

- MSI-H driver (AEL: 8467,85)

WRN vad típus (AEL: 8475,55),
- MSI-H driver (AEL: 8467,85)

IDO1 vad típus (AEL: 8470,75),
- MSI-H driver (AEL: 8467,85)

LAG3 vad típus (AEL: 8470,75),
- MSI-H driver (AEL: 8467,85)

ESR1 vad típus (AEL: 960,24),
- PIK3CA-E81K driver (AEL: -37,22) ;
- ER protein overexpression driver (AEL: 578,13) ;
- PTEN-R130Q driver (AEL: -71,70) ;
- KMT2C-L4419P driver (AEL: -1,72)

MTOR vad típus (AEL: 823,83),
- PIK3CB-L1049R driver (AEL: 8,87) ;
- PIK3CA-E81K driver (AEL: 37,22) ;
- PTPN11-R386K driver (AEL: 1,03) ;
- FBXW7-R479Q driver (AEL: 64,84) ;
- ER protein overexpression driver (AEL: 578,13) ;
- CDH1-I594fs*19 driver (AEL: 13,12) ;
- TSC2-I475T driver (AEL: 2,68) ;
- PTEN-R130Q driver (AEL: 71,70)

PIK3CA vad típus (AEL: 777,65),
- PTEN-R130Q driver (AEL: -71,70) ;
- PIK3CA-E81K driver (AEL: 37,22) ;
- CDH1-I594fs*19 driver (AEL: 13,12) ;
- ER protein overexpression driver (AEL: 578,13)

AKT1 vad típus (AEL: 724,59),
- ARID1A-Y551fs*68 driver (AEL: 2,45) ;
- PIK3CB-L1049R driver (AEL: 8,87) ;
- ARID1A-Q1519fs*8 driver (AEL: 2,46) ;
- CDH1-I594fs*19 driver (AEL: 13,12) ;
- PTEN-R130Q driver (AEL: 71,70) ;
- ER protein overexpression driver (AEL: 578,13) ;
- ARID1A-F2141fs*59 driver (AEL: 2,49) ;
- PIK3CA-E81K driver (AEL: 37,22) ;
- PPP2R2A-Y189* driver (AEL: 0,12)

CDK4 vad típus (AEL: 578,58),
- ER protein overexpression driver (AEL: 578,13)

CDK6 vad típus (AEL: 578,58),
- ER protein overexpression driver (AEL: 578,13)

PARP1 vad típus (AEL: 147,96),
- ATM-I1581fs*20 driver (AEL: 5,61) ;
- RECQL4-L339fs*20 driver (AEL: 10,28) ;
- ARID1A-Q1519fs*8 driver (AEL: 2,46) ;
- CDK12-G1271fs*23 driver (AEL: 0,35) ;
- DDX11-S407R driver (AEL: 0,00) ;
- ARID1A-Y551fs*68 driver (AEL: 2,45) ;
- XRCC2-K267fs*? driver (AEL: 0,45) ;
- PTEN-R130Q driver (AEL: 71,70) ;
- MRE11-R364* driver (AEL: 10,07) ;
- ARID2-D1758G driver (AEL: 0,41) ;
- TP53BP1-H964R driver (AEL: -0,30) ;
- RAD51D-P65L driver (AEL: 1,91) ;
- ARID1A-F2141fs*59 driver (AEL: 2,49) ;
- ZMYM3-C723F driver (AEL: 0,09) ;
- CDK12-A1174S driver (AEL: 0,34) ;
- SLX4-P1004L driver (AEL: 0,08) ;
- ATM-S214fs*16 driver (AEL: 15,61)

PIK3CB vad típus (AEL: 119,54),
- CDH1-I594fs*19 driver (AEL: 13,12) ;
- PTEN-R130Q driver (AEL: 71,70) ;
- PIK3CB-L1049R driver (AEL: 8,87)

ALK vad típus (AEL: 111,22),
- CDH1-I594fs*19 driver (AEL: 13,12) ;
- ALK-M830L driver (AEL: 2,50)

CTNNB1 vad típus (AEL: 90,80),
- CTNNB1-496-1G>T driver (AEL: 2,67) ;

MOLEKULÁRIS CÉLPONT ELEMZÉS

PRF1-K282R ismeretlen jelentőségű variáns (AEL: 0,00, AF/TR: 43.78%/90%),
ABCC2-K297fs*14 ismeretlen jelentőségű variáns (AEL: 0,00, AF/TR: 11.66%/90%),
MED13-W1662* ismeretlen jelentőségű variáns (AEL: 0,00, AF/TR: 5.16%/90%),
MIER3-G366E ismeretlen jelentőségű variáns (AEL: 0,00, AF/TR: 3.86%/90%),
CCNE1-S90A ismeretlen jelentőségű variáns (AEL: 0,00, AF/TR: 3.49%/90%),
ATP4A-V288fs*70 ismeretlen jelentőségű variáns (AEL: 0,00, AF/TR: 9.06%/90%),
TOP2A-A1437T ismeretlen jelentőségű variáns (AEL: 0,00, AF/TR: 9.06%/90%),
SLC9A9-R6fs*31 ismeretlen jelentőségű variáns (AEL: 0,00, AF/TR: 21.06%/90%),
KEL-E383G ismeretlen jelentőségű variáns (AEL: 0,00, AF/TR: 49.81%/90%),
BCORL1-D1109G ismeretlen jelentőségű variáns (AEL: 0,00, AF/TR: 3.15%/90%),
PIK3C2B-M1223L ismeretlen jelentőségű variáns (AEL: 0,00, AF/TR: 25.77%/90%),
MST1R-P862fs*9 ismeretlen jelentőségű variáns (AEL: 0,00, AF/TR: 30.05%/90%),
SCN11A-L1158P ismeretlen jelentőségű variáns (AEL: 0,00, AF/TR: 46.4%/90%),
USP16-V809A ismeretlen jelentőségű variáns (AEL: 0,00, AF/TR: 29.57%/90%),
GRM3-G24W ismeretlen jelentőségű variáns (AEL: 0,00, AF/TR: 4.43%/90%),
KMT2C-K339N nem driver (AEL: -2,03, AF/TR: 9.59%/90%),
BCR-D1106N nem driver (AEL: -4,98, AF/TR: 12.6%/90%),
PREX2-S977L nem driver (AEL: -4,99, AF/TR: 46.36%/90%)

- PIK3CA-E81K driver (AEL: 37,22) ;
- CTNNB1-Q26* driver (AEL: 2,67) ;
- CTNNB1-T41A driver (AEL: 41,88)

ATM vad típus (AEL: 72,55),
- PTEN-R130Q driver (AEL: 71,70)

NOTCH1 vad típus (AEL: 65,98),
- FBXW7-R479Q driver (AEL: 64,84)

MCL1 vad típus (AEL: 65,29),
- FBXW7-R479Q driver (AEL: 64,84)

TTK vad típus (AEL: 47,73),
- CTNNB1-Q26* driver (AEL: 2,67) ;
- CTNNB1-496-1G>T driver (AEL: 2,67) ;
- CTNNB1-T41A driver (AEL: 41,88)

AKT2 vad típus (AEL: 38,33),
- PIK3CA-E81K driver (AEL: 37,22)

AKT3 vad típus (AEL: 37,58),
- PIK3CA-E81K driver (AEL: 37,22)

JAK2 vad típus (AEL: 25,07),
- JAK2-C68R driver (AEL: 0,27) ;
- CDH1-I594fs*19 driver (AEL: 13,12) ;
- CBL-E196fs*16 driver (AEL: 0,72)

ATR vad típus (AEL: 24,40),
- ATM-S214fs*16 driver (AEL: 15,61) ;
- ATM-I1581fs*20 driver (AEL: 5,61)

ABL1 vad típus (AEL: 16,41),
- CDH1-I594fs*19 driver (AEL: 13,12) ;
- FH-A104T driver (AEL: 0,64)

JAK1 vad típus (AEL: 16,25),
- CBL-E196fs*16 driver (AEL: 0,72) ;
- CDH1-I594fs*19 driver (AEL: 13,12)

ROS1 vad típus (AEL: 15,62),
- CDH1-I594fs*19 driver (AEL: 13,12)

AURKC vad típus (AEL: 14,17),
- CDH1-I594fs*19 driver (AEL: 13,12)

AURKB vad típus (AEL: 14,17),
- CDH1-I594fs*19 driver (AEL: 13,12)

PIK3CG vad típus (AEL: 14,17),
- CDH1-I594fs*19 driver (AEL: 13,12)

AURKA vad típus (AEL: 14,17),
- CDH1-I594fs*19 driver (AEL: 13,12)

PIK3CD vad típus (AEL: 14,17),
- CDH1-I594fs*19 driver (AEL: 13,12)

PDGFRB vad típus (AEL: 13,63),
- CDH1-I594fs*19 driver (AEL: 13,12)

BCL2 vad típus (AEL: 13,63),
- CDH1-I594fs*19 driver (AEL: 13,12)

NTRK1 vad típus (AEL: 13,63),
- CDH1-I594fs*19 driver (AEL: 13,12)

FGFR1 vad típus (AEL: 13,63),
- CDH1-I594fs*19 driver (AEL: 13,12)

PDGFRA vad típus (AEL: 13,63),
- CDH1-I594fs*19 driver (AEL: 13,12)

JAK3 vad típus (AEL: 13,63),
- CDH1-I594fs*19 driver (AEL: 13,12)

SRC vad típus (AEL: 13,63),

Einsiedlerstrasse 23, 8834 Schindellegi, SWITZERLAND
E-mail: info@realtimeoncology.com **Web:** www.realtimeoncology.com

MOLEKULÁRIS CÉLPONT ELEMZÉS

- CDH1-I594fs*19 driver (AEL: 13,12)

NPY5R vad típus (AEL: 13,63),
- CDH1-I594fs*19 driver (AEL: 13,12)

CDK2 vad típus (AEL: 13,63),
- CDH1-I594fs*19 driver (AEL: 13,12)

CDK1 vad típus (AEL: 13,63),
- CDH1-I594fs*19 driver (AEL: 13,12)

RET vad típus (AEL: 13,63),
- CDH1-I594fs*19 driver (AEL: 13,12)

GBF1 vad típus (AEL: 13,63),
- CDH1-I594fs*19 driver (AEL: 13,12)

MET vad típus (AEL: 13,63),
- CDH1-I594fs*19 driver (AEL: 13,12)

HMGCR vad típus (AEL: 13,62),
- CDH1-I594fs*19 driver (AEL: 13,12)

EZH2 vad típus (AEL: 13,55),
- ARID1A-Y551fs*68 driver (AEL: 2,45) ;
- ARID1A-Q1519fs*8 driver (AEL: 2,46) ;
- ARID1A-F2141fs*59 driver (AEL: 2,49) ;
- SMARCA4-Q1195H driver (AEL: 0,66)

ARAF vad típus (AEL: 9,83),
- ARAF-S157N driver (AEL: 0,33)

KDM1A vad típus (AEL: 8,65),
- ARID1A-Y551fs*68 driver (AEL: 2,45) ;
- ARID1A-Q1519fs*8 driver (AEL: 2,46) ;
- ARID1A-F2141fs*59 driver (AEL: 2,49) ;
- SMARCA4-Q1195H driver (AEL: 0,66)

YES1 vad típus (AEL: 7,92),
- ARID1A-F2141fs*59 driver (AEL: 2,49) ;
- ARID1A-Q1519fs*8 driver (AEL: 2,46) ;
- ARID1A-Y551fs*68 driver (AEL: 2,45)

CD33 vad típus (AEL: 6,69),
- TET2-L1276fs*24 driver (AEL: 1,71)

ERBB4 vad típus (AEL: 6,32),
- ERBB4-G1109S driver (AEL: 0,11)

BRD4 vad típus (AEL: 3,86),
- KMT2C-L4419P driver (AEL: 1,72)

DOT1L vad típus (AEL: 2,98),
- DNMT3A-Q110fs*14 driver (AEL: 1,08)

LYN vad típus (AEL: 1,72),
- CBL-E196fs*16 driver (AEL: 0,72)

PRKACA vad típus (AEL: 1,33),
- GNAS-A36V driver (AEL: 0,83)

CHEK1 vad típus (AEL: 0,95),
- CDK12-G1271fs*23 driver (AEL: 0,35) ;
- CDK12-A1174S driver (AEL: 0,34)

COX2 vad típus (AEL: 0,51)
- ERBB4-G1109S driver (AEL: 0,11)

Einsiedlerstrasse 23, 8834 Schindellegi, SWITZERLAND
E-mail: info@realtimeoncology.com **Web:** www.realtimeoncology.com

Oncompass Report

A Realtime Oncology Molecular Treatment Calculator számításaival

AZONOSÍTÓ	431898
NÉV	Anonymous

DAGANAT MOLEKULÁRIS PROFILJÁVAL POZITÍV KAPCSOLATBAN ÁLLÓ HATÓANYAGOK

FORGALOMBAN LÉVŐ

11 listázott hatóanyag (összesen 110)

PEMBROLIZUMAB (liver - hepatocellular carcinoma [FDA]; bármely tumor - urothelial carcinoma [FDA+EMA]; gastric - adenocarcinoma [FDA]; cervix - bármely szövettan [FDA]; rectum - bármely szövettan [FDA+EMA]; endometrium - bármely szövettan [FDA]; skin - squamous cell carcinoma [FDA]; breast - bármely szövettan [FDA]; esophagus - squamous cell carcinoma [FDA]; bármely tumor - endometrioid carcinoma [FDA]; colon - bármely szövettan [FDA+EMA]; gastroesophageal junction - adenocarcinoma [FDA]; head-neck - squamous cell carcinoma [FDA+EMA]; bármely tumor - mediastinal B-cell lymphoma [FDA]; bármely tumor - renal cell carcinoma [FDA+EMA]; lung - non-small cell carcinoma [FDA+EMA]; bármely tumor - Hodgkin lymphoma [FDA+EMA]; bármely tumor - malignant melanoma [FDA+EMA]; lung - adenocarcinoma [FDA+EMA]; skin - Merkel cell carcinoma (MCC) [FDA]) (AEL: 24592,91)
- PTEN-R130Q driver (AEL: -71,70) ;
- TMB-H driver (AEL: 796,72) ;
- MSI-H driver (AEL: 8467,85) ;
- PD-1 vad típus target (AEL: 9342,33)

AVELUMAB (bladder - bármely szövettan [FDA+EMA]; ureter - bármely szövettan [FDA+EMA]; skin - Merkel cell carcinoma (MCC) [FDA+EMA]; bladder - urothelial carcinoma [FDA+EMA]; kidney - renal cell carcinoma [FDA+EMA]) (AEL: 18562,43)
- TMB-H driver (AEL: 796,72) ;
- PD-L1 vad típus target (AEL: 9236,18) ;
- MSI-H driver (AEL: 8467,85)

NIVOLUMAB (rectum - bármely szövettan [FDA]; bármely tumor - urothelial carcinoma [FDA+EMA]; kidney - renal cell carcinoma [FDA+EMA]; pleura - mesothelioma [FDA]; bármely tumor - malignant melanoma [FDA+EMA]; esophagus - squamous cell carcinoma [FDA+EMA]; colon - bármely szövettan [FDA]; head-neck - squamous cell carcinoma [FDA+EMA]; liver - hepatocellular carcinoma [FDA]; bone marrow - Hodgkin lymphoma [FDA+EMA]; lung - non-small cell carcinoma [FDA+EMA]) (AEL: 18071,38)
- MSI-H driver (AEL: 8467,85) ;
- PD-1 vad típus target (AEL: 9342,33) ;
- PTEN-R130Q driver (AEL: -71,70)

DOSTARLIMAB (bármely tumor - endometrioid carcinoma [EMA]; endometrium - bármely szövettan [EMA]) (AEL: 17837,38)
- MSI-H driver (AEL: 8467,85) ;
- PD-1 vad típus target (AEL: 9342,33)

CEMIPLIMAB (skin - basal cell carcinoma [FDA]; lung - squamous cell carcinoma [FDA]; lung - adenocarcinoma [FDA]; skin - squamous cell carcinoma [FDA+EMA]) (AEL: 9342,43)
- PD-1 vad típus target (AEL: 9342,33)

DURVALUMAB (lung - non-small cell carcinoma [FDA+EMA]; lung - small cell carcinoma [FDA+EMA]; bármely tumor - urothelial carcinoma [FDA]) (AEL: 9290,58)
- PD-L1 vad típus target (AEL: 9236,18)

ATEZOLIZUMAB (bármely tumor - urothelial carcinoma [FDA+EMA]; liver - hepatocellular carcinoma [FDA+EMA]; bármely tumor - malignant melanoma [FDA]; lung - small cell carcinoma [FDA+EMA]; lung - non-small cell carcinoma [FDA+EMA]; breast - bármely szövettan [FDA+EMA]) (AEL: 9252,06)
- PD-L1 vad típus target (AEL: 9236,18)

IPILIMUMAB (pleura - mesothelioma [FDA]; rectum - bármely szövettan [FDA]; lung - adenocarcinoma [FDA+EMA]; skin - malignant melanoma [FDA+EMA]; kidney - renal cell carcinoma [FDA+EMA]; colon - bármely szövettan [FDA]; liver - hepatocellular carcinoma [FDA]) (AEL: 9229,47)
- CTLA4 vad típus target (AEL: 9223,61)

PALBOCICLIB (breast - bármely szövettan [FDA+EMA]) (AEL: 2965,88)
- CDK6 vad típus target (AEL: 578,58) ;
- CDK4 vad típus target (AEL: 578,58) ;
- ESR1 protein overexpression driver (AEL: 578,13)

LETROZOLE (breast - bármely szövettan [FDA]) (AEL: 2819,30)
- ESR1 vad típus target (AEL: 960,24) ;
- ESR1 protein overexpression driver (AEL: 578,13)

DAGANAT MOLEKULÁRIS PROFILJÁVAL NEGATÍV KAPCSOLATBAN ÁLLÓ HATÓANYAGOK

FORGALOMBAN LÉVŐ

10 listázott hatóanyag (összesen 37)

5-FLUOROURACIL (pancreas - bármely szövettan [FDA]; breast - bármely szövettan [FDA]; colon - bármely szövettan [FDA]; rectum - bármely szövettan [FDA]; gastric - bármely szövettan [FDA]) (AEL: -8691,35)
- CBL-E196fs*16 driver (AEL: 0,72) ;
- MSI-H driver (AEL: -8467,85) ;
- PIK3CA-E81K driver (AEL: -37,22)

CISPLATIN (AEL: -8607,70)
- RECQL4-L339fs*20 driver (AEL: 10,28) ;
- CDK12-A1174S driver (AEL: 0,34) ;
- ARID2-D1758G driver (AEL: 0,41) ;
- CDK12-G1271fs*23 driver (AEL: 0,35) ;
- MSI-H driver (AEL: -8467,85) ;
- NSD1-F1799fs*22 driver (AEL: 0,45) ;
- IGF2R-D1317fs*5 driver (AEL: -0,28) ;
- NSD1-M1262fs*43 driver (AEL: 0,46) ;
- IGF2R-W53R driver (AEL: -0,26)

CAPECITABINE (rectum - bármely szövettan [FDA]; breast - bármely szövettan [FDA]; colon - bármely szövettan [FDA]) (AEL: -8528,25)
- MSI-H driver (AEL: -8467,85)

OXALIPLATIN (rectum - bármely szövettan [FDA]; colon - bármely szövettan [FDA]) (AEL: -8528,25)
- MSI-H driver (AEL: -8467,85)

CETUXIMAB (colon - bármely szövettan [FDA+EMA]; head-neck - squamous cell carcinoma [FDA+EMA]; rectum - bármely szövettan [FDA+EMA]) (AEL: -557,65)
- CDH1-I594fs*19 driver (AEL: -13,12) ;
- EGFR vad típus target (AEL: -203,82) ;
- PIK3CA-E81K driver (AEL: -37,22) ;
- PTEN-R130Q driver (AEL: -71,70) ;
- FBXW7-R479Q driver (AEL: -64,84)

PANITUMUMAB (colon - bármely szövettan [FDA+EMA]; rectum - bármely szövettan [FDA+EMA]) (AEL: -518,57)
- CDH1-I594fs*19 driver (AEL: -13,12) ;
- PIK3CA-E81K driver (AEL: -37,22) ;
- EGFR vad típus target (AEL: -203,82) ;
- PTEN-R130Q driver (AEL: -71,70) ;
- FBXW7-R479Q driver (AEL: -64,84)

GEFITINIB (lung - squamous cell carcinoma [FDA+EMA]; lung - adenocarcinoma [FDA+EMA]; lung - non-small cell carcinoma [FDA+EMA]) (AEL: -350,97)
- FBXW7-R479Q driver (AEL: -64,84) ;
- CIC-R507C driver (AEL: -2,69) ;
- PTEN-R130Q driver (AEL: -71,70) ;
- EGFR vad típus target (AEL: -203,82)

NERATINIB (breast - bármely szövettan [FDA+EMA]) (AEL: -320,50)
- ERBB2 vad típus target (AEL: -116,68) ;
- EGFR vad típus target (AEL: -203,82)

AFATINIB (lung - squamous cell carcinoma [FDA+EMA]; lung - non-small cell carcinoma [FDA+EMA]; lung - adenocarcinoma [FDA+EMA]) (AEL: -320,26)
- EGFR vad típus target (AEL: -203,82) ;
- ERBB2 vad típus target (AEL: -116,68)

ERLOTINIB (pancreas - bármely szövettan [FDA+EMA]; lung - non-small cell carcinoma [FDA+EMA]; lung - adenocarcinoma [FDA+EMA]; lung - squamous cell carcinoma [FDA+EMA]) (AEL: -252,69)
- PIK3CA-E81K driver (AEL: -37,22) ;
- PIK3CB-L1049R driver (AEL: -8,87) ;
- CIC-R507C driver (AEL: -2,69) ;
- EGFR vad típus target (AEL: -203,82)

Oncompass Report

A Realtime Oncology Molecular Treatment Calculator számításaival

AZONOSÍTÓ	431898
NÉV	Anonymous

DAGANAT MOLEKULÁRIS PROFILJÁVAL POZITÍV KAPCSOLATBAN ÁLLÓ HATÓANYAGOK	DAGANAT MOLEKULÁRIS PROFILJÁVAL NEGATÍV KAPCSOLATBAN ÁLLÓ HATÓANYAGOK
LENVATINIB (endometrium - bármely szövettan [FDA]; liver - hepatocellular carcinoma [FDA+EMA]; bármely tumor - endometrioid adenocarcinoma [FDA]; kidney - renal cell carcinoma [FDA+EMA]; thyroid - bármely szövettan [FDA+EMA]) (AEL: 42,96) • RET vad típus target (AEL: 13,63) ; • PDGFRB vad típus target (AEL: 13,63) ; • FGFR1 vad típus target (AEL: 13,63)	
KLINIKAI FEJLESZTÉS ALATT *10 listázott hatóanyag (összesen 239)* ENVAFOLIMAB (AEL: 17714,03) • PD-L1 vad típus target (AEL: 9236,18) ; • MSI-H driver (AEL: 8467,85) camrelizumab (AEL: 9343,22) • PD-1 vad típus target (AEL: 9342,33) TISLELIZUMAB (AEL: 9342,81) • PD-1 vad típus target (AEL: 9342,33) SINTILIMAB (AEL: 9342,61) • PD-1 vad típus target (AEL: 9342,33) GEPTANOLIMAB (AEL: 9342,53) • PD-1 vad típus target (AEL: 9342,33) TORIPALIMAB (AEL: 9342,33) • PD-1 vad típus target (AEL: 9342,33) ABBV-181 (AEL: 9342,33) • PD-1 vad típus target (AEL: 9342,33) CS1001 (AEL: 9236,44) • PD-L1 vad típus target (AEL: 9236,18) BINTRAFUSP ALFA (AEL: 9236,18) • PD-L1 vad típus target (AEL: 9236,18) PACMILIMAB (AEL: 9236,18) • PD-L1 vad típus target (AEL: 9236,18)	KLINIKAI FEJLESZTÉS ALATT *10 listázott hatóanyag (összesen 64)* EPIRUBICIN (AEL: -8619,45) • MSI-H driver (AEL: -8467,85) ALLITINIB (AEL: -320,50) • EGFR vad típus target (AEL: -203,82) ; • ERBB2 vad típus target (AEL: -116,68) AV-412 (AEL: -320,50) • ERBB2 vad típus target (AEL: -116,68) ; • EGFR vad típus target (AEL: -203,82) CUDC-101 (AEL: -320,50) • ERBB2 vad típus target (AEL: -116,68) ; • EGFR vad típus target (AEL: -203,82) PELITINIB (AEL: -320,50) • ERBB2 vad típus target (AEL: -116,68) ; • EGFR vad típus target (AEL: -203,82) TAK-285 (AEL: -320,50) • EGFR vad típus target (AEL: -203,82) ; • ERBB2 vad típus target (AEL: -116,68) EPERTINIB (AEL: -320,50) • ERBB2 vad típus target (AEL: -116,68) ; • EGFR vad típus target (AEL: -203,82) JNJ-26483327 (AEL: -314,18) • ERBB4 vad típus target (AEL: 6,32) ; • EGFR vad típus target (AEL: -203,82) ; • ERBB2 vad típus target (AEL: -116,68) AEE788 (AEL: -203,82) • EGFR vad típus target (AEL: -203,82) SAPITINIB (AEL: -203,82) • EGFR vad típus target (AEL: -203,82)

A hatóanyagok mellett megjelenő pontszámok a hatóanyagokra vonatkozó aggregált evidencia-szintet (AEL, aggregated evidence level) jelzik. Az AEL a tumor típusokat, molekuláris variánsokat, célpontokat és hatóanyagokat összekapcsoló evidenciák számát, tudományos hatását és klinikai relevanciáját reprezentálja. Az egyes evidencia relációk pontszámait az alapján normalizáljuk és súlyozzuk, hogy az egyes összefüggésekben leírt jellemzők milyen mértékben hasonlítanak a vizsgált beteg paramétereihez. A hatóanyagok pontszámait a releváns, hatóanyagokat, tumor típusokat, drivereket és célpontokat összekapcsoló relációk (és azok AEL-jeinek) összegzésével számítjuk. A hatóanyagokat AEL szerinti csökkenő sorrendben listázzuk.
(Rövidítések: AEL - aggregált evidencia-szint, AF - allél frekvencia, TR: tumor arány)

Einsiedlerstrasse 23, 8834 Schindellegi, SWITZERLAND
E-mail: info@realtimeoncology.com **Web:** www.realtimeoncology.com

KLINIKAI VIZSGÁLATOK

Keresési Kritériumok

ÁLLAPOT: Not yet recruiting,Active recruiting

AZONOSÍTÓ	LEÍRÁS
NCT04269200	A Randomised, Multicentre, Double-blind, Placebo-controlled, Phase III Study of First-line Carboplatin and Paclitaxel in Combination With Durvalumab, Followed by Maintenance Durvalumab With or Without Olaparib in Patients With Newly Diagnosed Advanced or Recurrent Endometrial Cancer (DUO-E)

Aktív, toboroz

Vonal	Fázis	Hatóanyag(ok)
1	3	CARBOPLATIN, DURVALUMAB, DURVALUMAB, OLAPARIB, PACLITAXEL

Ország(ok)	Allokáció	Maszkírozás
Estonia, Germany, Hong Kong, Israel, Belgium, Russian Federation, India, Japan, Korea, Republic of, Lithuania, China, Mexico, Greece, Colombia, Hungary, Brazil, Singapore, Australia, Poland, Canada, United States	Randomizált	Kettős Vak

AZONOSÍTÓ	LEÍRÁS
NCT03981796	A Phase 3, Randomized, Double-blind, Multicenter Study of Dostarlimab (TSR-042) Plus Carboplatin-paclitaxel Versus Placebo Plus Carboplatin-paclitaxel in Patients With Recurrent or Primary Advanced Endometrial Cancer (RUBY)

Aktív, toboroz

Vonal	Fázis	Hatóanyag(ok)
1	3	CARBOPLATIN, CARBOPLATIN, DOSTARLIMAB, PACLITAXEL, PACLITAXEL, PLACEBO

Ország(ok)	Allokáció	Maszkírozás
Norway, Germany, Finland, Israel, Belgium, Denmark, Italy, Greece, Ukraine, Hungary, Sweden, Czech Republic, Belarus, United Kingdom, Poland, Turkey, Netherlands, Canada, United States	Randomizált	Kettős Vak

AZONOSÍTÓ	LEÍRÁS
NCT03603184	Phase III Double-blind Randomized Placebo Controlled Trial of Atezolizumab in Combination With Paclitaxel and Carboplatin in Women With Advanced/Recurrent Endometrial Cancer

Aktív, toboroz

Vonal	Fázis	Hatóanyag(ok)
Adjuváns-1	3	ATEZOLIZUMAB, CARBOPLATIN, CARBOPLATIN, PACLITAXEL, PACLITAXEL, PLACEBO

Ország(ok)	Allokáció	Maszkírozás
Germany, Sweden, Austria, Japan, Italy, United Kingdom, Spain	Randomizált	Kettős Vak

AZONOSÍTÓ	LEÍRÁS
NCT04234113	A Multicenter Open-label Phase 1/1b Study to Evaluate the Safety and Preliminary Efficacy of SO-C101 as Monotherapy and in Combination With Pembrolizumab in Patients With Selected Advanced/Metastatic Solid Tumors

Aktív, toboroz

Vonal	Fázis	Hatóanyag(ok)
Neoadjuváns-10	1a-1b	PEMBROLIZUMAB, SO-C101, SO-C101

Ország(ok)	Allokáció	Maszkírozás
France, Spain, United States	Nem Randomizált	Egykaros Vizsgálat

Aktív, toboroz

Vonal	Fázis	Hatóanyag(ok)
Neoadjuváns-10	1a-1b	PEMBROLIZUMAB, SO-C101, SO-C101

Ország(ok)	Allokáció	Maszkírozás

Einsiedlerstrasse 23, 8834 Schindellegi, SWITZERLAND
E-mail: info@realtimeoncology.com **Web:** www.realtimeoncology.com

Oncompass Report

A Realtime Oncology Molecular Treatment Calculator számításaival

AZONOSÍTÓ	431898
NÉV	Anonymous

KLINIKAI VIZSGÁLATOK

France, Spain, United States | Nem Randomizált | Egykaros Vizsgálat

Aktív, toboroz

Vonal	Fázis	Hatóanyag(ok)
Neoadjuváns-10	1a-1b	PEMBROLIZUMAB, SO-C101, SO-C101

Ország(ok)	Allokáció	Maszkírozás
France, Spain, United States	Nem Randomizált	Egykaros Vizsgálat

Bekerülési Biomarker Kritérium

ERBB2 protein normál, ERBB2 protein lack of expression, ESR1 protein normál, ESR1 protein lack of expression, PGR protein lack of expression, PGR protein normál

NCT02628067 A Clinical Trial of Pembrolizumab (MK-3475) Evaluating Predictive Biomarkers in Subjects With Advanced Solid Tumors (KEYNOTE 158)

Aktív, toboroz

Vonal	Fázis	Hatóanyag(ok)
1-10	2	PEMBROLIZUMAB

Ország(ok)	Allokáció	Maszkírozás
Norway, Germany, Taiwan, Province of China, Israel, Russian Federation, Japan, Denmark, South Africa, Korea, Republic of, Italy, Mexico, France, Colombia, Spain, Brazil, Australia, Philippines, United Kingdom, Netherlands, United States, Canada	N/A	Egykaros Vizsgálat

NCT03503786 Carboplatin, Paclitaxel With or Without Avelumab in Advanced or Recurrent Endometrial Cancer (MITO END-3)

Még nem toboroz

Vonal	Fázis	Hatóanyag(ok)
1-10	2	AVELUMAB, CARBOPLATIN, CARBOPLATIN, PACLITAXEL, PACLITAXEL

Ország(ok)	Allokáció	Maszkírozás
Italy	Randomizált	Nyílt Jelölésű

A klinikai vizsgálatok listáját a Realtime Oncology Molecular Treatment Calculator segítségével állítottuk elő. A klinikai vizsgálatok esetében a szűréshez a beteg klinikai és molekuláris profiljában szereplő paramétereket vetettük össze a rendszerben található klinikai vizsgálatok beválogatási és kizárási feltételeivel. A manuálisan beállított keresési feltételek nem feltétlenül tartalmaznak minden szűrési kritériumot. Az Oncompass Medicine a rendszerben szereplő klinikai vizsgálatokért és az adatok helyességéért nem vállal felelősséget, és nem garantálja a beteg bekerülését a listán szereplő klinikai vizsgálatokba.

RÉSZLETES MOLEKULÁRIS PROFIL

GENETIKAI VARIÁNSOK

ABCC2-K297FS*14, ADGRB3-E227A, AKAP9-P1381L, AKAP9-R434W, ALK-M830L, ARAF-S157N, ARID1A-F2141FS*59, ARID1A-Q1519FS*8, ARID1A-Y551FS*68, ARID2-D1758G, ATM-I1581FS*20, ATM-S214FS*16, ATP4A-V288FS*70, BAZ2B-N2000S, BCORL1-D1109G, BCR-D1106N, CARD11-R404M, CARD11-R555FS*45, CBL-E196FS*16, CCNE1-S90A, CDC27-K319FS*24, CDH1-I594FS*19, CDK12-A1174S, CDK12-G1271FS*23, CIC-R507C, CSMD3-S3630Y, CTCF-E691FS*30, CTNNB1-496-1G>T, CTNNB1-Q26*, CTNNB1-T41A, DDX11-S407R, DMD-R1957Q, DMD-S3343FS*34, DNMT3A-Q110FS*14, ELMO1-N65S, EPHA3-T115N, EPHA7-I473V, ERBB4-G1109S, ESRP1-S625G, FANCF-G357D, FAT1-L3946P, FAT1-M3869T, FAT1-S1782N, FAT3-Q2328K, FBXW7-R479Q, FH-A104T, GATA2-G273FS*53, GATA4-P290S, GLI1-G162D, GNAS-A36V, GRM3-G24W, IGF2R-D1317FS*5, IGF2R-W53R, IGSF10-N579D, IL2RG-R226C, JAK2-C68R, KDM5C-R68FS*5, KEL-E383G, KMT2C-K339N, KMT2C-L4419P, LAMA2-R185C, MED12-R431L, MED13-W1662*, MIER3-G366E, MRE11-R364*, MST1R-P862FS*9, NSD1-F1799FS*22, NSD1-M1531FS*43, OTOP1-L104M, PAX3-P300T, PAX5-A322FS*11, PIK3C2B-M1223L, PIK3CA-E81K, PIK3CB-L1049R, PMS1-G417FS*6, PMS1-N489I, PPP2R2A-Y189*, PREX2-S977L, PRF1-K282R, PTEN-R130Q, PTPN11-R386K, RAD51D-P65L, RECQL4-L339FS*20, RPTOR-V1192I, SAMD9L-K21FS*3, SCN11A-K491FS*5, SCN11A-L1158P, SEC16A-P9L, SLC9A9-R6FS*31, SLIT2-K904FS*13, SLX4-P1004L, SMAD2-R410G, SMARCA4-Q1195H, SOX9-L60V, SYNE3-P559T, TAF1-R855C, TET2-L1276FS*24, TGFBR2-Q334H, THSD7B-P642A, TOP2A-A1437T, TP53BP1-H964R, TRIO-I957T, TRIO-L2277*, TSC2-I475T, USP16-V809A, WNK2-P1381FS*11, XRCC2-K267FS*?, ZBED4-V241I, ZMYM3-C723F, ZRSR2-P383A

VAD TÍPUSÚ GÉNEK

ABCB1, ABL1, ABL2, ABRAXAS1, ACVR1B, ACVRL1, AGTRAP, AIP, AKT1, AKT2, AKT3, AMER1, AMPH, APC, APEX1, AR, ARFRP1, ARID1B, ASXL1, ATP11B, ATP6V0D2, ATR, ATRX, AURKA, AURKB, AXIN1, AXIN2, AXL, B2M, BAP1, BARD1, BAX, BCL2, BCL2L1, BCL2L2, BCL6, BCL9, BCOR, BIM, BIRC2, BIRC3, BLM, BMPR1A, BRAF, BRCA1, BRCA2, BRD4, BRIP1, BTG1, BTK, BUB1B, CASP8, CASR, CBFB, CBLB, CBLC, CCDC178, CCDC6, CCND1, CCND2, CCND3, CD74, CD79A, CD79B, CDA, CDC73, CDK4, CDK6, CDK8, CDKN1A, CDKN1B, CDKN1C, CDKN2A, CDKN2B, CDKN2C, CEBPA, CEP57, CHD1, CHD2, CHD4, CHD7, CHEK1, CHEK2, CHIC2, CIT, CREBBP, CRKL, CRLF2, CSF1R, CSNK2A1, CTNNA1, CUBN, CUL3, CYLD, CYP19A1, CYP2A6, CYP2B6, CYP2C19, CYP2C9, CYP2D6, DAXX, DCC, DCUN1D1, DDB2, DDR1, DDR2, DDX3X, DICER1, DIS3L2, DOT1L, DPH3, DPYD, DSE, ECT2L, EED, EGFR, EML4, EMSY, EP300, EPCAM, EPHA2, EPHA5, EPHB1, ERBB2, ERBB3, ERCC1, ERCC2, ERCC3, ERCC4, ERCC5, ERG, ERRFI1, ESR1, ESR2, ETV6, EXOC2, EXT1, EXT2, EZH2, EZR, FANCA, FANCB, FANCC, FANCD2, FANCE, FANCG, FANCI, FANCL, FANCM, FAS, FBXO11, FBXO32, FGF10, FGF14, FGF19, FGF23, FGF3, FGF4, FGF5, FGF6, FGF9, FGFR1, FGFR2, FGFR3, FGFR4, FLCN, FLT1, FLT3, FLT4, FN1, FOXA1, FOXL2, FOXO1, FOXP1, FRS2, FSTL5, FUBP1, FZD3, G6PD, GABRA6, GALNT17, GAS6, GATA1, GATA3, GATA6, GEN1, GID4, GNA11,

Oncompass Report

A Realtime Oncology Molecular Treatment Calculator számításaival

AZONOSÍTÓ	431898
NÉV	Anonymous

RÉSZLETES MOLEKULÁRIS PROFIL

GNA13, GNAI2, GNAQ, GNAT2, GOPC, GPC3, GPR78, GREM1, GRIN2A, GRM8, GSK3B, GSTP1, GXYLT1, H3-3A, H3C2, HGF, HNF1A, HOXB13, HRAS, HSD3B1, HSP90AA1, HSPH1, IDH1, IDH2, IFITM1, IFITM3, IGF1R, IGF2, IKBKE, IKZF1, IKZF4, IL2RA, IL2RB, IL6, IL6ST, IL7R, INHBA, INPP4B, IRAK4, IRF2, IRF4, IRS2, ITCH, JAK1, JAK3, JUN, KAT6A, KDM4B, KDM5A, KDM6A, KDR, KEAP1, KIAA1549, KIF5B, KIT, KLF6, KLHL6, KMT2A, KMT2D, KNSTRN, KRAS, KREMEN1, LCK, LMO1, LPAR2, LRP1B, LRRK2, LTK, LYN, LZTR1, MAGI2, MAGI3, MAGOH, MAP2K1, MAP2K2, MAP2K4, MAP3K1, MAP3K4, MAP4K3, MAP7, MAPK1, MAPK3, MAS1L, MAX, MCL1, MDM2, MDM4, MEF2B, MEN1, MET, MITF, MLH1, MLLT3, MPL, MSH2, MSH3, MSH6, MTOR, MUC16, MUTYH, MYC, MYCL1, MYCN, MYD88, MYO18A, MYO1B, NBN, NCOA2, NCOR1, NEK2, NF1, NF2, NFE2L2, NFKBIA, NIPA2, NKX2-1, NKX2-8, NKX3-1, NOTCH1, NOTCH2, NOTCH3, NPM1, NRAS, NRCAM, NRG1, NRP2, NT5C2, NTRK1, NTRK2, NTRK3, NUP93, OR5L1, PAK3, PALB2, PAX7, PBRM1, PCBP1, PCGF2, PD-L1, PDGFRA, PDGFRB, PDK1, PDL2, PDZRN3, PHF6, PHOX2B, PIK3CD, PIK3CG, PIK3R1, PIK3R2, PLCG2, PLEKHS1, PMS2, PNP, POLD1, POLE, POT1, PPARG, PPM1L, PPP2R1A, PRDM1, PRKAR1A, PRKCI, PRKDC, PRKN, PRPF40B, PRSS8, PSMB1, PSMB2, PSMB5, PSMD1, PSMD2, PTCH1, PTGFR, PTPN12, PTPRD, QKI, RAC1, RAC2, RAD21, RAD50, RAD51, RAD51B, RAD51C, RAD54L, RAF1, RANBP2, RARA, RARB, RARG, RB1, RBM10, RECQL5, RET, RHBDF2, RHEB, RHOA, RICTOR, RIT1, RNF43, ROS1, RPS6KB1, RUNX1, RUNX1T1, RXRA, RXRB, RXRG, S1PR2, SBDS, SDC4, SDHA, SDHAF2, SDHB, SDHC, SDHD, SEPT9, SETBP1, SETD2, SF1, SF3A1, SF3B1, SH2B3, SHH, SHOC2, SLC22A1, SLC22A2, SLC31A1, SLC34A2, SLC45A3, SLC7A8, SLCO1B1, SMAD3, SMAD4, SMARCB1, SMARCE1, SMC1A, SMC3, SMO, SNCAIP, SOCS1, SOS1, SOX10, SOX2, SPEG, SPEN, SPOP, SPRED1, SPTA1, SRC, SRSF2, SSTR1, STAG2, STAT3, STAT4, STK11, SUFU, SUZ12, SYK, TACC3, TAS2R38, TBX20, TBX3, TCERG1, TCF7L2, TENT5C, TERC, TERT, TFG, TIAF1, TMEM127, TMPRSS2, TNFAIP3, TNFRSF14, TOP1, TP53, TP63, TPM3, TPM4, TPMT, TRAF5, TRRAP, TSC1, TSHR, TYK2, U2AF1, U2AF2, UBR3, UGT1A1, USP25, VCL, VEGFA, VHL, WDCP, WEE1, WISP3, WRN, WT1, WWP1, XPA, XPC, XPO1, YAP1, YES1, ZBTB2, ZFHX3, ZIC3, ZNF2, ZNF217, ZNF226, ZNF473, ZNF595, ZNF703

FISH/CNA/IHC POZITÍV GÉNEK

ESR1 PROTEIN OVEREXPRESSION

FISH/CNA/IHC NEGATÍV GÉNEK

ABL1 TRANSLOCATION ABSENCE, ALK TRANSLOCATION ABSENCE, BCR TRANSLOCATION ABSENCE, BRAF TRANSLOCATION ABSENCE, BRD4 TRANSLOCATION ABSENCE, CD74 TRANSLOCATION ABSENCE, EGFR TRANSLOCATION ABSENCE, FGFR1 TRANSLOCATION ABSENCE, FGFR2 TRANSLOCATION ABSENCE, FGFR3 TRANSLOCATION ABSENCE, KIF5B TRANSLOCATION ABSENCE, MET TRANSLOCATION ABSENCE, NRG1 TRANSLOCATION ABSENCE, NTRK1 TRANSLOCATION ABSENCE, NTRK2 TRANSLOCATION ABSENCE, NTRK3 TRANSLOCATION ABSENCE, PD-L1 PROTEIN NORMÁL, RAF1 TRANSLOCATION ABSENCE, RARA TRANSLOCATION ABSENCE, RET TRANSLOCATION ABSENCE, ROS1 TRANSLOCATION ABSENCE, TACC1 TRANSLOCATION ABSENCE, TACC3 TRANSLOCATION ABSENCE

MOLEKULÁRIS BIOLÓGIAI INTERPRETÁCIÓ

MOLEKULÁRIS ALTERÁCIÓK

MSI-H driver (AEL: 8467,85, AF/TR: NA/90%, NA/80%),
TMB-H driver (AEL: 796,72, AF/TR: NA/90%),
ER protein overexpression driver (AEL: 578,13, AF/TR: NA/80%),
PTEN-R130Q driver (AEL: 71,70, AF/TR: 68.98%/90%),
FBXW7-R479Q driver (AEL: 64,84, AF/TR: 30.4%/90%),
CTNNB1-T41A driver (AEL: 41,88, AF/TR: 24.8%/90%),
PIK3CA-E81K driver (AEL: 37,22, AF/TR: 5.64%/90%),
ATM-S214fs*16 driver (AEL: 15,61, AF/TR: 6.3%/90%),
CDH1-I594fs*19 driver (AEL: 13,12, AF/TR: 6.14%/90%),
RECQL4-L339fs*20 driver (AEL: 10,28, AF/TR: 8.7%/90%),
MRE11-R364* driver (AEL: 10,07, AF/TR: 21.43%/90%),
IL2RG-R226C driver (AEL: 10,00, AF/TR: 4.57%/90%),
PIK3CB-L1049R driver (AEL: 8,87, AF/TR: 18.24%/90%),
ATM-I1581fs*20 driver (AEL: 5,61, AF/TR: 3.28%/90%),
CIC-R507C VUS, driver gén (AEL: 2,69, AF/TR: 5.32%/90%),
TSC2-I475T VUS, driver gén (AEL: 2,68, AF/TR: 34.48%/90%),
CTNNB1-Q26* VUS, driver gén (AEL: 2,67, AF/TR: 3.35%/90%),
CTNNB1-496-1G>T VUS, driver gén (AEL: 2,67, AF/TR: 3.88%/90%),
ALK-M830L VUS, driver gén (AEL: 2,50, AF/TR: 3.32%/90%),
ARID1A-F2141fs*59 driver (AEL: 2,48, AF/TR: 4.43%/90%),
ARID1A-Q1519fs*8 driver (AEL: 2,46, AF/TR: 4.36%/90%),
ARID1A-Y551fs*68 driver (AEL: 2,45, AF/TR: 10.56%/90%),
RAD51D-P65L VUS, driver gén (AEL: 1,91, AF/TR: 6.6%/90%),
KMT2C-L4419P VUS, driver gén (AEL: 1,72, AF/TR: 29.12%/90%),
TET2-L1276fs*24 VUS, driver gén (AEL: 1,71, AF/TR: 12.38%/90%),
FAT1-S1782N VUS, driver gén (AEL: 1,46, AF/TR: 3.97%/90%),
FAT1-L3946P VUS, driver gén (AEL: 1,46, AF/TR: 6.35%/90%),
FAT1-M3869T VUS, driver gén (AEL: 1,46, AF/TR: 5.84%/90%),
SOX9-L60V VUS, driver gén (AEL: 1,12, AF/TR: 48.82%/90%),
DNMT3A-Q110fs*14 driver (AEL: 1,08, AF/TR: 23.53%/90%),
PTPN11-R386K VUS, driver gén (AEL: 1,03, AF/TR: 3.87%/90%),
GNAS-A36V VUS, driver gén (AEL: 0,83, AF/TR: 3.58%/90%),
CBL-E196fs*16 driver (AEL: 0,72, AF/TR: 25.24%/90%),
SMARCA4-Q1195H driver (AEL: 0,66, AF/TR: 4.5%/90%),
FH-A104T driver (AEL: 0,64, AF/TR: 6.76%/90%),
MED12-R431L VUS, driver gén (AEL: 0,60, AF/TR: 4.64%/90%),
EPHA7-I473V VUS, driver gén (AEL: 0,54, AF/TR: 5.51%/90%),
TGFBR2-Q334H VUS, driver gén (AEL: 0,50, AF/TR: 5.74%/90%),
KDM5C-R68fs*5 VUS, driver gén (AEL: 0,50, AF/TR: 3.12%/90%),
CARD11-R555fs*45 driver (AEL: 0,46, AF/TR: 7.38%/90%),
NSD1-M1531fs*43 driver (AEL: 0,46, AF/TR: 4.37%/90%),
NSD1-F1799fs*22 driver (AEL: 0,45, AF/TR: 3.05%/90%),
XRCC2-K267fs*? driver (AEL: 0,45, AF/TR: 6.13%/90%),
CARD11-R404M VUS, driver gén (AEL: 0,41, AF/TR: 3.84%/90%),
ARID2-D1758G VUS, driver gén (AEL: 0,41, AF/TR: 6.79%/90%),

INDIREKT CÉLPONT GÉNEK

PD-1 vad típus (AEL: 9342,33),
- MSI-H driver (AEL: 8467,85) ;
- TMB-H driver (AEL: 796,72) ;
- JAK2-C68R driver (AEL: -0,27) ;
- PTEN-R130Q driver (AEL: -71,70) ;
- EPHA7-I473V driver (AEL: 0,55)

CD274 vad típus (AEL: 9236,18),
- ARID1A-Y551fs*68 driver (AEL: 2,45) ;
- ARID1A-Q1519fs*8 driver (AEL: 2,46) ;
- ARID1A-F2141fs*59 driver (AEL: 2,49) ;
- TET2-L1276fs*24 driver (AEL: -1,71) ;
- CTNNB1-496-1G>T driver (AEL: -2,67) ;
- EPHA7-I473V driver (AEL: 0,55) ;
- TMB-H driver (AEL: 796,72) ;
- CTNNB1-T41A driver (AEL: -41,88) ;
- CTNNB1-Q26* driver (AEL: -2,67) ;
- MSI-H driver (AEL: 8467,85)

CTLA4 vad típus (AEL: 9223,61),
- EPHA7-I473V driver (AEL: 0,55) ;
- CTNNB1-T41A driver (AEL: -41,88) ;
- TMB-H driver (AEL: 796,72) ;
- CTNNB1-Q26* driver (AEL: -2,67) ;
- CTNNB1-496-1G>T driver (AEL: -2,67) ;
- MSI-H driver (AEL: 8467,85)

WRN vad típus (AEL: 8475,55),
- MSI-H driver (AEL: 8467,85)

IDO1 vad típus (AEL: 8470,75),
- MSI-H driver (AEL: 8467,85)

LAG3 vad típus (AEL: 8470,75),
- MSI-H driver (AEL: 8467,85)

ESR1 vad típus (AEL: 960,24),
- PIK3CA-E81K driver (AEL: -37,22) ;
- ER protein overexpression driver (AEL: 578,13) ;
- PTEN-R130Q driver (AEL: -71,70) ;
- KMT2C-L4419P driver (AEL: -1,72)

MTOR vad típus (AEL: 823,83),
- PIK3CB-L1049R driver (AEL: 8,87) ;

Einsiedlerstrasse 23, 8834 Schindellegi, SWITZERLAND
E-mail: info@realtimeoncology.com **Web:** www.realtimeoncology.com

Oncompass Report

A Realtime Oncology Molecular Treatment Calculator számításaival

AZONOSÍTÓ	431898
NÉV	Anonymous

RÉSZLETES MOLEKULÁRIS PROFIL

CDK12-G1271fs*23 driver (AEL: 0,35, AF/TR: 4.78%/90%),
CDK12-A1174S VUS, driver gén (AEL: 0,34, AF/TR: 3.78%/90%),
ARAF-S157N VUS, driver gén (AEL: 0,33, AF/TR: 4.09%/90%),
TP53BP1-H964R VUS, driver gén (AEL: 0,30, AF/TR: 49.19%/90%),
IGF2R-D1317fs*5 driver (AEL: 0,28, AF/TR: 5.18%/90%),
JAK2-C68R VUS, driver gén (AEL: 0,27, AF/TR: 3.07%/90%),
IGF2R-W53R VUS, driver gén (AEL: 0,26, AF/TR: 6.97%/90%),
PAX5-A322fs*11 driver (AEL: 0,23, AF/TR: 3.21%/90%),
FANCF-G357D VUS, driver gén (AEL: 0,18, AF/TR: 4.98%/90%),
CTCF-E691fs*30 driver (AEL: 0,14, AF/TR: 6.95%/90%),
ESRP1-S625G VUS, driver gén (AEL: 0,13, AF/TR: 4.24%/90%),
EPHA3-T115N VUS, driver gén (AEL: 0,12, AF/TR: 32.69%/90%),
PPP2R2A-Y189* VUS, driver gén (AEL: 0,12, AF/TR: 3.23%/90%),
ERBB4-G1109S VUS, driver gén (AEL: 0,11, AF/TR: 42.02%/90%),
WNK2-P1381fs*11 VUS, driver gén (AEL: 0,11, AF/TR: 3.01%/90%),
LAMA2-R185C VUS, driver gén (AEL: 0,10, AF/TR: 5.17%/90%),
DMD-S3343fs*34 driver (AEL: 0,10, AF/TR: 6.36%/90%),
DMD-R1957Q VUS, driver gén (AEL: 0,10, AF/TR: 3%/90%),
PMS1-N489I VUS, driver gén (AEL: 0,10, AF/TR: 48.43%/90%),
PMS1-G417fs*6 VUS, driver gén (AEL: 0,10, AF/TR: 27.58%/90%),
ZRSR2-P383A driver (AEL: 0,10, AF/TR: 47.59%/90%),
ZMYM3-C723F VUS, driver gén (AEL: 0,09, AF/TR: 29.17%/90%),
SLX4-P1004L VUS, driver gén (AEL: 0,08, AF/TR: 7.06%/90%),
CSMD3-S3630Y VUS, driver gén (AEL: 0,03, AF/TR: 5.43%/90%),
SCN11A-K491fs*5 driver (AEL: 0,03, AF/TR: 7.23%/90%),
SAMD9L-K21fs*3 driver (AEL: 0,02, AF/TR: 5.68%/90%),
TAF1-R855C VUS, driver gén (AEL: 0,02, AF/TR: 33.72%/90%),
SLIT2-K904fs*13 VUS, driver gén (AEL: 0,01, AF/TR: 3.43%/90%),
CDC27-K319fs*24 VUS, driver gén (AEL: 0,01, AF/TR: 7.52%/90%),
DDX11-S407R ellentmondásos driver (AEL: 0,00, AF/TR: 5.76%/90%),
BAZ2B-N2000S ellentmondásos driver (AEL: 0,00, AF/TR: 46.73%/90%),
THSD7B-P642A ellentmondásos driver (AEL: 0,00, AF/TR: 6.64%/90%),
GLI1-G162D ellentmondásos driver (AEL: 0,00, AF/TR: 5.54%/90%),
ADGRB3-E227A ellentmondásos driver (AEL: 0,00, AF/TR: 5.26%/90%),
ZBED4-V241I ellentmondásos driver (AEL: 0,00, AF/TR: 48.75%/90%),
RPTOR-V1192I ellentmondásos driver (AEL: 0,00, AF/TR: 6.16%/90%),
SMAD2-R410G ellentmondásos driver (AEL: 0,00, AF/TR: 6.6%/90%),
SEC16A-P9L ellentmondásos driver (AEL: 0,00, AF/TR: 10.95%/90%),
GATA2-G273fs*53 ellentmondásos driver (AEL: 0,00, AF/TR: 3.59%/90%),
TRIO-L2277* ellentmondásos driver (AEL: 0,00, AF/TR: 3.86%/90%),
AKAP9-P1381L ellentmondásos driver (AEL: 0,00, AF/TR: 8.82%/90%),
AKAP9-R434W ellentmondásos driver (AEL: 0,00, AF/TR: 11.13%/90%),
OTOP1-L104M ismeretlen jelentőségű variáns (AEL: 0,00, AF/TR: 33.9%/90%),
ELMO1-N65S ismeretlen jelentőségű variáns (AEL: 0,00, AF/TR: 3.39%/90%),
FAT3-Q2328K ismeretlen jelentőségű variáns (AEL: 0,00, AF/TR: 3.17%/90%),
TRIO-I957T ismeretlen jelentőségű variáns (AEL: 0,00, AF/TR: 6.64%/90%),
GATA4-P290S ismeretlen jelentőségű variáns (AEL: 0,00, AF/TR: 11.31%/90%),
PAX3-P300T ismeretlen jelentőségű variáns (AEL: 0,00, AF/TR: 5.29%/90%),
IGSF10-N579D ismeretlen jelentőségű variáns (AEL: 0,00, AF/TR: 46.82%/90%),
SYNE3-P559T ismeretlen jelentőségű variáns (AEL: 0,00, AF/TR: 46.3%/90%),
PRF1-K282R ismeretlen jelentőségű variáns (AEL: 0,00, AF/TR: 43.78%/90%),
ABCC2-K297fs*14 ismeretlen jelentőségű variáns (AEL: 0,00, AF/TR: 11.66%/90%),
MED13-W1662* ismeretlen jelentőségű variáns (AEL: 0,00, AF/TR: 5.16%/90%),
MIER3-G366E ismeretlen jelentőségű variáns (AEL: 0,00, AF/TR: 3.86%/90%),
CCNE1-S90A ismeretlen jelentőségű variáns (AEL: 0,00, AF/TR: 3.49%/90%),
ATP4A-V288fs*70 ismeretlen jelentőségű variáns (AEL: 0,00, AF/TR: 9.06%/90%),
TOP2A-A1437T ismeretlen jelentőségű variáns (AEL: 0,00, AF/TR: 9.06%/90%),
SLC9A9-R6fs*31 ismeretlen jelentőségű variáns (AEL: 0,00, AF/TR: 21.06%/90%),
KEL-E383G ismeretlen jelentőségű variáns (AEL: 0,00, AF/TR: 49.81%/90%),
BCORL1-D1109G ismeretlen jelentőségű variáns (AEL: 0,00, AF/TR: 3.15%/90%),

- PIK3CA-E81K driver (AEL: 37,22) ;
- PTPN11-R386K driver (AEL: 1,03) ;
- FBXW7-R479Q driver (AEL: 64,84) ;
- ER protein overexpression driver (AEL: 578,13) ;
- CDH1-I594fs*19 driver (AEL: 13,12) ;
- TSC2-I475T driver (AEL: 2,68) ;
- PTEN-R130Q driver (AEL: 71,70)

PIK3CA vad típus (AEL: 777,65),
- PTEN-R130Q driver (AEL: -71,70) ;
- PIK3CA-E81K driver (AEL: 37,22) ;
- CDH1-I594fs*19 driver (AEL: 13,12) ;
- ER protein overexpression driver (AEL: 578,13)

AKT1 vad típus (AEL: 724,59),
- ARID1A-Y551fs*68 driver (AEL: 2,45) ;
- PIK3CB-L1049R driver (AEL: 8,87) ;
- ARID1A-Q1519fs*8 driver (AEL: 2,46) ;
- CDH1-I594fs*19 driver (AEL: 13,12) ;
- PTEN-R130Q driver (AEL: 71,70) ;
- ER protein overexpression driver (AEL: 578,13) ;
- ARID1A-F2141fs*59 driver (AEL: 2,49) ;
- PIK3CA-E81K driver (AEL: 37,22) ;
- PPP2R2A-Y189* driver (AEL: 0,12)

CDK4 vad típus (AEL: 578,58),
- ER protein overexpression driver (AEL: 578,13)

CDK6 vad típus (AEL: 578,58),
- ER protein overexpression driver (AEL: 578,13)

PARP1 vad típus (AEL: 147,96),
- ATM-I1581fs*20 driver (AEL: 5,61) ;
- RECQL4-L339fs*20 driver (AEL: 10,28) ;
- ARID1A-Q1519fs*8 driver (AEL: 2,46) ;
- CDK12-G1271fs*23 driver (AEL: 0,35) ;
- DDX11-S407R driver (AEL: 0,00) ;
- ARID1A-Y551fs*68 driver (AEL: 2,45) ;
- XRCC2-K267fs*? driver (AEL: 0,45) ;
- PTEN-R130Q driver (AEL: 71,70) ;
- MRE11-R364* driver (AEL: 10,07) ;
- ARID2-D1758G driver (AEL: 0,41) ;
- TP53BP1-H964R driver (AEL: -0,30) ;
- RAD51D-P65L driver (AEL: 1,91) ;
- ARID1A-F2141fs*59 driver (AEL: 2,49) ;
- ZMYM3-C723F driver (AEL: 0,09) ;
- CDK12-A1174S driver (AEL: 0,34) ;
- SLX4-P1004L driver (AEL: 0,08) ;
- ATM-S214fs*16 driver (AEL: 15,61)

PIK3CB vad típus (AEL: 119,54),
- CDH1-I594fs*19 driver (AEL: 13,12) ;
- PTEN-R130Q driver (AEL: 71,70) ;
- PIK3CB-L1049R driver (AEL: 8,87)

ALK vad típus (AEL: 111,22),
- CDH1-I594fs*19 driver (AEL: 13,12) ;
- ALK-M830L driver (AEL: 2,50)

CTNNB1 vad típus (AEL: 90,80),
- CTNNB1-496-1G>T driver (AEL: 2,67) ;
- PIK3CA-E81K driver (AEL: 37,22) ;
- CTNNB1-Q26* driver (AEL: 2,67) ;
- CTNNB1-T41A driver (AEL: 41,88)

ATM vad típus (AEL: 72,55),
- PTEN-R130Q driver (AEL: 71,70)

NOTCH1 vad típus (AEL: 65,98),
- FBXW7-R479Q driver (AEL: 64,84)

MCL1 vad típus (AEL: 65,29),
- FBXW7-R479Q driver (AEL: 64,84)

TTK vad típus (AEL: 47,73),
- CTNNB1-Q26* driver (AEL: 2,67) ;
- CTNNB1-496-1G>T driver (AEL: 2,67) ;
- CTNNB1-T41A driver (AEL: 41,88)

AKT2 vad típus (AEL: 38,33),

RÉSZLETES MOLEKULÁRIS PROFIL

PIK3C2B-M1223L ismeretlen jelentőségű variáns (AEL: 0,00, AF/TR: 25.77%/90%),
MST1R-P862fs*9 ismeretlen jelentőségű variáns (AEL: 0,00, AF/TR: 30.05%/90%),
SCN11A-L1158P ismeretlen jelentőségű variáns (AEL: 0,00, AF/TR: 46.4%/90%),
USP16-V809A ismeretlen jelentőségű variáns (AEL: 0,00, AF/TR: 29.57%/90%),
GRM3-G24W ismeretlen jelentőségű variáns (AEL: 0,00, AF/TR: 4.43%/90%),
KMT2C-K339N nem driver (AEL: -2,03, AF/TR: 9.59%/90%),
BCR-D1106N nem driver (AEL: -4,98, AF/TR: 12.6%/90%),
PREX2-S977L nem driver (AEL: -4,99, AF/TR: 46.36%/90%)

- PIK3CA-E81K driver (AEL: 37,22)

AKT3 vad típus (AEL: 37,58),
- PIK3CA-E81K driver (AEL: 37,22)

JAK2 vad típus (AEL: 25,07),
- JAK2-C68R driver (AEL: 0,27) ;
- CDH1-I594fs*19 driver (AEL: 13,12) ;
- CBL-E196fs*16 driver (AEL: 0,72)

ATR vad típus (AEL: 24,40),
- ATM-S214fs*16 driver (AEL: 15,61) ;
- ATM-I1581fs*20 driver (AEL: 5,61)

ABL1 vad típus (AEL: 16,41),
- CDH1-I594fs*19 driver (AEL: 13,12) ;
- FH-A104T driver (AEL: 0,64)

JAK1 vad típus (AEL: 16,25),
- CBL-E196fs*16 driver (AEL: 0,72) ;
- CDH1-I594fs*19 driver (AEL: 13,12)

ROS1 vad típus (AEL: 15,62),
- CDH1-I594fs*19 driver (AEL: 13,12)

AURKC vad típus (AEL: 14,17),
- CDH1-I594fs*19 driver (AEL: 13,12)

AURKB vad típus (AEL: 14,17),
- CDH1-I594fs*19 driver (AEL: 13,12)

PIK3CG vad típus (AEL: 14,17),
- CDH1-I594fs*19 driver (AEL: 13,12)

AURKA vad típus (AEL: 14,17),
- CDH1-I594fs*19 driver (AEL: 13,12)

PIK3CD vad típus (AEL: 14,17),
- CDH1-I594fs*19 driver (AEL: 13,12)

PDGFRB vad típus (AEL: 13,63),
- CDH1-I594fs*19 driver (AEL: 13,12)

BCL2 vad típus (AEL: 13,63),
- CDH1-I594fs*19 driver (AEL: 13,12)

NTRK1 vad típus (AEL: 13,63),
- CDH1-I594fs*19 driver (AEL: 13,12)

FGFR1 vad típus (AEL: 13,63),
- CDH1-I594fs*19 driver (AEL: 13,12)

PDGFRA vad típus (AEL: 13,63),
- CDH1-I594fs*19 driver (AEL: 13,12)

JAK3 vad típus (AEL: 13,63),
- CDH1-I594fs*19 driver (AEL: 13,12)

SRC vad típus (AEL: 13,63),
- CDH1-I594fs*19 driver (AEL: 13,12)

NPY5R vad típus (AEL: 13,63),
- CDH1-I594fs*19 driver (AEL: 13,12)

CDK2 vad típus (AEL: 13,63),
- CDH1-I594fs*19 driver (AEL: 13,12)

CDK1 vad típus (AEL: 13,63),
- CDH1-I594fs*19 driver (AEL: 13,12)

RET vad típus (AEL: 13,63),
- CDH1-I594fs*19 driver (AEL: 13,12)

GBF1 vad típus (AEL: 13,63),
- CDH1-I594fs*19 driver (AEL: 13,12)

MET vad típus (AEL: 13,63),
- CDH1-I594fs*19 driver (AEL: 13,12)

Einsiedlerstrasse 23, 8834 Schindellegi, SWITZERLAND
E-mail: info@realtimeoncology.com **Web:** www.realtimeoncology.com

RÉSZLETES MOLEKULÁRIS PROFIL

HMGCR vad típus (AEL: 13,62),
- CDH1-I594fs*19 driver (AEL: 13,12)

EZH2 vad típus (AEL: 13,55),
- ARID1A-Y551fs*68 driver (AEL: 2,45) ;
- ARID1A-Q1519fs*8 driver (AEL: 2,46) ;
- ARID1A-F2141fs*59 driver (AEL: 2,49) ;
- SMARCA4-Q1195H driver (AEL: 0,66)

ARAF vad típus (AEL: 9,83),
- ARAF-S157N driver (AEL: 0,33)

KDM1A vad típus (AEL: 8,65),
- ARID1A-Y551fs*68 driver (AEL: 2,45) ;
- ARID1A-Q1519fs*8 driver (AEL: 2,46) ;
- ARID1A-F2141fs*59 driver (AEL: 2,49) ;
- SMARCA4-Q1195H driver (AEL: 0,66)

YES1 vad típus (AEL: 7,92),
- ARID1A-F2141fs*59 driver (AEL: 2,49) ;
- ARID1A-Q1519fs*8 driver (AEL: 2,46) ;
- ARID1A-Y551fs*68 driver (AEL: 2,45)

CD33 vad típus (AEL: 6,69),
- TET2-L1276fs*24 driver (AEL: 1,71)

ERBB4 vad típus (AEL: 6,32),
- ERBB4-G1109S driver (AEL: 0,11)

BRD4 vad típus (AEL: 3,86),
- KMT2C-L4419P driver (AEL: 1,72)

DOT1L vad típus (AEL: 2,98),
- DNMT3A-Q110fs*14 driver (AEL: 1,08)

LYN vad típus (AEL: 1,72),
- CBL-E196fs*16 driver (AEL: 0,72)

PRKACA vad típus (AEL: 1,33),
- GNAS-A36V driver (AEL: 0,83)

CHEK1 vad típus (AEL: 0,95),
- CDK12-G1271fs*23 driver (AEL: 0,35) ;
- CDK12-A1174S driver (AEL: 0,34)

COX2 vad típus (AEL: 0,51)
- ERBB4-G1109S driver (AEL: 0,11)

MOLEKULÁRIS BIOLÓGIAI INTERPRETÁCIÓ

Mikroszatellita instabilitás (MSI-H) endometrium daganatban

A mikroszatellita vizsgálat a DNS hibajavító enzimek defektusának kimutatására alkalmas. A teszt során normál és daganatos szövetből származó izolált DNS-ben 5 biomarker instabilitását vizsgálják. Háromféle eredmény lehetséges: mikroszatellita stabilitás, alacsony és magas fokú mikroszatellita instabilitás (MSS, MSI-L és MSI-H).

Egy tanulmány szerint endometrium daganatok 15-25%-ban mutattak ki mikroszatellita instabilitást (1), míg egy másik tanulmányban ez az érték 25% (2) volt, ami a mikroszatellita instabilitás fontos szerepét jelzi a sporadikus endometrium daganatok kialakulásában (3). Az endometrium carcinomás betegek esetében a mikroszatellita instabilitás jelenléte kedvezőbb klinikai kimenetellel asszociált (4, 5). A tudományos irodalom szerint mikroszatellita instabil (MMR deficiens) daganatok esetén az immunterápiák hatékonysága nagyobb, mint mikroszatellita stabil daganatoknál (6, 7).

Az FDA törzskönyvezte a PEMBROLIZUMAB PD-1 gátló antitestet bármilyen szolid daganat esetén, ami MSI-H státuszú vagy MMR deficiens fenotípusú. Az EMA pozitív véleményben részesítette a DOSTARLIMAB (PD-1 inhibitor) törzskönyvezési beadványát rekurrens vagy előrehaladott MSI-H/dMMR endometrium carcinoma betegek kezelésére, akik platina alapú kemoterápián vagy azt követően progrediáltak.

Egy fázis II vizsgálatban a pembrolizumab kezelés 7 MMR deficiens nem colorectalis daganatos beteg körében 71%-os válaszadási arányt ért el. A vizsgálatban két endometrium carcinomás beteg vett részt, egyiküknél teljes választ, a másik betegnél részleges választ írtak el (6). Egy másik vizsgálatban 12 különböző tumortípusú, MMR deficiens betegek vettek részt. A pembrolizumab kezelésre a válaszadási arány 53% volt, a

Einsiedlerstrasse 23, 8834 Schindellegi, SWITZERLAND
E-mail: info@realtimeoncology.com **Web:** www.realtimeoncology.com

MOLEKULÁRIS BIOLÓGIAI INTERPRETÁCIÓ

betegek 21%-ánál teljes választ írtak le. A medián progressziómentes túlélést (progression-free survival, PFS) és teljes túlélést (overall survival, OS) nem érték el az adatok publikálásáig. A vizsgálatban 15 endometrium tumoros beteg vett részt, akik közül 3 betegnél teljes választ, 5 betegnél részleges választ és 3 betegnél stabil betegséget írtak le (8).
Egy klinikai vizsgálat előzetes eredményei szerint a pembrolizumab + lenvatinib kombinációs kezelés 36,7%-os válaszadási arányt ért el MSI státusz szerint nem szelektált endometrium carcinomás betegek között. A 3 MSI-H beteg közül egynél részleges tumorválaszt, egynél stabil betegséget és egynél progresszív betegséget írtak le (9). A kombinációs kezelés nem MSI-H vagy MMR deficiens endometrium daganatos betegek számára FDA törzskönyvezett.

A dostarlimab (TSR-042, PD-1 gátló) MSI-H endometrium carcinomás betegek körében 50%-os válaszadási arányt ért el (10).
Az fázis I GARNET vizsgálatban a DOSTARLIMAB (TSR-042, PD-1 inhibitor) hatékonyságát vizsgálták endometrium carcinoma indikációkban. Előzetesen kezelt, rekurrens vagy előrehaladott EC betegek (n=110) esetében a dostarlimab MSI-H státusz esetén 50,0%-os, MSS státusz esetén 19,1%-os ORR-t eredményezett (teljes ORR: 27,7%) (10).
A dMMR (n=126) és az MMR proficiens (n=145) státuszú betegeket vizsgáló kohortokban az ORR 44,7% és 13,4%, a betegség kontroll ráta (DCR) 57,3% és 35,2%, és a 18 hónapos válaszadási idő ráta 79,2% és 61,3% volt (11). A DOSTARLIMAB törzskönyvi jóváhagyása ennek a vizsgálatnak az eredményein alapult.

Az avelumab (PD-L1 gátló) kezelés MMR deficiens vagy POLE mutáns endometrium carcinomás betegek között 26,7%-os válaszadási arányt eredményezett, és a betegek 40%-a ért el legalább 6 hónapos PFS-t (12).

Referenciák:

(1) Esteller M et al., MLH1 promoter hypermethylation is associated with the microsatellite instability phenotype in sporadic endometrial carcinomas. Oncogene. 1998;17(18):2413-7. Epub 1998/11/12. PubMed PMID: 9811473

(2) Kandoth C et al., Integrated genomic characterization of endometrial carcinoma. Nature. 2013;497(7447):67-73. Epub 2013/05/03. PubMed PMID: 23636398

(3) Dec G et al., Microsatellite instability (MSI) analysis in patients with endometrial cancer. Polish journal of pathology : official journal of the Polish Society of Pathologists. 2005;56(1):15-9. Epub 2005/06/01. PubMed PMID: 15921009

(4) Black D et al., Clinicopathologic significance of defective DNA mismatch repair in endometrial carcinoma. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2006;24(11):1745-53. Epub 2006/03/22. PubMed PMID: 16549821

(5) Haruma T et al., Clinical impact of endometrial cancer stratified by genetic mutational profiles, POLE mutation, and microsatellite instability. PloS one. 2018;13(4):e0195655. Epub 2018/04/17. PubMed PMID: 29659608

(6) Le DT et al., PD-1 blockade in tumors with mismatch-repair deficiency. New England Journal of Medicine. 2015;372(26):2509-20. PubMed PMID: PubMed PMID: 26028255

(7) Le DT et al., PD-1 blockade in mismatch repair deficient non-colorectal gastrointestinal cancers. American Society of Clinical Oncology; 2016.

(8) Le DT et al., Mismatch repair deficiency predicts response of solid tumors to PD-1 blockade. Science (New York, NY). 2017;357(6349):409-13. Epub 2017/06/10. PubMed PMID: 28596308

(9) Makker V et al., Lenvatinib+ pembrolizumab in patients with advanced endometrial cancer: Updated results. American Society of Clinical Oncology; 2018.

(10) Oaknin A et al., Preliminary safety, efficacy, and pharmacokinetic/pharmacodynamic characterization from GARNET, a phase I/II clinical trial of the anti–PD-1 monoclonal antibody, TSR-042, in patients with recurrent or advanced MSI-h and MSS endometrial cancer. Gynecologic Oncology, 2019, 154: 17.

(11) Oaknin A et al., Safety and antitumor activity of dostarlimab in patients (pts) with advanced or recurrent DNA mismatch repair deficient (dMMR) or proficient (MMRp) endometrial cancer (EC): Results from GARNET. Annals of Oncology. 2020;31(suppl_4):S1142-S1215. doi: 10.1016/j.annonc.2020.08.2266.

(12) Konstantinopoulos PA et al., Phase 2, two-group, two-stage study of avelumab in patients (pts) with microsatellite stable (MSS), microsatellite instable (MSI), and polymerase epsilon (POLE) mutated recurrent/persistent endometrial cancer (EC). 2019.

A tumor mutational burden (TMB) vizsgálat eredménye

A vizsgált mintában a szekvencia analízis (NGS) során kapott 1 megabázisra vonatkozó mutációk száma (TMB) 32,19. Az adatbázisunkban lévő kalkulált TMB értékek (n=605) eloszlása alapján az eseteink 100%-ában ennél alacsonyabb TMB értéket kaptunk.
A TMB érték klinikai interpretációja egyelőre nem egyértelmű, az eredmény tájékoztató jellegű.
A magas TMB érték pozitív asszociációban áll a PD-1 és PD-L1 inhibitorokra adott válasszal különböző tumortípusokban.
Goodman és munkatársai 151 olyan beteg adatait elemezték, akik immunterápiás kezelésben részesültek, és ismert volt esetükben a TMB érték. Különböző – összesen 21 féle – tumortípus szerepelt a vizsgálatban. A magas TMB értéket minimum 20 mutáció/megabázis-ként definiálták. A magas TMB értékkel rendelkező betegcsoport válaszadási aránya immunterápiára 58% volt, míg alacsony vagy közepes TMB érték esetén 20%.

Einsiedlerstrasse 23, 8834 Schindellegi, SWITZERLAND
E-mail: info@realtimeoncology.com **Web:** www.realtimeoncology.com

MOLEKULÁRIS BIOLÓGIAI INTERPRETÁCIÓ

A PD-1/PD-L1 gátló terápiában részesülő betegek között is korreláció volt megfigyelhető a TMB érték és a kezelés kedvező kimenetele között (1). Hasonló terápiás előnyt tapasztaltak a magas TMB értékű csoportban az alacsony/közepes TMB értékűhöz képest PD-1/PD-L1 gátló kezelés hatására, mikroszatellita stabil (MSS) beteg (n=60, 14 különböző hisztológia) mintáinak analízise során. A medián progressziómentes túlélés 26,8 és 4,3 hónapnak bizonyult (2).
Egy másik tanulmányban 1662 immunterápiával kezelt beteg adatait elemezték. Magas TMB értéknek tekintették minden szövettani típusban a TMB értékek legmagasabb 20%-át. A magas TMB betegcsoportban szignifikánsan hosszabb volt a túlélés. Különböző küszöbértékekkel számolva azt állapították meg, hogy minél magasabb a TMB érték, annál nagyobb túlélési előnyt élveznek az immunterápiát kapó betegek (3).

Forgalomban lévő PD-1 vagy PD-L1 gátló hatóanyagok a NIVOLUMAB, PEMBROLIZUMAB, AVELUMAB, ATEZOLIZUMAB, DURVALUMAB és CEMIPLIMAB.
A PEMBROLIZUMAB az FDA által törzskönyvezett magas TMB értékű, előrehaladott vagy metasztatikus, szolid tumorral rendelkező, felnőtt és gyermek betegek számára.
A törzskönyv alapjául a KEYNOTE-158 fázis II klinikai vizsgálat (NCT02628067) előre tervezett retrospektív analízise szolgált. A vizsgálat eredményei alapján a magas TMB státusz (a vizsgálatban 10 mutáció/mb-nek definiálták) kedvezőbb kimenetellel volt asszociált pembrolizumab monoterápia esetén előzetesen kezelt előrehaladott szolid daganatos betegek körében (n=790, 10-féle tumor típus). Az objektív válaszadási ráta 29%-nak (30/102) bizonyult magas TMB státusz esetén, 28%-nak (23/81) magas TMB esetén a magas vagy ismeretlen MSI státuszú betegek eredményeit kizárva és 6%-nak (43/688) az alacsony TMB értékű csoportban. Az adatok kiértékelésekor, 37,1 hónapos medián követési idő mellett, a medián válaszadási idő nem került elérésre a magas TMB értékű csoportban, míg az alacsony TMB státuszú kohort esetén 33,1 hónap volt (4).

Referenciák:

(1) Goodman AM et al., Tumor Mutational Burden as an Independent Predictor of Response to Immunotherapy in Diverse Cancers. Mol Cancer Ther. 2017 Nov;16(11):2598-2608. Epub 2017 Aug 23. PMID: 28835386

(2) Goodman AM et al., Microsatellite-Stable Tumors with High Mutational Burden Benefit from Immunotherapy. Cancer Immunol Res. 2019 Oct;7 (10):1570-1573. Epub 2019 Aug 12. PMID: 31405947

(3) Samstein RM, et al. Tumor mutational load predicts survival after immunotherapy across multiple cancer types. Nat Genet. 2019 Feb;51(2):202-206. Epub 2019 Jan 14. PMID: 30643254

(4) Marabelle A et al. Association of tumour mutational burden with outcomes in patients with advanced solid tumours treated with pembrolizumab: prospective biomarker analysis of the multicohort, open-label, phase 2 KEYNOTE-158 study. Lancet Oncol. 2020 Sep 10:S1470-2045(20)30445-9. Epub ahead of print. PMID: 32919526

Mutációs mintázat (Mutational Signature; Signature 20)

A detektált variánsokkal minőségi és funkcionális filterezéseket követően mutációs mintázat (mutational signature) (1, 2) analízist végeztünk. A tumorban kialakult alterációk etiológiájában jelentős szerepet játszik az össze nem illő párok javításának defektusa (mutational signature 20: Defective DNA MMR / MSI (small INDELs)). Ezzel a mutációs mintázattal az immunterápiák említhetőek pozitív asszociációban (3, 4).

Referenciák:

(1) Alexandrov LB et al., Signatures of mutational processes in human cancer. Nature. 2013 Aug 22;500(7463):415-21. PMID: 23945592

(2) cancer.sanger.ac.uk/cosmic/signatures

(3) Van Hoeck A et al., Portrait of a cancer: mutational signature analyses for cancer diagnostics. BMC Cancer. 2019 May 15;19(1):457. PMID: 31092228

(4) Haradhvala NJ et al., Distinct mutational signatures characterize concurrent loss of polymerase proofreading and mismatch repair. Nat Commun. 2018 May 1;9(1):1746. PMID: 29717118

A kópiaszám-variáció (copy number variation, CNV) vizsgálat eredménye

Az NGS vizsgálat során CNV analízist végeztünk. Kópiaszám-variációnak tekintjük, ha a detektált kópiaszám a normál kópiaszámtól (n=2) eltérő. NGS alapú technológiával a kópiaszám-változások becslése lehetséges.
A vizsgált mintában releváns kópiaszám-változást nem detektáltunk.

Az újgenerációs szekvenálás (NGS) eredménye

591 gén NGS szekvenálása 6556 genetikai variánst mutatott ki a mintában. A molekuláris profilba feltöltött 110 variáns bioinformatikai és funkcionális szűrések eredményeként került kiválasztásra. Ezek a variánsok szerepelnek a Realtime Oncology Calculatorban további funkcionális interpretáció és orvosi döntéstámogatás céljából.

Einsiedlerstrasse 23, 8834 Schindellegi, SWITZERLAND
E-mail: info@realtimeoncology.com **Web:** www.realtimeoncology.com

MOLEKULÁRIS BIOLÓGIAI INTERPRETÁCIÓ

A molekuláris profilban szereplő variánslista összeállítása során az Ingenuity Variant Analysis szoftver alábbi szűrőit használtuk:
- CONFIDENCE: Olvasási mélység, allél frakció, illetve genotípus kvalitás szerinti filterezést tesz lehetővé. A bioinformatikai szűrés során azokat a variánsokat zártuk ki, amelyeknek a jelenléte bizonytalan a szekvenálási minőségértékek alapján.
- COMMON VARIANTS: Segítségével kiszűrhetőek azok a variánsok, amelyek nagy gyakorisággal megfigyelhetők az egészséges populációban. Kizártuk azokat a variánsokat, amelyek legalább 10%-os gyakorisággal fordulnak elő az egészséges populációban az 1000 Genomes Project, az ExAC vagy az NHLBI ESP exomes adatbázis szerint.
- PREDICTED DELETERIOUS: Azonosítja azokat az alterációkat, amelyek szakirodalmi evidenciák alapján befolyásolják a génfunkciót, génexpressziót. A szűrő alkalmazásával kizártuk az olyan alterációkat, amelyek az ACMG guideline szerint "Benign" vagy "Likely Benign" kategóriába esnek, vagyis erős evidenciák támasztják alá, hogy nem okoznak öröklődő genetikai betegséget.
- CANCER DRIVER VARIANTS: Olyan mutációk azonosítását teszi lehetővé, amelyek valószínűsíthetően tumorigenezishez vagy metasztázisok kialakulásához vezetnek. Kiválasztottuk azokat a variánsokat, amelyek szakirodalmi adatok szerint daganat kialakulásához köthető útvonalakat, szabályozó egységeket vagy sejtes folyamatokat érintenek. Továbbá kiválasztásra kerültek azok a variánsok is, amelyekről a szakirodalomban szerepel daganat-indikációban leírt adat.

A molekuláris profilban szereplő variánslista összeállítása során az Ingenuity Variant Analysis szoftveren kívül alkalmazott lépések:
- A listából kiszűrtük a nem exonikus régiókat érintő variánsokat
- További bioinformatikai szűréseket hajtottunk végre egyéb szekvenálási minőségértékek alapján

A variánsok klinikai jelentőségének felméréséhez használt adatbázisok:
COSMIC (Catalog of Somatic Mutations in Cancer): Ebben az adatbázisban tumorszövetben detektált szomatikus mutációkat gyűjtenek össze.
NCBI dbSNP (National Center for Biotechnology Information Single Nucleotide Polymorphism database): Ebben az adatbázisban egészséges és különböző (nem kizárólag daganatos) megbetegedésekben szenvedő betegekben leírt csíravonalas (minden sejtben jelenlévő) alterációk szerepelnek.
NCBI ClinVar: Az adatbázis genotipikus és fenotipikus jellemzők közötti kapcsolatok gyűjteménye, a variánsok klinikai jelentőségéről elérhető evidenciákat összegzi, nem csak daganatos betegségekkel összefüggésben.
SNPEffect: Egypontos nukleotid polimorfizmusok/mutációk klinikai jelentőségét tartalmazza az OMIM és más adatbázisok, valamint in silico predikciók alapján.
IARC (International Agency for Research on Cancer) TP53 Database: Az IARC TP53 adatbázis daganatos megbetegedésekhez köthető TP53 gént érintő mutációk gyűjteménye. A különböző irodalmi és más generális adatbázisokból származó adatok mellett a mutációk 8 különböző promoteren mutatott transzkripciós aktivitásának átlagán alapuló funkcionális klasszifikációja is megtalálható az adatbázisban.
BRCA Exchange: Ebben az adatbázisban a BRCA1 és BRCA2 génekben azonosított mutációk funkcionális adatai és klasszifikációja található meg.
UniProt: A UniProt adatbázisban különböző fehérjék (géntermékek) szekvenciális és funkcionális adatai találhatóak.

A detektált genetikai variánsok funkcionális interpretációja
A Molecular Treatment Calculator (MTC) az adatbázisában szereplő evidenciák súlyozott összegzése alapján a következő kategóriákba sorolja a detektált variánsokat: driver, driver gén ismeretlen jelentőségű variánsa (VUS, driver gén), nem megerősített driver, biomarker, ismeretlen jelentőségű variáns (VUS, variant of unknown significance), nem driver.

Az algoritmus pozitív pontszámmal veszi figyelembe azokat a tudományos adatokat, amelyek szerint egy variáns vagy egy mutáns gén hozzájárul a daganatképződéshez, és negatív pontszámot ad azoknak az adatoknak, amelyek szerint egy variáns nem serkenti a daganatképződést. Egy variáns osztályozása során az algoritmus súlyozza és összegzi azokra az evidenciákra vonatkozó pontszámot, amik az adott variánsról, a mutáns génről vagy a gén más mutációiról tartalmaznak információt. Az így kapott súlyozott összeg az aggregált evidenciaszint (aggregated evidence level, AEL).

Driver kategóriába sorolja az algoritmus azokat a variánsokat, amelyekre vonatkozóan az AEL pozitív, és az adott variánsról szerepel evidencia az adatbázisban.

Driver gén ismeretlen jelentőségű variánsaként, VUS, driver gén jelöléssel szerepelnek a riportban azok a variánsok, amelyekkel kapcsolatban nem szerepel információ az evidencia adatbázisban, de ismert, hogy a gén más mutációi hozzájárulhatnak a daganatképződéshez.

Ismeretlen jelentőségű variáns (variant of unknown significance, VUS) kategóriába kerülnek azok a variánsok, amelyekről nem szerepel információ az evidencia adatbázisban, és a gén más mutációiról, vagy a mutáns génről sem áll rendelkezésre adat.

Einsiedlerstrasse 23, 8834 Schindellegi, SWITZERLAND
E-mail: info@realtimeoncology.com **Web:** www.realtimeoncology.com

MOLEKULÁRIS BIOLÓGIAI INTERPRETÁCIÓ

Biomarkerként szerepelnek a riportban azok a variánsok, amik az adott eltérésekre vonatkozó evidenciák alapján összefüggést mutatnak valamilyen hatóanyag hatékonyságával, de driver tulajdonságuk jelenleg nem ismert, bizonytalan, vagy biztosan nem driverek.

Nem megerősített driver kategóriába kerülnek azok a variánsok, ahol a driverként való osztályozás alapjául szolgáló evidenciák száma és evidenciaszintje alacsony.

Nem driver kategóriába sorolja az algoritmus azokat a variánsokat, melyeknek aggregált evidenciaszintje negatív.

ER overexpresszió endometrium daganatban

Az ösztrogénreceptor (ER) overexpresszió ismert jelenség endometrium carcinomában, jobb prognózissal asszociál (1, 2). A tumor pozitív hormonreceptor státusza alapján az endokrin terápiák említhetőek pozitív asszociációban, melyeket endometrium carcinomában is alkalmaznak (3, 4). Endokrin terápiákra rezisztenciát okozat többek között a HER2, EGFR, FGFR1 és PIK3CA gének amplifikációja, az FGFR aktiváció, illetve a PIK3CA, RB1, AKT1 és PTEN gének mutációja (5-9).

Referenciák:

(1) Srijaipracharoen S et al., Expression of ER, PR, and Her-2/neu in endometrial cancer: a clinicopathological study. Asian Pac J Cancer Prev. 2010;11(1):215-20. PubMed PMID: 20593959

(2) Felix AS et al., Survival outcomes in endometrial cancer patients are associated with CXCL12 and estrogen receptor expression. Int J Cancer. 2012 Jul 15;131(2):E114-21. Epub 2012 Jan 3. PubMed PMID: 22025313

(3) Carlson MJ et al., Past, present, and future of hormonal therapy in recurrent endometrial cancer. Int J Womens Health. 2014 May 2;6:429-35. eCollection 2014. Review. PubMed PMID: 24833920

(4) Lee WL et al., Hormone therapy for patients with advanced or recurrent endometrial cancer. J Chin Med Assoc. 2014 May;77(5):221-6. Epub 2014 Mar 30. Review. PubMed PMID: 24694672

(5) Musgrove EA et al., Biological determinants of endocrine resistance in breast cancer. Nat Rev Cancer. 2009 Sep;9(9):631-43. Review. PubMed PMID: 19701242.

(6) Turner N et al., FGFR1 amplification drives endocrine therapy resistance and is a therapeutic target in breast cancer. Cancer Res. 2010 Mar 1; 70(5):2085-94. PubMed PMID: 20179196

(7) McCubrey JA et al., Alteration of Akt activity increases chemotherapeutic drug and hormonal resistance in breast cancer yet confers an achilles heel by sensitization to targeted therapy. Adv Enzyme Regul. 2008;48:113-35. PubMed PMID: 18423407

(8) Turczyk L et al., FGFR2-Driven Signaling Counteracts Tamoxifen Effect on ER-Positive Breast Cancer Cells. Neoplasia. 2017 Oct;19(10):791-804. Epub 2017 Sep 1. PubMed PMID: 28869838

(9) MAO, Pingping, et al. Acquired FGFR and FGF alterations confer resistance to estrogen receptor (ER) targeted therapy in ER+ metastatic breast cancer. bioRxiv, 2019, 605436.

PTEN-R130Q

A variáns szerepel a COSMIC adtabázisban, a ClinVar adatbázis szerint patogén besorolású alteráció. A LOVD adatbázisban 2 esetben patogén, 1 esetben vélhetően patogén, és 2 esetben VUS besorolással szerepel.

Preklinikai, valamint glioblastoma és endometrium tumoros minták vizsgálata alapján a mutáció a PTEN foszfatáz aktivitásnak megszűnéséhez vezet (1, 2).

Referenciák:

(1) Han SY, et ak. Functional evaluation of PTEN missense mutations using in vitro phosphoinositide phosphatase assay. Cancer Res. 2000 Jun 15;60(12):3147-51. PubMed PMID: 10866302

(2) Papa A, et al. Cancer-associated PTEN mutants act in a dominant-negative manner to suppress PTEN protein function. Cell. 2014 Apr 24;157 (3):595-610. PubMed PMID: 24766807

PTEN mutáns gén - célpontok

A PTEN (phosphatidylinositol 3,4,5-trisphosphate 3-phosphatase and dual-specificity protein phosphatase) egy tumorszupresszor, ami a foszfoinozitok defoszforilációjával a PI3K-AKT-mTOR jelpálya negatív regulátora.

A PTEN funkcióvesztéssel kapcsolatban említhető indirekt targetek a PI3K (1), az AKT (2) és az mTOR (2, 4-6), bár az mTOR gátlással kapcsolatos szakirodalmi adatok ellentmondásosak. Leírták továbbá, hogy PTEN-deficiens sejtek érzékenyek PARP (7) és ATM (8) inhibitorokra (a PTEN

Einsiedlerstrasse 23, 8834 Schindellegi, SWITZERLAND
E-mail: info@realtimeoncology.com **Web:** www.realtimeoncology.com

MOLEKULÁRIS BIOLÓGIAI INTERPRETÁCIÓ

deficiencia és a paralel ATM/PARP gátlás szintetikus letális hatást okoz). A PTEN funkcióvesztéses alterációval pozitív asszociációban említhető, más indikációban törzskönyvezett hatóanyag az mTOR gátló EVEROLIMUS, TEMSIROLIMUS, METFORMIN és SIROLIMUS, a PARP gátló OLAPARIB, RUCAPARIB, NIRAPARIB és TALAZOPARIB, a PI3K delta inhibitor IDELALISIB, DUVELISIB (FDA).

A PTEN funkcióvesztése rezisztenciát okozhat EGFR gátló terápiákkal szemben (9, 10). Preklinikai eredmények szerint PTEN vesztés esetén a MEK + mTOR kombinált gátlás szinergisztikus hatású (11). A PTEN funkcióvesztése továbbá rezisztenciát okozhat PIK3CA gátlásra, és a PIK3CA gátló alpelisibre (12, 13), valamint a HER2 gátlásra is (14-16).
Több tanulmány eredményei alapján a PTEN génvesztés vagy mutáció csökkent T sejt infiltrációval, megváltozott tumor mikrokörnyezettel és anti-PD-1 terápiára való rezisztenciával asszociált (17, 18). Egér modellekben a szelektív PI3Kbeta inhibitor (GSK2636771) alkalmazása növelte az anti-PD-1 és anti-CTLA-4 ellenanyagok hatékonyságát (18).

Referenciák:

(1) Conley-LaComb MK et al., PTEN loss mediated Akt activation promotes prostate tumor growth and metastasis via CXCL12/CXCR4 signaling. Mol Cancer. 2013 Jul 31;12(1):85. PMID: 23902739

(2) Neshat MS et al., Enhanced sensitivity of PTEN-deficient tumors to inhibition of FRAP/mTOR. Proc Natl Acad Sci U S A. 2001 Aug 28;98(18): 10314-9. PMID: 11504908

(3) Patel M et al., PTEN deficiency mediates a reciprocal response to IGFI and mTOR inhibition. Mol Cancer Res. 2014 Nov;12(11):1610-20. PMID: 24994750

(4) DeGraffenried LA et al., Reduced PTEN expression in breast cancer cells confers susceptibility to inhibitors of the PI3 kinase/Akt pathway. Ann Oncol. 2004 Oct;15(10):1510-6. PMID: 15367412

(5) Seront E et al., PTEN deficiency is associated with reduced sensitivity to mTOR inhibitor in human bladder cancer through the unhampered feedback loop driving PI3K/Akt activation. Br J Cancer. 2013 Sep 17;109(6):1586-92. PMID: 23989949

(6) Weigelt B et al., PIK3CA mutation, but not PTEN loss of function, determines the sensitivity of breast cancer cells to mTOR inhibitory drugs. Oncogene. 2011 Jul 21;30(29):3222-33. PMID: 21358673

(7) Mendes-Pereira AM et al., Synthetic lethal targeting of PTEN mutant cells with PARP inhibitors. EMBO Mol Med. 2009 Sep;1(6-7):315-22. PMID: 20049735

(8) McCabe N et al. Mechanistic Rationale to Target PTEN-Deficient Tumor Cells with Inhibitors of the DNA Damage Response Kinase ATM. Cancer Res. 2015 Jun 1;75(11):2159-65. Epub 2015 Apr 13. PMID: 25870146

(9) Frattini M et al., PTEN loss of expression predicts cetuximab efficacy in metastatic colorectal cancer patients. Br J Cancer. 2007 Oct 22;97(8): 1139-45. Epub 2007 Oct 16. PMID: 17940504

(10) Stewart EL et al., Known and putative mechanisms of resistance to EGFR targeted therapies in NSCLC patients with EGFR mutations-a review. Transl Lung Cancer Res. 2015 Feb;4(1):67-81. Review. PMID: 25806347

(11) Milella M et al., PTEN status is a crucial determinant of the functional outcome of combined MEK and mTOR inhibition in cancer. Sci Rep. 2017 Feb 21;7:43013. PMID: 28220839

(12) Juric D et al. Convergent loss of PTEN leads to clinical resistance to a PI(3)K inhibitor. Nature. 2015 Feb 12;518(7538):240-4. PMID: 25409150

(13) Razavi P et al. Alterations in PTEN and ESR1 promote clinical resistance to alpelisib plus aromatase inhibitors. Nat Cancer. 2020 Apr;1(4):382-393. PMID: 32864625

(14) Vu T, Claret FX. Trastuzumab: updated mechanisms of action and resistance in breast cancer. Front Oncol. 2012 Jun 18;2:62. doi: 10.3389 /fonc.2012.00062. PMID: 22720269.

(15) Rexer BN, Arteaga CL. Intrinsic and acquired resistance to HER2-targeted therapies in HER2 gene-amplified breast cancer: mechanisms and clinical implications. Crit Rev Oncog. 2012;17(1):1-16. doi: 10.1615/critrevoncog.v17.i1.20. PMID: 22471661.

(16) Tortora G. Mechanisms of resistance to HER2 target therapy. J Natl Cancer Inst Monogr. 2011;2011(43):95-8. doi: 10.1093/jncimonographs /lgr026. PubMed PMID: 22043051.

(17) Zhao J et al., Immune and genomic correlates of response to anti-PD-1 immunotherapy in glioblastoma. Nat Med. 2019 Mar;25(3):462-469. Epub 2019 Feb 11. Erratum in: Nat Med. 2019 Apr 17;: PMID: 30742119

(18) Peng W et al., Loss of PTEN Promotes Resistance to T Cell-Mediated Immunotherapy. Cancer Discov. 2016 Feb;6(2):202-16. Epub 2015 Dec 8. PMID: 26645196

PTEN mutáns, hormonreceptor pozitív daganat

Szakirodalmi evidenciák alapján a PI3K/AKT/mTOR jelátviteli útvonal aktivációja (például PTEN funkcióvesztésen keresztül (1-3)) rezisztenciát okozhat hormonterápiákra (így az ER gátlásra is); ilyen esetben a PI3K/AKT/mTOR útvonal gátlószereinek hormonterápiával való kombinációja lehet hatékony (4-7).
Leírták továbbá, hogy a PI3K/AKT/mTOR útvonal gátlása esetén az ER fokozott transzkripciós aktivitása figyelhető meg, ezért is javasolt az endokrin terápiák és a PI3K/AKT/mTOR gátló hatóanyagok együttes alkalmazása (8, 9).

Einsiedlerstrasse 23, 8834 Schindellegi, SWITZERLAND
E-mail: info@realtimeoncology.com **Web:** www.realtimeoncology.com

MOLEKULÁRIS BIOLÓGIAI INTERPRETÁCIÓ

Referenciák:

(1) Fu X et al., Overcoming endocrine resistance due to reduced PTEN levels in estrogen receptor-positive breast cancer by co-targeting mammalian target of rapamycin, protein kinase B, or mitogen-activated protein kinase kinase. Breast Cancer Res. 2014 Sep 11;16(5):430. PubMed PMID: 25212826

(2) Maggi LB Jr, Weber JD. Targeting PTEN-defined breast cancers with a one-two punch. Breast Cancer Res. 2015 Apr 8;17:51. PubMed PMID: 25888162

(3) Musgrove EA, Sutherland RL. Biological determinants of endocrine resistance in breast cancer. Nat Rev Cancer. 2009 Sep;9(9):631-43. Review. PubMed PMID: 19701242

(4) Bitting RL, Armstrong AJ. Targeting the PI3K/Akt/mTOR pathway in castration-resistant prostate cancer. Endocr Relat Cancer. 2013 May20; 20 (3):R83-99. Print 2013 Jun. Review. PubMed PMID: 23456430

(5) Jiao J et al., Murine cell lines derived from Pten null prostate cancer show the critical role of PTEN in hormone refractory prostate cancer development. Cancer Res. 2007 Jul 1;67(13):6083-91. PubMed PMID: 17616663

(6) Liu L, Dong X. Complex impacts of PI3K/AKT inhibitors to androgen receptor gene expression in prostate cancer cells. PLoS One. 2014 Oct 31; 9(10):e108780. eCollection 2014. PubMed PMID: 25360799

(7) Reid AH et al., Molecular characterisation of ERG, ETV1 and PTEN gene loci identifies patients at low and high risk of death from prostate cancer. Br J Cancer. 2010 Feb 16;102(4):678-84. Epub 2010 Jan 26. PubMed PMID: 20104229

(8) Shrivastav A, Murphy L et al., Interactions of PI3K/Akt/mTOR and estrogen receptor signaling in breast cancer." Breast Cancer Management 1, no. 3 (2012): 235-249.

(9) Bosch A et al., PI3K inhibition results in enhanced estrogen receptor function and dependence in hormone receptor-positive breast cancer. Sci Transl Med. 2015 Apr 15;7(283):283ra51. Erratum in: Sci Transl Med. 2018 Oct 24;10(464):. PubMed PMID: 25877889

FBXW7-R479Q

A variáns szerepel a COSMIC adatbázisban. A ClinVar adatbázis alapján valószínűsíthetően patogén alteráció. Az OncoKB adatbázis szerint a mutáció onkogenikus hatású.

Az FBXW7-R479Q az FBXW7 fehérje 3. ismétlődő WD szakaszában található (UniProt.org). Az R479Q csökkenti az FBXW7-szubsztrát interakciót, és rontja a szubsztrát FBXW7 általi lebomlását, ami tartós Notch1 intracelluláris domén és Myc expressziót eredményez (1, 2), illetve aberráns szubcelluláris nukleáris lokalizációt, valamint a Notch1 intracelluláris domén kötődésének elvesztését okozza (3).

Az R479Q mutáció ismert funkcióvesztő, domináns negatív tulajdonsággal rendelkező variáns (4, 5), vagyis gátolja a normál allélról képződő vad típusú fehérje működését is.

Egy preklinikai vizsgálatban T-sejtes akut limfoblasztikus leukémia (T-ALL) sejtvonalakban az FBXW7-R479Q rezisztenciát okozott a gamma-szekretáz inhibitor, MRK-003-mal szemben a NOTCH útvonal aktiválása és a MYC stabilizálása révén (1).

Referenciák:

(1) O'Neil J et al., FBW7 mutations in leukemic cells mediate NOTCH pathway activation and resistance to gamma-secretase inhibitors. J Exp Med. 2007 Aug 6;204(8):1813-24. Epub 2007 Jul 23. PubMed PMID: 17646409

(2) Chang CC et al., FBXW7 mutation analysis and its correlation with clinicopathological features and prognosis in colorectal cancer patients. Int J Biol Markers. 2015 Feb 24;30(1):e88-95. PubMed PMID: 25450649

(3) Close V et al., FBXW7 mutations reduce binding of NOTCH1, leading to cleaved NOTCH1 accumulation and target gene activation in CLL. Blood. 2019 Feb 21;133(8):830-839. Epub 2018 Dec 3. PubMed PMID: 30510140

(4) Akhoondi S et al., FBXW7/hCDC4 is a general tumor suppressor in human cancer. Cancer Res. 2007 Oct 1;67(19): 9006-12. PubMed PMID: 17909001

(5) Bailey ML et al., Dependence of Human Colorectal Cells Lacking the FBW7 Tumor Suppressor on the Spindle Assembly Checkpoint. Genetics. 2015 Nov;201(3):885-95. PubMed PMID: 26354767

FBXW7 mutáns gén - célpont gének

Az FBXW7 (F-box and WD repeat domain containing 7) egy tumorszuppresszor gén, ami az SCF komplex részeként részt vesz proto-onkogének (MYC, cyclin E, NOTCH és JUN) ubiquitin-függő degradációjában (1). A mutáns fehérje következtében, az FBXW7 általi szubsztrátfelismerés és -lebontás gátlódhat, így a NOTCH1 és MYC útvonalak aktívak maradnak (2).

Preklinikai adatok alapján az FBXW7 mutációk érzékenyítenek az mTOR inhibitorokra, ezt klinikai vizsgálat keretein belül is vizsgálták (3, 4). In vivo az mTOR inhibitorok alkalmazása csökkentette az FBXW7 funkcióvesztés okozta tumornövekedést (5). Forgalomban lévő, mTOR gátló hatással rendelkező készítmények az EVEROLIMUS, a TEMSIROLIMUS, SIROLIMUS és a METFORMIN. Egy FBXW7 mutáns tüdő tumoros beteg esettanulmánya alapján a temsirolimus (mTOR gátló) terápia hatékonynak bizonyult (6).

Einsiedlerstrasse 23, 8834 Schindellegi, SWITZERLAND
E-mail: info@realtimeoncology.com **Web:** www.realtimeoncology.com

MOLEKULÁRIS BIOLÓGIAI INTERPRETÁCIÓ

Egyes publikációk alapján az FBXW7 mutáció okozta aktivitás hatása függ a TP53 státusztól, a TP53 inaktiváció szükséges a sejtek folyamatos osztódása és túlélése szempontjából, amely instabilitáshoz és tumorképződéshez vezet (7).

A vad típusú FBXW7 fehérje gátolja a NOTCH jelátvitelt. Az FBXW7 konzervált kötőzsebében elhelyezkedő mutációk (pl. R505) a NOTCH kötődést akadályozzák, így növelik a NOTCH aktivitását (8). Ez alapján FBXW7 inaktiváció esetén a NOTCH jelátviteli útvonal gátlása lehet hatékony (9). NOTCH gátlószerek jelenleg klinikai vizsgálatok keretében elérhetők.

További publikációk alapján az FBXW7 mutáns sejtek nagyobb szenzitivitást mutatnak a sorafenibre (10). Ennek magyarázata, hogy a sorafenib a tumornövekedésben és angiogenezisben résztvevő receptor tirozin kinázok (PDGF, VEGF, RAF) gátlószere. A RAF kináz enzim képes a MAPK szignalizációs útvonalat aktiválni. A sorafenib azáltal, hogy inaktiválja a MAPK kinázt, csökkenti a MCL-1 szintet. Kimutatták továbbá, hogy MCL-1 gátló hatással is rendelkezik. Az FBXW7 -/- sejtek esetében az apoptotikus útvonal elkerülésében a megnövekedett szintű MCL-1 kritikus szerepet játszik. Így az FBXW7-deficiens sejtek sokkal érzékenyebbek a sorafenibre, mint az FBXW7 vad típusú sejtek, az MCL-1 target génnek tekinthető (11). Az FBXW7 mutáció rezisztenciát okozhat a taxán és a vincristine kemoterápiákkal szemben (11), valamint EGFR gátló kezeléssel szemben (12).

Referenciák:

(1) Akhoondi S et al. FBXW7/hCDC4 is a general tumor suppressor in human cancer. Cancer Res. 2007 Oct 1;67(19):9006-12. PubMed PMID: 17909001

(2) Welcker M et al. FBW7 ubiquitin ligase: a tumour suppressor at the crossroads of cell division, growth and differentiation. Nat Rev Cancer. 2008 Feb;8(2):83-93. PubMed PMID: 18094723

(3) Mao JH et al. FBXW7 targets mTOR for degradation and cooperates with PTEN in tumor suppression. Science. 2008 Sep 12;321(5895):1499-502. PubMed PMID: 18787170

(4) Jardim DL et al. FBXW7 mutations in patients with advanced cancers: clinical and molecular characteristics and outcomes with mTOR inhibitors. PLoS One. 2014 Feb 19;9(2):e89388. PubMed PMID: 24586741

(5) Liu Y et al. Temporal mTOR inhibition protects Fbxw7-deficient mice from radiation-induced tumor development. Aging (Albany NY). 2013 Feb; 5(2):111-9. PubMed PMID: 23454868

(6) Villaruz LC et al. Temsirolimus therapy in a patient with lung adenocarcinoma harboring an FBXW7 mutation. Lung Cancer. 2014 Feb;83(2): 300-1. PubMed PMID: 24360397

(7) Crusio KM et al. The ubiquitous nature of cancer: the role of the SCF(Fbw7) complex in development and transformation. Oncogene. 2010 Sep 2;29(35):4865-73. Review. PubMed PMID: 20543859

(8) Baldus CD et al. Prognostic implications of NOTCH1 and FBXW7 mutations in adult acute T-lymphoblastic leukemia. Haematologica. 2009 Oct;94(10):1383-90. PubMed PMID: 19794083

(9) Aydin IT et al. FBXW7 mutations in melanoma and a new therapeutic paradigm. J Natl Cancer Inst. 2014 May 16;106(6). PubMed PMID: 24838835

(10) Inuzuka H et al. SCF(FBW7) regulates cellular apoptosis by targeting MCL1 for ubiquitylation and destruction. Nature. 2011 Mar 3;471(7336): 104-9. PubMed PMID: 21368833

(11) Wang Z et al. The two faces of FBW7 in cancer drug resistance. Bioessays. 2011 Nov;33(11):851-9. PubMed PMID: 22006825

(12) Lupini L et al., Prediction of response to anti-EGFR antibody-based therapies by multigene sequencing in colorectal cancer patients. BMC Cancer. 2015 Oct 27;15:808. PubMed PMID: 26508446

CTNNB1-T41A

A variáns magas esetszámmal szerepel a COSMIC adatbázisban. Az NCBI ClinVar adatbázisban ellentmondásos adatok szerepelnek a variáns patogenitását illetően, azonban legtöbb esetben (9/12) valószínűsíthetően patogén mutációként történt a besorolása.

A mutáció a beta-catenin N-terminális régióját érinti, ahol a szerin/treonin kináz GSK-3beta fehérje foszforilációs helyei találhatóak (Ser33, Ser37, Thr41 and Ser45).

Egy tanulmány során desmoid daganat indikációban vizsgálták a CTNNB1-T41A variánst; nem találtak összefüggést a tumor kialakulása és a mutáció jelenléte között (1). Egy másik, Wilm's tumort vizsgáló tanulmányban megállapították, hogy a T41A mutációval rendelkező betegek túlélése szignifikánsan alacsonyabb (p = 0,000517) volt az átlagnál. Továbbá a variáns jelenlétében elvész a fehérje GSK-3beta foszforilációs régiója, ami a beta-katenin stabilitásához vezet és domináns hatást fejt ki a beta-katenin=TCF által közvetített transzkripció szintjén; ezért a mutáció hozzájárulhat Wilm's tumor kialakulásához (2). Melanoma indikációban jellemző driver a CTNNB1 (beta-catenin) overexpressziója és a génben detektált aktiváló mutációk (3).

Preklinikai evidencia szerint a T41A funkcionyerő mutáció a fehérje stabilizációját, nukleáris akkumulációját, valamint a Ctnnb1-függő transzkripció fokozódását eredményezi (4-6).

Referenciák:

Einsiedlerstrasse 23, 8834 Schindellegi, SWITZERLAND
E-mail: info@realtimeoncology.com **Web:** www.realtimeoncology.com

MOLEKULÁRIS BIOLÓGIAI INTERPRETÁCIÓ

(1) Mullen JT et al. -Catenin mutation status and outcomes in sporadic desmoid tumors. Oncologist. 2013;18(9):1043-9. Epub 2013 Aug 19. PubMed PMID: 23960186

(2) Cardoso LC et al. WT1, WTX and CTNNB1 mutation analysis in 43 patients with sporadic Wilms' tumor. Oncol Rep. 2013 Jan;29(1):315-20. Epub 2012 Oct 19. PubMed PMID: 23117548

(3) Worm J et al. Genetic and epigenetic alterations of the APC gene in malignant melanoma. Oncogene. 2004 Jul 1;23(30):5215-26. PubMed PMID: 15133491

(4) Wei Y et al. Activation of beta-catenin in epithelial and mesenchymal hepatoblastomas. Oncogene. 2000 Jan 27;19(4):498-504. PubMed PMID: 10698519

(5) Lévy L et al. Transcriptional activation of interleukin-8 by beta-catenin-Tcf4. J Biol Chem. 2002 Nov 1;277(44):42386-93. Epub 2002 Aug 27. PubMed PMID: 12200448

(6) Nhieu JT et al. Nuclear accumulation of mutated beta-catenin in hepatocellular carcinoma is associated with increased cell proliferation. Am J Pathol. 1999 Sep;155(3):703-10. PubMed PMID: 10487827

CTNNB1 mutáns gén - célpontok

CTNNB1 aktiváció esetén szakirodalmi evidencia alapján pozitív asszociációban említhető molekuláris célpont a CTNNB1 önmaga (1) és a TTK gén (2). CTNNB1 és TTK (másnéven Mps1) inhibitorok jelenleg klinikai vizsgálatok keretében érhetők el.

Referenciák:

(1) Bahrami A et al., Therapeutic Potential of Targeting Wnt/-Catenin Pathway in Treatment of Colorectal Cancer: Rational and Progress. J Cell Biochem. 2017 Aug;118(8):1979-1983. Epub 2017 Apr 25. Review. PubMed PMID: 28109136

(2) Zaman GJR et al., TTK Inhibitors as a Targeted Therapy for CTNNB1 (-catenin) Mutant Cancers. Mol Cancer Ther. 2017 Nov;16(11):2609-2617. Epub 2017 Jul 27. PubMed PMID: 28751540

PIK3CA-E81K

A variáns szerepel a COSMIC adatbázisban (n>100). A variáns a PIK3CA fehérje PI3K-ABD doménjében lokalizálódik. A ClinVar adatbázis adatai szerint valószínűsíthetően patogén variáns. A LOVD adatbázisban patogén alterációként klasszifikálták. In silico predikciók szerint károsító hatású eltérés (PolyPhen, SIFT).

Egy tanulmány szerint a mutáció jelenléte az AKT fokozott foszforilációjához és az mTOR jelátviteli út aktivációjához vezet (1).

Referenciák:

(1) Loconte DC et al., Molecular and Functional Characterization of Three Different Postzygotic Mutations in PIK3CA-Related Overgrowth Spectrum (PROS) Patients: Effects on PI3K/AKT/mTOR Signaling and Sensitivity to PIK3 Inhibitors. PLoS One. 2015 Apr 27;10(4):e0123092. PubMed PMID: 25915946

PIK3CA mutáns gén - célpontok

A PIK3CA (phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha) a PI3K-Akt jelátviteli útvonal részeként fontos szerepet tölt be a sejtproliferációban és a sejtek túlélésében, így a tumorigenezis során is.

PIK3CA génben detektált driver mutáció esetén a daganat molekuláris profiljával pozitív asszociációban említhetőek a PIK3CA/AKT/mTOR gátló hatóanyagok (1-3).

Az ALPELISIB és a COPANLISIB (FDA) törzskönyvezett PIK3CA gátló hatóanyagok. Forgalomban lévő mTOR-gátló készítmény az EVEROLIMUS, a METFORMIN, SIROLIMUS és a TEMSIROLIMUS. Az EVEROLIMUS emlő indikációban törzskönyvezett. A METFORMIN és a SIROLIMUS tumor indikációban nem törzskönyvezett. A TEMSIROLIMUS vesesejtes carcinoma indikációban elfogadott hatóanyag.

A TASELISIB fejlesztés alatt álló PIK3CA gátló hatóanyag fázis I vizsgálatban 36%-os válaszadási arányt eredményezett PIK3CA mutáns szolid tumoros betegek között, míg egyetlen PIK3CA vad típusú betegnél sem írtak le válaszadást (4). Egy nagyobb fázis I vizsgálatban többszörösen előkezelt PIK3CA mutáns szolid tumoros betegek között a taselisib 8,9%-os válaszadási arányt ért el (5). Az ALPELISIB kezelés PIK3CA mutáns vagy amplifikált szolid tumoros betegek között 6%-os válaszadási arányt és 58,2%-os betegség kontroll arányt ért el (6).

A Molecular Treatment Calculator algoritmusa az aktuális evidencia adatbázis alapján az aktiváló PIK3CA mutáció jelenlétében az ESR1 és EGFR inhibitorokat a beteg molekuláris profiljával negatív asszociációban sorolja.

Referenciák:

(1) Beaver JA et al., PIK3CA and AKT1 mutations have distinct effects on sensitivity to targeted pathway inhibitors in an isogenic luminal breast cancer model system. Clin Cancer Res. 2013 Oct 1;19(19):5413-22. PubMed PMID: 23888070

Einsiedlerstrasse 23, 8834 Schindellegi, SWITZERLAND
E-mail: info@realtimeoncology.com **Web:** www.realtimeoncology.com

MOLEKULÁRIS BIOLÓGIAI INTERPRETÁCIÓ

(2) Weigelt B et al., PIK3CA mutation, but not PTEN loss of function, determines the sensitivity of breast cancer cells to mTOR inhibitory drugs. Oncogene. 2011 Jul 21;30(29):3222-33. PubMed PMID: 21358673

(3) Janku F et al., PIK3CA mutations in patients with advanced cancers treated with PI3K/AKT/mTOR axis inhibitors. Mol Cancer Ther. 2011 Mar;10 (3):558-65. PubMed PMID: 21216929

(4) Juric D et al., Phase I Dose-Escalation Study of Taselisib, an Oral PI3K Inhibitor, in Patients with Advanced Solid Tumors. Cancer Discov. 2017 Jul;7(7):704-715. Epub 2017 Mar 22. PubMed PMID: 28331003

(5) Jhaveri K et al. Abstract CT046: A phase I basket study of the PI3K inhibitor taselisib (GDC-0032) in PIK3CA-mutated locally advanced or metastatic solid tumors. 2018.

(6) Juric D et al. Phosphatidylinositol 3-Kinase -Selective Inhibition With Alpelisib (BYL719) in PIK3CA-Altered Solid Tumors: Results From the First-in-Human Study. J Clin Oncol. 2018 May 1;36(13):1291-1299. Epub 2018 Feb 5. Erratum in: J Clin Oncol. 2019 Feb 1;37(4):361. J Clin Oncol. 2019 Feb 1;37(4):361. PubMed PMID: 29401002

PIK3CA mutáns endometrium daganat

Egy klinikai vizsgálatban 8 PIK3CA vagy AKT mutáns és ER pozitív endometrium daganatos beteg között a miransertib (AKT gátló) és anastrozole (aromatáz inhibitor) kombinációja 50%-os válaszadási arányt eredményezett (1).

Egy retrospektív vizsgálat szerint cukorbeteg endometrium daganatos betegek között a metformin használat növekedett betegségmentes túléléssel és teljes túléléssel mutatott összefüggést (2). Egy metaanalízis is megerősítette, hogy a metformin használat növekedett teljes túléléssel és progressziómentes túléléssel asszociál endometrium daganatban (3).

Egy fázis II vizsgálatban everolimus + letrozol kombinációs kezelés 32%-os válaszadási arányt eredményezett endometrium daganatos betegek között (9 teljes, 2 részleges tumorválasz). Az 5 PIK3CA mutáns résztvevő közül egynél teljes tumorválaszt, egynél stabil betegséget írtak le (4).

Egy fázis II vizsgálatban az everolimus+letrozole+metformin kombinációs kezelés 29%-os válaszadási arányt eredményezett, és az előrehaladott vagy rekurrens endometrium carcinomás betegek 38%-ánál stabil betegséget tapasztaltak (5).

Referenciák:

(1) Hyman D et al., Abstract CT035: A phase Ib study of miransertib (ARQ 092) in combination with anastrozole in patients with PIK3CA or AKT1-mutant ER+ endometrial or ovarian cancer. 2018.

(2) Ko EM et al., Metformin is associated with improved survival in endometrial cancer. Gynecol Oncol. 2014 Feb;132(2):438-42. Epub 2013 Nov 22. PubMed PMID: 24269517

(3) Xie W et al., Metformin use and survival outcomes in endometrial cancer: a systematic review and meta-analysis. Oncotarget. 2017 Aug 22;8 (42):73079-73086. eCollection 2017 Sep 22. PubMed PMID: 29069850

(4) Slomovitz BM et al., Phase II study of everolimus and letrozole in patients with recurrent endometrial carcinoma. J Clin Oncol. 2015 Mar 10;33 (8):930-6. Epub 2015 Jan 26. PubMed PMID: 25624430

(5) Soliman PT et al., Phase II study of everolimus, letrozole, and metformin in women with advanced/recurrent endometrial cancer. 2016.

ATM-S214fs*16

A variáns megtalálható a COSMIC adatbázisban, a ClinVar adatbázis szerint patogén elváltozás. A leolvasási kereteltolódást okozó mutáció (frameshift mutation) következtében egy jelentősen rövidebb fehérjeváltozatot kódoló ATM variáns jön létre, így a funkcióvesztés nagymértékben valószínűsíthető.

ATM-I1581fs*20

A mutáció megtalálható a COSMIC adatbázisban. A leolvasási kereteltolódást okozó mutáció (frameshift mutation) következtében egy jelentősen rövidebb fehérjeváltozatot kódoló ATM variáns jön létre, így a funkcióvesztés nagymértékben valószínűsíthető.

ATM mutáns gén - célpontok

Az ATM egy szerin/treonin protein kináz, ami a DNS károsodás hatására aktiválódó DNS hibajavító mechanizmusok szabályozásában vesz részt. ATM mutációk esetén az ATR (1) és PARP (2-6) target gének említhetők pozitív asszociációban. Egy retrospektív tanulmány szerint ATM mutáció esetén hatékonyabb a sugárkezelés, mint ATM vad típusú betegeknél (7).

Preklinikai vizsgálatokban az ATR inhibitor berzosertib (VX-970) gátolta az ATR aktivitását és növelte a cisplatin hatékonyságát tüdődaganatos xenograftokban, köztük cisplatin-rezisztens modellekben is (8). Egy fázis I vizsgálatban a berzosertib antitumor aktivitást mutatott monoterápiaként és carboplatinnal kombinálva előrehaladott, standard kezelésre refrakter, szolid tumoros betegekben. A berzosertib monoterápia teljes választ és 29 hónapos progressziómentes túlélést (PFS) eredményezett egy ATM-vesztéssel és ARID1A mutációval rendelkező metasztatikus colorectalis daganatos beteg esetén (9). Egy randomizált fázis II vizsgálatban a berzosertib és gemcitabine kombinációja előnyösebbnek bizonyult a gemcitabine monoterápiához képest platina-rezisztens high-grade serosus ovárium carcinomás betegek esetén, a medián PFS 22,9 hét (n=34) és 14,7 hét (n=36) volt a két csoportban (10).

Einsiedlerstrasse 23, 8834 Schindellegi, SWITZERLAND
E-mail: info@realtimeoncology.com **Web:** www.realtimeoncology.com

MOLEKULÁRIS BIOLÓGIAI INTERPRETÁCIÓ

Egy fázis I vizsgálatban a BAY1895344 (ATR inhibitor) terápia 4 részleges választ és 8 esetben stabil betegséget eredményezett szolid daganatos betegek esetén. Mindegyik részleges válasszal reagáló beteg esetén kimutattak ATM fehérjevesztést és/vagy károsító ATM mutációt (11).

Egy preklinikai vizsgálat szerint az ATM funkcióvesztő mutációi szintetikus letális hatásúak MEK1/2 inhibitorokkal. ATM vesztés fokozta KRAS vagy BRAF mutáns tüdő tumoros sejtek, illetve MEK inhibitor rezisztens tüdő tumoros sejtek érzékenységét MEK gátlásra. Az eredmények alapján az ATM szükséges az AKT/mTOR és MEK/ERK jelátviteli útvonalak közti kapcsolathoz (12).

Referenciák:

(1) Reaper PM et al., Selective killing of ATM- or p53-deficient cancer cells through inhibition of ATR. Nat Chem Biol. 2011 Apr 13;7(7):428-30. PubMed PMID: 21490603

(2) Bang YJ et al., Randomized, Double-Blind Phase II Trial With Prospective Classification by ATM Protein Level to Evaluate the Efficacy and Tolerability of Olaparib Plus Paclitaxel in Patients With Recurrent or Metastatic Gastric Cancer. J Clin Oncol. 2015 Nov 20;33(33):3858-65. Epub 2015 Aug 17. PubMed PMID: 26282658

(3) Nappi L, Gleave ME. PARP inhibition in castration-resistant prostate cancer. Future Oncol. 2016 Mar;12(5):577-80. Epub 2016 Jan 21. PubMed PMID: 26792387

(4) Ledermann JA et al., Homologous recombination deficiency and ovarian cancer. Eur J Cancer. 2016 Jun;60:49-58. Epub 2016 Apr 9. Review. PubMed PMID: 27065456

(5) Weston VJ et al., The PARP inhibitor olaparib induces significant killing of ATM-deficient lymphoid tumor cells in vitro and in vivo. Blood. 2010 Nov 25;116(22):4578-87. Epub 2010 Aug 25. PubMed PMID: 20739657

(6) Wang C et al., ATM-Deficient Colorectal Cancer Cells Are Sensitive to the PARP Inhibitor Olaparib. Transl Oncol. 2017 Apr;10(2):190-196. Epub 2017 Feb 6. PubMed PMID: 28182994

(7) Lee J et al., Genomic analysis reveals somatic mutations of ATM gene in DNA repair confer exceptional target lesion response to radiation therapy. J Glob Oncol 5, 2019 (suppl 1; abstr 130)

(8) Hall AB et al., Potentiation of tumor responses to DNA damaging therapy by the selective ATR inhibitor VX-970. Oncotarget. 2014 Jul 30;5(14): 5674-85. doi: 10.18632/oncotarget.2158. PMID: 25010037

(9) Yap TA et al., Phase I Trial of First-in-Class ATR Inhibitor M6620 (VX-970) as Monotherapy or in Combination With Carboplatin in Patients With Advanced Solid Tumors. J Clin Oncol. 2020 Jun 22:JCO1902404. doi: 10.1200/JCO.19.02404. Epub ahead of print. PMID: 32568634

(10) Konstantinopoulos PA et al. Berzosertib plus gemcitabine versus gemcitabine alone in platinum-resistant high-grade serous ovarian cancer: a multicentre, open-label, randomised, phase 2 trial. Lancet Oncol. 2020 Jul;21(7):957-968. doi: 10.1016/S1470-2045(20)30180-7. Epub 2020 Jun 15. PMID: 32553118

(11) Yap TA et al., First-in-Human Trial of the Oral Ataxia Telangiectasia and Rad3-Related Inhibitor BAY 1895344 in Patients with Advanced Solid Tumors. Cancer Discov. 2020 Sep 28:CD-20-0868. doi: 10.1158/2159-8290.CD-20-0868. Epub ahead of print. PMID: 32988960

(12) Smida M, et al. MEK inhibitors block growth of lung tumours with mutations in ataxia-telangiectasia mutated. Nat Commun. 2016 Dec 6;7: 13701. doi: 10.1038/ncomms13701. PMID: 27922010

CDH1-I594fs*19

A mutáció megtalálható a COSMIC adatbázisban, a ClinVar adatbázis szerint patogén elváltozás. A leolvasási kereteltolódást okozó mutáció (frameshift mutation) következtében egy jelentősen rövidebb fehérjeváltozatot kódoló CDH1 variáns jön létre, így a funkcióvesztés nagymértékben valószínűsíthető.

CDH1 mutáns gén - célpontok

A CDH1 gén alapján képződő E-cadherin fehérje tumorszupresszor funkcióval bír, funkcióvesztéssel járó mutációit daganatok kialakulásával hozták összefüggésbe (1, 2).

Az ún. sztatinok, HMG-CoA enzim (HMGCR) inhibitorok (atorvastatin, lovastatin, simvastatin) szintén szintetikus letális fenotípust értek el a CDH1-et nem expresszáló emlő sejtvonalon, illetve szinergikus hatást mutattak HDAC vagy SRC inhibitorokkal való együttes alkalmazás esetén (3).

Szintetikus letális kapcsolatot írtak le emlő daganatos sejtvonalon CDH1 és ROS1 között, ezért CDH1 funkcióvesztés esetén targetként említhető a ROS1 (4). Klinikai forgalomban lévő ROS1 gátló hatással bíró hatóanyag a CRIZOTINIB és a LORLATINIB.

Nem daganatos, CDH1-et nem expresszáló sejtvonal nagyobb érzékenységet mutatott HDAC (Mocetinostat, Entinostat, Quisinostat, Pracinostat, LAQ824, Panobinostat, Vorinostat), ROS1 (Crizotinib), ALK (Crizotinib), MET (Crizotinib), PI3K (PI103, GSK2126458, PIK-75 hydrochloride), NPY5R (CGP 71683 hydrochloride), EGFR (Tyrphostin A9), PDGFR (Tyrphostin A9), mTOR (AZD8055, PI103, GSK2126458), BCL2 (Obatoclax Mesylate), GBF1 (Brefeldin A), JAK (LY2784544), mitokondriális oxidatív foszforiláció gátló (FCCP), CDK (JNJ-7706621), Aurora kináz (JNJ-7706621, Danusertib), ABL (Danusertib), RET (Danusertib), FGFR1 (Danusertib, PD-166285 hydrate), NTRK1 (Danusertib), AKT (10-DEBC hydrochloride) és SRC (PD-166285 hydrate, Saracatinib) inhibitorokkal szemben, mint a CDH1-et expresszáló sejtvonal (5).

Einsiedlerstrasse 23, 8834 Schindellegi, SWITZERLAND
E-mail: info@realtimeoncology.com **Web:** www.realtimeoncology.com

MOLEKULÁRIS BIOLÓGIAI INTERPRETÁCIÓ

Egy örökletes diffúz gyomorrákos betegből származó, germline funkcióvesztő CDH1 mutációt hordozó sejtvonalban egérmodell vizsgálattal a PI3K/mTOR, MEK, c-Src kináz, FAK, PKC és TOPO2 inhibitorok megnövekedett hatékonysága igazolódott egy másik, a mutációt nem hordozó gyomorrákos betegből származó sejtvonalhoz viszonyítva (6). A két vizsgálat eredményei átfedőek a PI3K, mTOR, Aurora kináz és ALK/ROS-1 inhibitorokkal szembeni hatékonyság tekintetében (7).

A HDAC, ROS1, ALK, MET, PI3K, NPY5R, EGFR, PDGFR, mTOR, BCL2, GBF1, JAK, CDK, Aurora kináz, ABL, RET, FGFR1, NTRK1, AKT és SRC inhibitorok CDH1 driver eltérés esetén pozitív asszociációban említhetőek.

A sztatinok (ATORVASTIN, FLUVASTATIN, LOVASTATIN, PITAVASTATIN, PRAVASTATIN, ROSUVASTATIN, SIMVASTATIN) HMGCR inhibitor aktivitással rendelkező forgalomban lévő koleszterincsökkentő szerek. A HDAC inhibitor PANOBINOSTAT myeloma multiplex indikációban elfogadott. A VALPROINSAV HDAC gátló hatással rendelkező epilepsziaellenes gyógyszer. A VORINOSTAT, a BELINOSTAT és a ROMIDEPSIN csak az FDA által törzskönyvezettek hematológiai indikációkban. Forgalomban lévő ALK/ROS1/MET inhibitor a CRIZOTINIB, az ALK/ROS1 inhibitor LORLATINIB, az ALK inhibitor ALECTINIB, CERITINIB és a BRIGATINIB. Elérhető MET gátló a CABOZANTINIB, FDA által elfogadott MET gátló a CAPMATINIB, PI3K gátló az IDELALISIB és COPANLISIB, PDGFR gátló az IMATINIB, LENVATINIB, NILOTINIB, NINTEDANIB, PAZOPANIB, REGORAFENIB, SORAFENIB, SUNITINIB, PONATINIB, AXITINIB és MIDOSTAURIN. Elérhető mTOR gátló a EVEROLIMUS, TEMSIROLIMUS, METFORMIN és SIROLIMUS, BCL-2 gátló a VENETOCLAX, JAK gátló a RUXOLITINIB és TOFACITINIB, ABL gátló a BOSUTINIB, DASATINIB, IMATINIB MESYLATE, NILOTINIB, REGORAFENIB és PONATINIB, RET gátló a REGORAFENIB, CABOZANTINIB, ALECTINIB, PONATINIB, NINTEDANIB, LENVATINIB, SORAFENIB, VANDETANIB és SUNITINIB, FGFR1 gátló PONATINIB, LENVATINIB, NINTEDANIB, PAZOPANIB, REGORAFENIB, SORAFENIB, SUNITINIB és ERDAFITINIB (csak FDA), SRC gátló a NINTEDANIB, BOSUTINIB és DASATINIB. Az AKT, CDK1, CDK2, NPY5R, NTRK1 és Aurora kináz inhibitorok klinikai vizsgálatban hozzáférhetőek. GBF1 inhibitorok jelenleg preklinikai fejlesztés alatt állnak.

Referenciák:

(1) Semb H, Christofori G. The tumor-suppressor function of E-cadherin. Am J Hum Genet. 1998 Dec;63(6):1588-93. Review. PMID: 9837810

(2) Pećina-Slaus N. Tumor suppressor gene E-cadherin and its role in normal and malignant cells. Cancer Cell Int. 2003 Oct 14;3(1):17. PMID: 14613514

(3) Single A et al., Abstract B41: Statins show synthetic lethality in E-cadherin-deficient cells and are synergistic with SRC and HDAC inhibitors. (2017): B41-B41.

(4) Bajrami I et al., E-Cadherin/ROS1 Inhibitor Synthetic Lethality in Breast Cancer. Cancer Discov. 2018 Apr;8(4):498-515. PMID: 29610289

(5) Telford BJ et al., Synthetic Lethal Screens Identify Vulnerabilities in GPCR Signaling and Cytoskeletal Organization in E-Cadherin-Deficient Cells. Mol Cancer Ther. 2015 May;14(5):1213-23. doi: 10.1158/1535-7163.MCT-14-1092. Epub 2015 Mar 16. PMID: 25777964

(6) Chen I et al., Transcriptomic profiling and quantitative high-throughput (qHTS) drug screening of CDH1 deficient hereditary diffuse gastric cancer (HDGC) cells identify treatment leads for familial gastric cancer. J Transl Med. 2017 May 1;15(1):92. PMID: 28460635

(7) Li D et al., Merging perspectives: genotype-directed molecular therapy for hereditary diffuse gastric cancer (HDGC) and E-cadherin-EGFR crosstalk. Clin Transl Med. 2018 Feb 22;7(1):7. PMID: 29468433

RECQL4-L339fs*20

A mutáció megtalálható a COSMIC adatbázisban. A ClinVar adatbázis alapján patogén elváltozás. A leolvasási kereteltolódást okozó mutáció (frameshift mutation) a RECQL4 gén nonsense-mediated decay (NMD) rezisztens pozícióját érinti, ezért nagy valószínűséggel az NMD folyamat nem vezet a mutáns mRNS lebomlásához (1). Így a mutáns génről egy megváltozott C terminális szekvenciával rendelkező, kismértékben csonka fehérjeváltozat képződik, ezért lehetséges, hogy funkcióvesztéssel jár.

Referenciák:

(1) Litchfield K et al., Escape from nonsense mediated decay associates with anti-tumor immunogenicity. 2019. doi: 10.1101/823716.

RECQL4 mutáns gén - célpontok

A RECQL4 gén tumorszupresszor és onkogén szerepet is betölthet különböző daganatokban (1-3).

A RECQL4 génnek a DNS hibajavításban van szerepe. Preklinikai adatok alapján funkcióvesztő RECQL4 mutációk esetén a PARP inhibitorok és a cisplatin említhetők pozitív asszociációban (4). A RECQL4 gén funkcióvesztésének hatása hasonlít a BRCA1-deficiencia hatásához a PARP-gátlásra és a cisplatinra való szenzitivitás terén (4).

Forgalomban lévő PARP gátló gyógyszerek az OLAPARIB, RUCAPARIB, NIRAPARIB és a TALAZOPARIB.

Referenciák:

(1) Arora A et al., RECQL4 helicase has oncogenic potential in sporadic breast cancers. J Pathol. 2016 Mar;238(4):495-501. Epub 2016 Feb 2. PubMed PMID: 26690729

(2) Su Y et al., Human RecQL4 helicase plays critical roles in prostate carcinogenesis. Cancer Res. 2010 Nov 15;70(22):9207-17. Epub 2010 Nov 2. PubMed PMID: 21045146

Einsiedlerstrasse 23, 8834 Schindellegi, SWITZERLAND
E-mail: info@realtimeoncology.com **Web:** www.realtimeoncology.com

MOLEKULÁRIS BIOLÓGIAI INTERPRETÁCIÓ

(3) Wang LL et al., Association between osteosarcoma and deleterious mutations in the RECQL4 gene in Rothmund-Thomson syndrome. J Natl Cancer Inst. 2003 May 7;95(9):669-74. PubMed PMID: 12734318

(4) Santarpia L et al., DNA repair gene patterns as prognostic and predictive factors in molecular breast cancer subtypes. Oncologist. 2013;18(10): 1063-73. Epub 2013 Sep 26. PubMed PMID: 24072219

PIK3CB-L1049R

A mutáció megtalálható a COSMIC adatbázisban. Preklinikai kísérlet szerint a variáns onkogenikus hatású (1).

Referenciák:

(1) Mateo J et al., A First-Time-in-Human Study of GSK2636771, a Phosphoinositide 3 Kinase Beta-Selective Inhibitor, in Patients with Advanced Solid Tumors. Clin Cancer Res. 2017 Oct 1;23(19):5981-5992. Epub 2017 Jun 23. PMID: 28645941

PIK3CB mutáns gén - célpontok

A PIK3CB a PI3K katalitikus alegységének egyik izoformáját kódolja. Aktiváló mutációi esetén a PIK3CB gátlás hatékonyságát preklinikai eredmények igazolják (1). PIK3CB mutációk esetén preklinikai eredmények szerint hatékonyak lehetnek az AKT és az mTOR gátló gyógyszerek is (2). EGFR gátló hatóanyagokra rezisztencát okoznak (3).
A COPANLISIB PIK3CB gátló hatással is rendelkező FDA törzskönyvezett hatóanyag.

Referenciák:

(1) Pazarentzos E et al., Oncogenic activation of the PI3-kinase p110 isoform via the tumor-derived PIK3C(D1067V) kinase domain mutation. Oncogene. 2016 Mar 3;35(9):1198-205. Epub 2015 May 18. PubMed PMID: 25982275

(2) Nakanishi Y et al., Activating Mutations in PIK3CB Confer Resistance to PI3K Inhibition and Define a Novel Oncogenic Role for p110. Cancer Res. 2016 Mar 1;76(5):1193-203. Epub 2016 Jan 12. PubMed PMID: 26759240

(3) Whale AD et al., Functional characterization of a novel somatic oncogenic mutation of PIK3CB. Signal Transduct Target Ther. 2017 Dec 22;2: 17063. eCollection 2017. PubMed PMID: 29279775

ARID1A-F2141fs*59

A variáns megtalálható a COSMIC adatbázisban. A leolvasási kereteltolódást okozó mutáció (frameshift mutation) az ARID1A gén nonsense-mediated decay (NMD) rezisztens pozícióját érinti, ezért nagy valószínűséggel az NMD folyamat nem vezet a mutáns mRNS lebomlásához (1). Így a mutáns génről egy megváltozott C terminális szekvenciával rendelkező, kismértékben csonka fehérjeváltozat képződik, ezért lehetséges, hogy funkcióvesztéssel jár.

Referenciák:

(1) Litchfield K et al., Escape from nonsense mediated decay associates with anti-tumor immunogenicity. 2019. doi: 10.1101/823716.

ARID1A-Q1519fs*8

A variáns szerepel a COSMIC adatbázisban. A leolvasási kereteltolódást okozó mutáció (frameshift mutation) az ARID1A gén nonsense-mediated decay (NMD) rezisztens pozícióját érinti, ezért nagy valószínűséggel az NMD folyamat nem vezet a mutáns mRNS lebomlásához (1). Így a mutáns génről egy megváltozott C terminális szekvenciával rendelkező, csonka fehérjeváltozat képződik, ami a BAF250 domén elvesztésével jár (ebi.ac.uk/interpro), ezért valószínűsíthető, hogy funkcióvesztéssel jár.

Referenciák:

(1) Litchfield K et al., Escape from nonsense mediated decay associates with anti-tumor immunogenicity. 2019. doi: 10.1101/823716.

ARID1A-Y551fs*68

A variáns szerepel a COSMIC adatbázisban. A leolvasási kereteltolódást okozó mutáció (frameshift mutation) következtében egy jelentősen rövidebb fehérjeváltozatot kódoló ARID1A variáns jön létre, így a funkcióvesztés nagymértékben valószínűsíthető.

ARID1A mutáns gén - célpontok

Az ARID1A elvesztése esetén csökken a mismatch repair funkció. Az ARID1A deficiencia preklinikai vizsgálatban, továbbá gyomor- és colorectalis daganatos betegekben korrelált a mikroszatellita instabilitással (1, 2). Egy vizsgálatban gasztrointesztinális eredetű tumorokból származó adatokat elemeztek és az ARID1A mutáns daganatok esetén magasabb TMB értéket, valamint magasabb PD-L1 expressziót tapasztaltak (3). Preklinikai adatok szerint ARID1A mutáns ováriumtumoros egér modelleken hatékony volt a PD-L1 gátló immunterápia alkalmazása, míg vad típusú ARID1A esetén nem (1). További pozitív asszociációban említhető célpont gének az EZH2 (4), a YES1 (5), a PI3K/AKT (6) és a PARP (7). A

Einsiedlerstrasse 23, 8834 Schindellegi, SWITZERLAND
E-mail: info@realtimeoncology.com **Web:** www.realtimeoncology.com

MOLEKULÁRIS BIOLÓGIAI INTERPRETÁCIÓ

forgalomban lévő dasatinibbel szintetikus letális hatás volt kimutatható ARID1A vesztés esetén (5). A TAZEMETOSTAT FDA által elfogadott EZH2 gátló hatóanyag. Forgalomban lévő PD-L1 gátlók az AVELUMAB, az ATEZOLIZUMAB és a DURVALUMAB. Forgalomban lévő YES1 gátló a DASATINIB. Forgalomban lévő PI3K gátlók az IDEALISIB, ALPELISIB és az FDA által törzskönyvezett COPANLISIB és DUVELISIB. Forgalomban lévő PARP gátló gyógyszerek az OLAPARIB, RUCAPARIB, TALAZOPARIB és a NIRAPARIB.

Referenciák:

(1) Shen J et al., ARID1A deficiency promotes mutability and potentiates therapeutic antitumor immunity unleashed by immune checkpoint blockade. Nat Med. 2018 May;24(5):556-562. Epub 2018 May 7. PubMed PMID: 29736026

(2) Kim YS et al. Unique characteristics of ARID1A mutation and protein level in gastric and colorectal cancer: A meta-analysis. Saudi J Gastroenterol. 2017 Sep-Oct;23(5):268-274. doi: 10.4103/sjg.SJG_184_17. PMID: 28937020.

(3) Li L et al. ARID1A Mutations Are Associated with Increased Immune Activity in Gastrointestinal Cancer. Cells. 2019 07 04;8(7):. doi: 10.3390 /cells8070678. Epub 2019 Nov 04. PubMed PMID: 31277418.

(4) Bitler BG et al., Synthetic lethality by targeting EZH2 methyltransferase activity in ARID1A-mutated cancers. Nat Med. 2015 Mar;21(3):231-8. Epub 2015 Feb 16. PubMed PMID: 25686104

(5) Miller RE et al., Synthetic Lethal Targeting of ARID1A-Mutant Ovarian Clear Cell Tumors with Dasatinib. Mol Cancer Ther. 2016 Jul;15(7):1472-84. Epub 2016 Jun 30. PubMed PMID: 27364904

(6) Samartzis EP et al., Loss of ARID1A expression sensitizes cancer cells to PI3K- and AKT-inhibition. Oncotarget. 2014 Jul 30;5(14):5295-303. PubMed PMID: 24979463

(7) Shen J et al., ARID1A Deficiency Impairs the DNA Damage Checkpoint and Sensitizes Cells to PARP Inhibitors. Cancer Discov. 2015 Jul;5(7): 752-67. Epub 2015 Jun 11. PubMed PMID: 26069190

DNMT3A-Q110fs*14

A mutáció megtalálható a COSMIC adatbázisban. A leolvasási kereteltolódást okozó mutáció (frameshift mutation) következtében egy jelentősen rövidebb fehérjeváltozatot kódoló DNMT3A variáns jön létre, így a funkcióvesztés nagymértékben valószínűsíthető.

DNMT3A mutáns gén - célpontok

A DNMT3A egy DNS metiltranszferáz fehétjét kódol, amely proto-onkogén és tumorszupresszor funkciókkal is rendelkezik (1). DNMT3A funkcióvesztő mutációk esetén a DOT1L target gén és a pinometostat hatóanyag említhető pozitív asszociációban (1).

Referenciák:

(1) Zhang J, et al. DNA Methyltransferases in Cancer: Biology, Paradox, Aberrations, and Targeted Therapy. Cancers (Basel). 2020 Jul 31;12(8): 2123. doi: 10.3390/cancers12082123. PMID: 32751889; PMCID: PMC7465608.

(2) Rau RE et al., DOT1L as a therapeutic target for the treatment of DNMT3A-mutant acute myeloid leukemia. Blood. 2016 Aug 18;128(7):971-81. Epub 2016 Jun 22. PubMed PMID: 27335278

CDK12-G1271fs*23

A mutáció szerepel a COSMIC adatbázisban. A leolvasási kereteltolódást okozó mutáció (frameshift mutation) a CDK12 gén nonsense-mediated decay (NMD) rezisztens pozícióját érinti, ezért nagy valószínűséggel az NMD folyamat nem vezet a mutáns mRNS lebomlásához (1). Így a mutáns génről egy megváltozott C terminális szekvenciával rendelkező, kismértékben csonka fehérjeváltozat képződik, ezért lehetséges, hogy funkcióvesztéssel jár.

Referenciák:

(1) Litchfield K et al., Escape from nonsense mediated decay associates with anti-tumor immunogenicity. 2019. doi: 10.1101/823716.

CDK12 mutáns gén - célpontok

A CDK12 gént tumorszupresszorként (elsősorban ováriumdaganatokban) és proto-onkogénként (elsősorban emlődaganatokban) egyaránt jellemzi a szakirodalom (1, 2).

A CDK12 a DNS hibajavításban résztvevő gének transzkripcióját szabályozza, funkcióvesztése a DNS hibajavító képesség romlásával jár, és összefüggést mutat a CHEK1 (3) és PARP gátló hatóanyagokra való érzékenységgel, platina-alapú kemoterápiák és alkiláló szerek hatékonyságával (4-6).

Forgalomban lévő PARP gátló hatóanyagok az OLAPARIB, a RUCAPARIB, a NIRAPARIB és a TALAZOPARIB.

Referenciák:

Einsiedlerstrasse 23, 8834 Schindellegi, SWITZERLAND
E-mail: info@realtimeoncology.com **Web:** www.realtimeoncology.com

MOLEKULÁRIS BIOLÓGIAI INTERPRETÁCIÓ

(1) Paculová H, Kohoutek J. The emerging roles of CDK12 in tumorigenesis. Cell Div. 2017 Oct 27;12:7. eCollection 2017. Review. PubMed PMID: 29090014

(2) Naidoo K et al., Evaluation of CDK12 Protein Expression as a Potential Novel Biomarker for DNA Damage Response-Targeted Therapies in Breast Cancer. Mol Cancer Ther. 2018 Jan;17(1):306-315. Epub 2017 Nov 13. PubMed PMID: 29133620

(3) Paculová H et al., BRCA1 or CDK12 loss sensitizes cells to CHK1 inhibitors. Tumour Biol. 2017 Oct;39(10):1010428317727479. PubMed PMID: 29025359

(4) Bajrami I et al., Genome-wide profiling of genetic synthetic lethality identifies CDK12 as a novel determinant of PARP1/2 inhibitor sensitivity. Cancer Res. 2014 Jan 1;74(1):287-97. Epub 2013 Nov 15. PubMed PMID: 24240700

(5) Vrábel D et al., Function of CDK12 in Tumor initiation and progression and its clinical consequences. Klin Onkol. 2014;27(5):340-6. Review. Czech. PubMed PMID: 25312711

(6) Joshi PM et al., Ovarian cancer-associated mutations disable catalytic activity of CDK12, a kinase that promotes homologous recombination repair and resistance to cisplatin and poly(ADP-ribose) polymerase inhibitors. J Biol Chem. 2014 Mar 28;289(13):9247-53. Epub 2014 Feb 19. PubMed PMID: 24554720

NSD1-M1531fs*43

A variáns szerepel a COSMIC adatbázisban. A leolvasási kereteltolódást okozó mutáció (frameshift mutation) következtében egy jelentősen rövidebb fehérjeváltozatot kódoló NSD1 variáns jön létre, így a funkcióvesztés nagy mértékben valószínűsíthető.

NSD1-F1799fs*22

A mutáció megtalálható a COSMIC adatbázisban. A leolvasási kereteltolódást okozó mutáció (frameshift mutation) következtében egy jelentősen rövidebb fehérjeváltozatot kódoló NSD1 variáns jön létre, így a funkcióvesztés nagymértékben valószínűsíthető.

NSD1 mutáns gén - célpontok

Az NSD1 (nuclear receptor binding SET domain protein 1) egy transzkripciós regulátorként funkcionáló hiszton metiltranszferáz (1). Prosztatadaganat-eredetű sejtekből származó eredmények alapján az NSD1 a szteroid receptorok koregulátoraként is működik (2). Az NSD1 funkcióvesztő mutációi hozzájárulhatnak a tumorigenezishez (3).

Preklinikai kísérletek szerint az NSD1 gén funkcióvesztése a genom hipometilációjával és cisplatin érzékenységgel mutatott összefüggést. Fejnyak daganatos betegek között, ahol a cisplatin a standard terápia része, az NSD1 mutáns betegcsoportban 55%-kal alacsonyabb volt a halálozás kockázata, mint az NSD1 vad típusú betegek között (4). Preklinikai eredmények alapján feltételezik, hogy az NSD1 mutáns daganatok kevésbé érzékenyek immunterápiára (5).

Referenciák:

(1) Qiao Q et al., The structure of NSD1 reveals an autoregulatory mechanism underlying histone H3K36 methylation. J Biol Chem. 2011 Mar 11; 286(10):8361-8. PMID: 21196496

(2) Wang X et al., Identification and characterization of a novel androgen receptor coregulator ARA267-alpha in prostate cancer cells. J Biol Chem. 2001 Nov 2;276(44):40417-23. PMID: 11509567

(3) Cancer Genome Atlas Network. Comprehensive genomic characterization of head and neck squamous cell carcinomas. Nature. 2015 Jan 29; 517(7536):576-82. PubMed PMID: 25631445

(4) Bui N et al., Disruption of NSD1 in Head and Neck Cancer Promotes Favorable Chemotherapeutic Responses Linked to Hypomethylation. Mol Cancer Ther. 2018 Jul;17(7):1585-1594. Epub 2018 Apr 10. PubMed PMID: 29636367

(5) Brennan K et al., NSD1 inactivation defines an immune cold, DNA hypomethylated subtype in squamous cell carcinoma. Sci Rep. 2017 Dec 6;7 (1):17064. PubMed PMID: 29213088

DMD-S3343fs*34

A mutáció megtalálható a COSMIC adatbázisban. A leolvasási kereteltolódást okozó mutáció (frameshift mutation) következtében egy jelentősen rövidebb fehérjeváltozatot kódoló DMD variáns jön létre, így a funkcióvesztés nagymértékben valószínűsíthető.

A DMD gén egy tumorszuppresszor (1), csíravonalas mutációja Duchenne izomdisztrófiát okoz. A golodirsen, a viltolarsen és a casimersen az FDA által törzskönyvezett génterápiák bizonyos csíravonalas DMD mutációval rendelkező betegek számára (2, 3). DMD szomatikus funkcióvesztő mutációival összefüggésben nem ismert célzott, tumorellenes terápia.

Referenciák:

(1) Wang Y et al. Dystrophin is a tumor suppressor in human cancers with myogenic programs. Nat Genet. 2014 Jun;46(6):601-6. doi: 10.1038/ng. 2974. Epub 2014 May 4. PubMed PMID: 24793134; PubMed Central PMCID: PMC4225780.

Einsiedlerstrasse 23, 8834 Schindellegi, SWITZERLAND
E-mail: info@realtimeoncology.com **Web:** www.realtimeoncology.com

MOLEKULÁRIS BIOLÓGIAI INTERPRETÁCIÓ

(2) Frank DE et al. Golodirsen Leads to Sarcolemmal Dystrophin Expression in Patients With Genetic Mutations Amenable to Exon 53 Skipping. 2019.

(3) Roshmi RR, Yokota T. Viltolarsen for the treatment of Duchenne muscular dystrophy. Drugs Today (Barc). 2019 Oct;55(10):627-639. doi: 10.1358/dot.2019.55.10.3045038. PMID: 31720560.

PAX5-A322fs*11

A variáns alacsony frekvenciával szerepel a COSMIC adatbázisban (n>5). A mutációt kimutatták akut limfoid leukémiában (ALL) szenvedő betegeknél (1) és ALL sejtvonalakban is (2). A leolvasási kereteltolódást okozó mutáció (frameshift mutation) következtében egy jelentősen rövidebb fehérjeváltozatot kódoló PAX5 variáns jön létre, így a funkcióvesztés nagymértékben valószínűsíthető.

Referenciák:

(1) Santoro A et al., Altered mRNA expression of PAX5 is a common event in acute lymphoblastic leukaemia. Br J Haematol. 2009 Sep;146(6): 686-9. Epub 2009 Nov 13. PubMed PMID: 19604238

(2) Hart MR et al., Activating PAX gene family paralogs to complement PAX5 leukemia driver mutations. PLoS Genet. 2018 09;14(9):e1007642. Epub 2018 Nov 14. PubMed PMID: 30216339

PAX5 funkcióvesztés

A PAX5 (Paired box 5) transzkripciós faktor szerepet játszik a limfoid progenitorok B-sejtvonal felé történő differenciálódásának korlátozásában, pro-B-sejt stádiumában a PAX5 egyenletesen expresszálódik, majd a plazmasejekké történő differenciálódás során alulszabályozottá válik az expresszója. Onkogenikus és tumorszupresszor szerepet is betölthet (1).

A gyermekkori B-progenitor ALL (akut limfoid leukémia) esetek 31,7%-ában detektáltak PAX5 alterációkat. Az azonosított PAX5 mutációk csökkent PAX5 protein szintet vagy hipomorf allélok képződését eredményezték (2).

A késői B-sejtekben a PAX5 elvesztése limfóma kialakulásához vezethet, egér modellekben PAX5 hiányos érett B-sejtekkel agresszív limfómák alakultak ki, amelyeket gén-expressziós profiljuk alapján progenitorsejt-tumorokként azonosítottak (3).

A PAX5 csendesítése MCL-ben (köpenysejtes limfóma) *in vitro* fokozott sejtproliferációt, *in vivo* fokozott tumor infiltrációt eredményezett, amely alapján a csökkent PAX5-szint elősegíti tumorok progresszióját. A géncsendesített sejtek rezisztensnek bizonyultak bortezomib, és doxorubicin kezelésre is (1).

Referenciák:

(1) Teo AE et al., Differential PAX5 levels promote malignant B-cell infiltration, progression and drug resistance, and predict a poor prognosis in MCL patients independent of CCND1. Leukemia. 2016 Mar;30(3):580-93. doi: 10.1038/leu.2015.140. PMID: 26073757.

(2) Mullighan CG et al., Genome-wide analysis of genetic alterations in acute lymphoblastic leukaemia. Nature. 2007 Apr 12;446(7137):758-64. doi: 10.1038/nature05690. PMID: 17344859.

(3) Cobaleda C et al., Conversion of mature B cells into T cells by dedifferentiation to uncommitted progenitors. Nature. 2007 Sep 27;449(7161): 473-7. doi: 10.1038/nature06159. PMID: 17851532.

TET2-L1276fs*24

A leolvasási kereteltolódást okozó mutáció (frameshift mutation) következtében egy jelentősen rövidebb fehérjeváltozatot kódoló TET2 variáns jön létre, így a funkcióvesztés nagymértékben valószínűsíthető.

A TET2 funkcióvesztő mutációi elsősorban hematopoietikus malignus folyamatokban jellemzőek, szolid tumorokban inkább a csökkent aktivitású variánsok vannak jelen. A TET2 az interferon (IFN)-JAK-STAT szignalizációban vesz részt, a kemokin és PD-L1 expressziót szabályozza. A TET2 deléció rágcsáló melanoma és colon tumorsejtekben lecsökkentette a kemokin expressziót és a TIL mennyiséget, amely elősegíti a tumor-ellenes immunaktivitás elekerülését és az anti-PD-L1 terápiával szembeni rezisztencia kialakulását (1). Egy tanulmányban immunterápiában részesülő nem-kissejtes tüdődaganatos betegek között hosszabb teljes túlélést írtak le TET2 mutációk jelenléte esetén, de a detektált TET2 mutációk többsége nem volt ismert funkcióvesztő variáns (2).

Referenciák:

(1) Xu YP et al., Tumor suppressor TET2 promotes cancer immunity and immunotherapy efficacy. J Clin Invest. 2019 Jul 16;130:4316-4331. PubMed PMID: 31310587

(2) Zhao D, Mambetsariev I, et al. Association of molecular characteristics with survival in advanced non-small cell lung cancer patients treated with checkpoint inhibitors. Lung Cancer. 2020;146:174-181. doi:10.1016/j.lungcan.2020.05.025

KDM5C-R68fs*5

Einsiedlerstrasse 23, 8834 Schindellegi, SWITZERLAND
E-mail: info@realtimeoncology.com **Web:** www.realtimeoncology.com

MOLEKULÁRIS BIOLÓGIAI INTERPRETÁCIÓ

A leolvasási kereteltolódást okozó mutáció (frameshift mutation) következtében egy jelentősen rövidebb fehérjeváltozatot kódoló KDM5C variáns jön létre, így a funkcióvesztés nagymértékben valószínűsíthető.

KDM5C (lizin (K)-demetiláz 5C) egy Jumonji domain típusú hiszton demetiláz, a KDM5 alcsalád tagja, mely a kromatin újramodellezés és ezáltal a transzkripciós reguláció folyamatában vesz részt. A tudományos irodalom szerint a KDM5C egyaránt tölthet be tumorszupresszor és proto-onkogenikus szerepet, az alteráció funkcióvesztő vagy funkciónyerő jellege és a sejttípus függvényében.
In vitro, a KDM5C funkcióvesztés fokozott tumornövekedést eredményezett világossejtes vesesejtes carcinoma sejtekben (ccRCC) (3). Egy fázis II-es vizsgálatban a KDM5C mutációk megnövekedett progressziómentes túléléssel asszociáltak elsővonalas sunitinib kezelésre metasztatikus ccRCC betegekben (4).

Referenciák:

(1) Chang S et al., The cancer driver genes IDH1/2, JARID1C/ KDM5C, and UTX/ KDM6A: crosstalk between histone demethylation and hypoxic reprogramming in cancer metabolism. Exp Mol Med. 2019 Jun 20;51(6):1-17. PMID: 31221981

(2) Plch J et al., KDM5 demethylases and their role in cancer cell chemoresistance. Int J Cancer. 2019 Jan 15;144(2):221-231. Epub 2018 Nov 26. PMID: 30246379

(3) Niu X et al., The von Hippel-Lindau tumor suppressor protein regulates gene expression and tumor growth through histone demethylase JARID1C. Oncogene. 2012 Feb 9;31(6):776-86. Epub 2011 Jul 4. PMID: 21725364

(4) Hsieh JJ et al., Genomic Biomarkers of a Randomized Trial Comparing First-line Everolimus and Sunitinib in Patients with Metastatic Renal Cell Carcinoma. Eur Urol. 2017 Mar;71(3):405-414. Epub 2016 Oct 15. PMID: 27751729

CTCF-E691fs*30

A mutáció szerepel a COSMIC adatbázisban. A leolvasási kereteltolódást okozó mutáció (frameshift mutation) a CTCF gén nonsense-mediated decay (NMD) rezisztens pozícióját érinti, ezért nagy valószínűséggel az NMD folyamat nem vezet a mutáns mRNS lebomlásához (1). Így a mutáns génről egy megváltozott C terminális szekvenciával rendelkező, kismértékben csonka fehérjeváltozat képződik, ezért lehetséges, hogy funkcióvesztéssel jár.

A CTCF egy tumorszupresszor gén, mely a konzervált, cink-ujjas DNS-kötő CTCF fehérjét kódolja.
A CTCF a 16q22.1 kromoszóma régióban található, melynek delécióját gyakori tumoros megbetegedésekben, főként emlődaganatokban (2). A CTCF gén mutációja gyakori endometriális daganatokban és CTCF haploinszufficienciát eredményez a mutáns transzkriptumok non-sense mediated decay" folyamata vagy funkcióvesztő mutációja által. CTCF deléció gyakran fordul elő a szerózus altípusban és rossz prognózissal bír (3).
Egy preklinikai vizsgálatban az egy CTCF allélvesztés serkentette a tumorképződést és a malignus progressziót (2).

Referenciák:

(1) Litchfield K et al., Escape from nonsense mediated decay associates with anti-tumor immunogenicity. 2019. doi: 10.1101/823716.

(2) Kemp CJ et al., CTCF haploinsufficiency destabilizes DNA methylation and predisposes to cancer. Cell Rep. 2014 May 22;7(4):1020-9. Epub 2014 May 1. PMID: 24794443

(3) Marshall AD et al., CTCF genetic alterations in endometrial carcinoma are pro-tumorigenic. Oncogene. 2017 Jul 20;36(29):4100-4110. Epub 2017 Mar 20. PMID: 28319062

PPP2R2A-Y189*

A korai STOP kodon megjelenését eredményező mutáció (nonsense mutation) következtében egy jelentősen rövidebb fehérjeváltozatot kódoló PPP2R2A variáns jön létre, így a funkcióvesztés nagymértékben valószínűsíthető.

A PPP2R2A (B55alfa) egy heterotrimer szerin/treronin foszfotáz, amely részt vesz a sejtnövekedés és osztódás negatív kontrolljában (1). A PPP2R2A gén egy ismert tumorszupresszor (2).
Egy preklinikai vizsgálat alapján a PPP2R2A funkcióvesztő mutációi csökkentik a B55alfa fehérje expresszióját, ezáltal hozzájárulnak az AKT aktivációjához. A vizsgált PPP2R2A mutáns sejtek érzékenynek bizonyultak az AKT inhibitor MK2206 kezelésre (3).
Egy tanulmány szerint a PPP2R2A funkciójának kiesése megnövekedett ATM foszforilációt eredményezett, amely jelentős mértékben felülszabályozta a downstream effektor kináz CHK2 aktivitását, ami G1-S-fázisú sejtciklus leállításához és a BRCA1 és RAD51 csökkent regulációjához vezetett. Nem-kissejtes tüdődaganatból származó tumorsejteken végzett kísérletek során a PPP2R2A funkciójának blokkolása negatívan hatott a homológ rekombinációs javítási útvonal működésére és szenzibilizálta a tumorsejteket a PARP kismolekulájú inhibitorokkal szemben (4).

Einsiedlerstrasse 23, 8834 Schindellegi, SWITZERLAND
E-mail: info@realtimeoncology.com **Web:** www.realtimeoncology.com

MOLEKULÁRIS BIOLÓGIAI INTERPRETÁCIÓ

Referenciák:

(1) Kurimchak A, Graña X. PP2A: more than a reset switch to activate pRB proteins during the cell cycle and in response to signaling cues. Cell Cycle. 2015;14(1):18-30. doi: 10.4161/15384101.2014.985069. PubMed PMID: 25483052; PubMed Central PMCID: PMC4612414.

(2) Beca F et al. Altered PPP2R2A and Cyclin D1 expression defines a subgroup of aggressive luminal-like breast cancer. BMC Cancer. 2015 Apr 15;15:285. doi: 10.1186/s12885-015-1266-1. Epub 2015 Feb 15. PubMed PMID: 25879784

(3) Shouse G. Novel B55-PP2A mutations in AML promote AKT T308 phosphorylation and sensitivity to AKT inhibitor-induced growth arrest. Oncotarget. 2016 Sep 20;7(38):61081-61092. doi: 10.18632/oncotarget.11209. PubMed PMID: 27531894

(4) Kalev P. et al. Loss of PPP2R2A inhibits homologous recombination DNA repair and predicts tumor sensitivity to PARP inhibition. Cancer Res. 2012 Dec 15;72(24):6414-24. doi: 10.1158/0008-5472.CAN-12-1667. Epub 2012 Oct 18.

XRCC2-K267fs*?

A mutáció megtalálható a COSMIC adatbázisban. A leolvasási kereteltolódást okozó mutáció (frameshift mutation) következtében egy jelentősen rövidebb fehérjeváltozatot kódoló XRCC2 variáns jön létre, így a funkcióvesztés nagymértékben valószínűsíthető.

XRCC2 mutáns gén – célpontok

Az XRCC2 gén a RAD51 egyik paralógja, mely részt vesz a homológ rekombináció folyamatában.

Preklinikai evidencia alapján funkcióvesztő XRCC2 mutációk esetén a PARP inhibitorok említhetők pozitív asszociációban (1, 2). Forgalomban lévő PARP gátló gyógyszerek az OLAPARIB, RUCAPARIB, NIRAPARIB és a TALAZOPARIB.

Colorectalis sejtvonalakon végzett kísérletben kimutatták, hogy az XRCC2 expressziójának hiánya magasabb szenzitivitással asszociált 5-FU alapú terápiákra (3); valamint érzékenyített radioterápiára (4).

Referenciák:

(1) Somyajit K et al., Enhanced non-homologous end joining contributes toward synthetic lethality of pathological RAD51C mutants with poly (ADP-ribose) polymerase. Carcinogenesis. 2015 Jan;36(1):13-24. Epub 2014 Oct 7. PMID: 25292178

(2) Bryant HE et al., Specific killing of BRCA2-deficient tumours with inhibitors of poly(ADP-ribose) polymerase. Nature. 2005 Apr 14;434(7035): 913-7. Erratum in: Nature. 2007 May 17;447(7142):346. PMID: 15829966

(3) Zhang YZ et al., XRCC2-Deficient Cells are Highly Sensitive to 5-Fluorouracil in Colorectal Cancer. Cell Physiol Biochem. 2017;43(3):1207-1219. Epub 2017 Oct 5. PMID: 28977800

(4) Qin CJ et al., XRCC2 as a predictive biomarker for radioresistance in locally advanced rectal cancer patients undergoing preoperative radiotherapy. Oncotarget. 2015 Oct 13;6(31):32193-204. PMID: 26320178

PMS1-G417fs*6

A leolvasási kereteltolódást okozó mutáció (frameshift mutation) a PMS1 gén nonsense-mediated decay (NMD) rezisztens pozícióját érinti, ezért nagy valószínűséggel az NMD folyamat nem vezet a mutáns mRNS lebomlásához (1). Így a mutáns génről egy megváltozott C terminális szekvenciával rendelkező, kismértékben csonka fehérjeváltozat képződik, ezért lehetséges, hogy funkcióvesztéssel jár.

A gén valószínűleg része a DNS "mismatch repair" (MMR) rendszernek (UniProt). Csíravonalas mutációi Lynch szindrómát okozhatnak (2).

A PMS1 az MLH1-el képes dimerizálódni, együtt alkotják a MutLbeta komplexet, amely képes elnyomni a mutagenezist élesztőkben, azonban humán sejtekben ismeretlen a funkciója, az MLH1-PMS1 heterodimer nem része a kanonikus humán MMR rendszernek (3, 4).

PD-1 és PD-L1 gátló immunterápiák hatékonyságát MMR deficiens daganatok esetén klinikai evidencia támasztja alá (5).

Az FDA törzskönyvezte a PEMBROLIZUMAB PD-1 gátló antitestet standard terápiákon progrediált bármilyen szolid daganat esetén, ami MSI-H státuszú vagy MMR deficiens fenotípusú.

MMR deficiencia esetén rezisztenciát írtak le kemoterápiás kezelésekkel szemben, mint az 5-FU, cisplatin és carboplatin, de nem tapasztaltak csökkent érzékenységet oxaliplatin kezelés esetén (6).

Referenciák:

(1) Litchfield K et al., Escape from nonsense mediated decay associates with anti-tumor immunogenicity. 2019. doi: 10.1101/823716.

(2) Yang J, et al. Associations of Genetic Variations in Mismatch Repair Genes MSH3 and PMS1 with Acute Adverse Events and Survival in Patients with Rectal Cancer Receiving Postoperative Chemoradiotherapy. Cancer Res Treat. 2019 Jul;51(3):1198-1206. doi: 10.4143/crt.2018.527. PMID: 30590005.

(3) Boland CR, Goel A. Microsatellite instability in colorectal cancer. Gastroenterology. 2010 Jun;138(6):2073-2087.e3. doi: 10.1053/j.gastro. 2009.12.064. PMID: 20420947.

(4) Leung WK et al., Identification of a second MutL DNA mismatch repair complex (hPMS1 and hMLH1) in human epithelial cells. J Biol Chem. 2000;275(21):15728-15732. doi:10.1074/jbc.M908768199. PMID: 10748105.

Einsiedlerstrasse 23, 8834 Schindellegi, SWITZERLAND
E-mail: info@realtimeoncology.com **Web:** www.realtimeoncology.com

MOLEKULÁRIS BIOLÓGIAI INTERPRETÁCIÓ

(5) Viale G et al., Mismatch Repair Deficiency as a Predictive Biomarker for Immunotherapy Efficacy. Biomed Res Int. 2017;2017:4719194. Epub 2017 Jul 10. Review. PubMed PMID: 28770222

(6) Devaud N, Gallinger S. Chemotherapy of MMR-deficient colorectal cancer. Fam Cancer. 2013 Jun;12(2):301-6. Review. PubMed PMID: 23539382

WNK2-P1381fs*11

A leolvasási kereteltolódást okozó mutáció (frameshift mutation) a WNK2 gén nonsense-mediated decay (NMD) rezisztens pozícióját érinti, ezért nagy valószínűséggel az NMD folyamat nem vezet a mutáns mRNS lebomlásához (1). Így a mutáns génről egy megváltozott C terminális szekvenciával rendelkező, kismértékben csonka fehérjeváltozat képződik, ezért lehetséges, hogy funkcióvesztéssel jár.

A WNK2 gén tumorszupresszor funkcióját leírták már glioma és hepatocelluláris indikációkban (2, 3).
A WNK2 részt vesz a tumoros sejtek növekedési faktorok által indukált proliferációjában a MEK1/ERK1/2 jelátviteli útvonalon keresztül (4).

Referenciák:

(1) Litchfield K et al., Escape from nonsense mediated decay associates with anti-tumor immunogenicity. 2019. doi: 10.1101/823716.

(2) Costa AM et al., Silencing of the tumor suppressor gene WNK2 is associated with upregulation of MMP2 and JNK in gliomas. Oncotarget. 2015 Jan 30;6(3):1422-34. PMID: 25596741

(3) Zhou SL et al., Genomic sequencing identifies WNK2 as a driver in hepatocellular carcinoma and a risk factor for early recurrence. J Hepatol. 2019 Dec;71(6):1152-1163. Epub 2019 Jul 23. PMID: 31349001

(4) Moniz Set al., Protein kinase WNK2 inhibits cell proliferation by negatively modulating the activation of MEK1/ERK1/2. Oncogene. 2007 Sep 6; 26(41):6071-81. Erratum in: Oncogene. 2008 Jan 3;27(1):155. Kotevelets, L [corrected to Kotelevets, L]. PMID: 17667937.

MRE11-R364*

A mutáció megtalálható a COSMIC adatbázisban, a ClinVar adatbázis szerint patogén elváltozás. A korai STOP kodon megjelenését eredményező mutáció (nonsense mutation) következtében egy jelentősen rövidebb fehérjeváltozatot kódoló MRE11 variáns jön létre, így a funkcióvesztés nagymértékben valószínűsíthető.

CARD11-R555fs*45

A variáns szerepel a COSMIC adatbázisban (<40). A leolvasási kereteltolódást okozó mutáció (frameshift mutation) következtében egy jelentősen rövidebb fehérjeváltozatot kódoló CARD11 variáns jön létre, így a funkcióvesztés nagymértékben valószínűsíthető.

CBL-E196fs*16

A mutáció megtalálható a COSMIC adatbázisban. A leolvasási kereteltolódást okozó mutáció (frameshift mutation) következtében egy jelentősen rövidebb fehérjeváltozatot kódoló CBL variáns jön létre, így a funkcióvesztés nagymértékben valószínűsíthető.

SCN11A-K491fs*5

A mutáció szerepel a COSMIC adatbázisban. A leolvasási kereteltolódást okozó mutáció (frameshift mutation) következtében egy jelentősen rövidebb fehérjeváltozatot kódoló SCN11A variáns jön létre, így a funkcióvesztés nagymértékben valószínűsíthető. A gén funkcióvesztő mutációinak nincs ismert szerepük a tumorképződésben.

SAMD9L-K21fs*3

Az alteráció szerepel a COSMIC adatbázisban. A leolvasási kereteltolódást okozó mutáció (frameshift mutation) a SAMD9L gén nonsense-mediated decay (NMD) rezisztens pozícióját érinti, ezért nagy valószínűséggel az NMD folyamat nem vezet a mutáns mRNS lebomlásához (1). Így a mutáns génről egy megváltozott C terminális szekvenciával rendelkező, kismértékben csonka fehérjeváltozat képződik, ezért lehetséges, hogy funkcióvesztéssel jár.

Referenciák:

(1) Litchfield K et al., Escape from nonsense mediated decay associates with anti-tumor immunogenicity. 2019. doi: 10.1101/823716.

IGF2R-D1317fs*5

A mutáció szerepel a COSMIC adatbázisban. A leolvasási kereteltolódást okozó mutáció (frameshift mutation) következtében egy jelentősen rövidebb fehérjeváltozatot kódoló IGF2R variáns jön létre, így a funkcióvesztés nagymértékben valószínűsíthető.

SLIT2-K904fs*13

Einsiedlerstrasse 23, 8834 Schindellegi, SWITZERLAND
E-mail: info@realtimeoncology.com **Web:** www.realtimeoncology.com

MOLEKULÁRIS BIOLÓGIAI INTERPRETÁCIÓ

A leolvasási kereteltolódást okozó mutáció (frameshift mutation) következtében egy jelentősen rövidebb fehérjeváltozatot kódoló SLIT2 variáns jön létre, így a funkcióvesztés nagymértékben valószínűsíthető.

CDC27-K319fs*24

A leolvasási kereteltolódást okozó mutáció (frameshift mutation) következtében egy jelentősen rövidebb fehérjeváltozatot kódoló CDC27 variáns jön létre, így a funkcióvesztés nagymértékben valószínűsíthető.

Frameshift mutációk (SAMD9L-K21fs*3, PMS1-G417fs*6, CTCF-E691fs*30, CDK12-G1271fs*23, RECQL4-L339fs*20, ARID1A-F2141fs*59, ARID1A-Q1519fs*8, WNK2-P1381fs*11)

A rövid inszerciók és deléciók következtében kialakuló frameshift mutációk korai stop kodont (premature termination codon, PTC) eredményezhetnek és fokozottan érzékennyé válhatnak a nonsense-mediated decay (NMD) folyamat általi mRNS-szintű degradációra. Az NMD az eukarióta génexpresszió alapvető minőségbiztosítási rendszere, mely normál sejtekben megakadályozza a csonka fehérjék toxikus felhalmozódását. A frameshift mutációk egy része azonban elkerülheti az NMD degradációt (1), ezáltal alternatív leolvasási keretek (ORF) jöhetnek létre, melyek új, a vad típusú génektől különböző, tumorspecifikus (neoantigén) szekvenciával rendelkeznek (2). Ezek a neoantigének hozzájárulhatnak a tumorellenes immunválasz kialakulásához alacsony tumor mutation burden (TMB) értékkel rendelkező daganatokban (1, 3), ezáltal az immunterápiás kezelések célpontjául szolgálhatnak. Így a frameshift mutációk nagy jelentőséggel rendelkezhetnek a pontmutációkhoz (SNV-k) képest, kis előfordulási gyakoriságuk ellenére (4, 5).

Az NMD degradációt elkerülő mutációk nagyobb arányban fordulnak elő a gének utolsó exonjában és az utolsó előtti exon utolsó 50 nukleotidja között, az első exon első mintegy 150 nukleotidjában, illetve a 400 nukleotidnál hosszabb exonokban mint más exonokban (6). Egy tanulmányban az allélspecifikus frameshift indelek (fs-indelek) detektálása párosított DNS és RNS szekvenálási adatokban (n=453, TCGA) azt mutatta, hogy az expresszált fs-indelek jelenléte olyan genomiális pozíciókban volt megfigyelhető, amelyek valószínűsíthetően elkerülik az NMD-t és magasabb fehérje expresszióval társulnak, összhangban az NMD elkerülés szabályaival (3).

A TCGA adatbázis vizsgálata szerint frameshift mutáció miatt keletkezett neoantigének minden tumortípusban előfordulnak (4). Vesesejtes carcinomában, lobuláris emlőcarcinomában és colorectalis carcinomában a leggyakoribbak (7).

Több tumortípusban, köztük melanomában, vesesejtes carcinomában, fej-nyak laphámcarcinomában és tüdődaganatokban is megfigyelték, hogy az aminosavcserét eredményező pontmutációkhoz képest a frameshift mutációk nagyobb mennyiségben képeznek magas kötési affinitású neoantigéneket (4, 5, 7). Jelenlétük összefüggést mutat a citotoxikus T-sejtek infiltrációjával, valamint az immun checkpoint inhibitorokra (ICI) adott tumorválasszal (3, 4, 7, 8). Melanomás betegcsoportban a kifejeződő frameshift mutációk száma jobb prediktornak bizonyult immunterápiák hatásosságára nézve, mint a pontmutációk száma (1, 3).

A frameshift mutációk egy alcsoportját képező, hosszú leolvasási keretű neoantigénekkel (neoORF) rendelkező betegek nagyobb érzékenységet mutattak immunterápiára (1, 3).

Referenciák:

(1) Litchfield et al., Contrasting the drivers of response to immunotherapy across solid tumour types: Results from analysis of n > 1000 cases. Annals of Oncology. 2019; 30(7):1-35. doi: 10.1093/annonc/mdz238.012.

(2) Richters MM et al., Best practices for bioinformatic characterization of neoantigens for clinical utility. Genome Med. 2019 Aug 28;11(1):56. PMID: 31462330

(3) Litchfield K et al., Escape from nonsense-mediated decay associates with anti-tumor immunogenicity. Nat Commun. 2020 Jul 30;11(1):3800. PMID: 32733040

(4) Turajlic S et al., Insertion-and-deletion-derived tumour-specific neoantigens and the immunogenic phenotype: a pan-cancer analysis. Lancet Oncol. 2017 Aug;18(8):1009-1021. Epub 2017 Jul 7. PMID: 28694034

(5) Hanna GJ et al., Frameshift events predict anti-PD-1/L1 response in head and neck cancer. JCI Insight. 2018 Feb 22;3(4):e98811. PMID: 29467336

(6) Litchfield K et al., Escape from nonsense-mediated decay associates with anti-tumor immunogenicity. Nat Commun. 2020 Jul 30;11(1):3800. PMID: 32733040

(7) Chae YK et al., Clinical and immunological implications of frameshift mutations in lung cancer. J Thorac Oncol. 2019 Oct;14(10):1807-1817. Epub 2019 Jun 22. PMID: 31238177

(8) Maby P et al., Correlation between density of CD8+ T-cell infiltrate in microsatellite unstable colorectal cancers and frameshift mutations: a rationale for personalized immunotherapy. Cancer Res. 2015 Sep 1;75(17):3446-55. Epub 2015 Jun 9. PMID: 26060019

Törzskönyvezett célzott terápiák endometrium carcinomában

Az FDA törzskönyvezte a LENVATINIB (multi tirozin-kináz inhibitor) + PEMBROLIZUMAB (PD-1 inhibitor) kombinációs kezelést nem MSI-H és nem MMR-deficiens, endometrium daganat indikációjában, szisztémás terápiát követően. Egy fázis Ib/II klinikai vizsgálatban (NCT02501096; Study 111 /KEYNOTE-146) a kombináció MSI/MMR státusztól függetlenül bíztató eredményt ért el endometrium daganatos betegekben (24. héten mért

Einsiedlerstrasse 23, 8834 Schindellegi, SWITZERLAND
E-mail: info@realtimeoncology.com **Web:** www.realtimeoncology.com

MOLEKULÁRIS BIOLÓGIAI INTERPRETÁCIÓ

teljes válaszadási arány 50%; teljes adathalmazon mért teljes válaszadási arány 36,7%; progressziómentes túlélés: 10,1 hónap) (1). A fázis III KEYNOTE-775 (NCT03517449) klinikai vizsgálat, mely során a pembrolizumab és lenvatinib kombinációját vizsgálják előrehaladott, endometrium carcinomás betegek körében, elsővonalas platina-alapú terápiát követően,
teljesítette az elsődleges végpontnak kitűzött célokat a teljes túlélés (OS), a progressziómentes túlélés (PFS) és objektív válaszadási ráta (ORR) értékekben.

Elsővonalas kezelésként egyre gyakrabban alkalmazzák a kombinált kemoterápiákat endometrium carcinomás betegek esetén. Ugyanakkor a ritka teljes válaszadás, a gyakori kiújulás és progresszió arra enged következtetni, hogy a daganat gyorsan ellenállóvá válik a további kezelésre. A tumorsejtek rezisztenssé válhatnak a taxán-alapú szerekre (paclitaxel) a multidrog rezisztencia gén (MDR-1) overexpressziója miatt, mely efflux pumpaként számos toxikus anyag eltávolítását végzi a szervezetből. Emellett megfigyelték, hogy a tubulin kötőhelyben lokalizálódó pontmutációk is prediktív faktorai a rezisztencia kialakulásának. A magas béta-tubulin expresszió rövidebb progressziómentes túléléssel és rosszabb prognózissal asszociál (2).

Egy fázis III vizsgálatban doxorubicin + cisplatin, valamint doxorubicin + cisplatin + paclitaxel (TAP) kombinációk hatását vizsgálták endometrium tumoros betegeknél, ahol szignifikánsan nagyobb válaszarány (34% vs. 57%), progressziómentes túlélés (5,3 hónap vs. 8,3 hónap) és teljes túlélés (12,3 hónap vs. 15,3 hónap) adódott a TAP kezelés során (2).
Egy fázis II vizsgálatba 56 endometrium daganatos beteget válogattak be, akik bevacizumab (VEGFR gátló) terápiában részesültek. A betegek közül összesen hét esetben (13,5%) figyeltek meg klinikai válaszadást: egy teljes válasz, és 6 részleges válasz mutatkozott (3). Endometrium carcinomás betegek vizsgálata során bevacizumab és temsirolimus (mTOR gátló) kombinációs kezelés hatására 12 személy esetében (24,5%) klinikai válaszadást (1 teljes válasz, 11 részleges válasz), és 23 beteg esetében (46,9%) legalább 6 hónapig tartó progressziómentes túlélést figyeltek meg (4).

Referenciák:

(1) Makker V et al. Lenvatinib + pembrolizumab in patients with advanced endometrial cancer: Updated results. Journal of Clinical Oncology. May 20, 2018;36(no. 15_suppl):5596-5596. doi: 10.1200/JCO.2018.36.15_suppl.5596.

(2) Aghajanian C et al. Phase II trial of bevacizumab in recurrent or persistent endometrial cancer: a Gynecologic Oncology Group study. J Clin Oncol. 2011 Jun 1;29(16):2259-65. Epub 2011 May 2. PMID: 21537039.

(3) Alvarez EA et al. Phase II trial of combination bevacizumab and temsirolimus in the treatment of recurrent or persistent endometrial carcinoma: a Gynecologic Oncology Group study. Gynecol Oncol. 2013 Apr;129(1):22-7. Epub 2012 Dec 20. PMID: 23262204.

(4) Moxley KM et al. Endometrial carcinoma: a review of chemotherapy, drug resistance, and the search for new agents. Oncologist. 2010;15(10): 1026-33. Epub 2010 Oct 7. Review. PMID: 20930101.

Einsiedlerstrasse 23, 8834 Schindellegi, SWITZERLAND
E-mail: info@realtimeoncology.com **Web:** www.realtimeoncology.com

HATÓANYAG NEVE	REFERENCIA
PEMBROLIZUMAB	Grob JJ, Gonzalez Mendoza R, Basset-Seguin N, et al. LBA72 Pembrolizumab for recurrent/metastatic cutaneous squamous cell carcinoma (cSCC): efficacy and safety results from the phase II KEYNOTE-629 study. Ann Oncol. 2019;30:(mdz394.069):v908. doi: 10.1093/annonc/mdz394.069 Gandhi L, Rodríguez-Abreu D, Gadgeel S, Esteban E, Felip E, De Angelis F, Domine M, Clingan P, Hochmair MJ, Powell SF, Cheng SY, Bischoff HG, Peled N, Grossi F, Jennens RR, Reck M, Hui R, Garon EB, Boyer M, Rubio-Viqueira B, Novello S, Kurata T, Gray JE, Vida J, Wei Z, Yang J, Raftopoulos H, Pietanza MC, Garassino MC, . Pembrolizumab plus Chemotherapy in Metastatic Non-Small-Cell Lung Cancer. N Engl J Med. 2018 May 31;378(22): 2078-2092. doi: 10.1056/NEJMoa1801005. Epub 2018 Sep 16. PubMed PMID: 29658856. Eggermont AMM, Blank CU, Mandala M, Long GV, Atkinson V, Dalle S, Haydon A, Lichinitser M, Khattak A, Carlino MS, Sandhu S, Larkin J, Puig S, Ascierto PA, Rutkowski P, Schadendorf D, Koornstra R, Hernandez-Aya L, Maio M, van den Eertwegh AJM, Grob JJ, Gutzmer R, Jamal R, Lorigan P, Ibrahim N, Marreaud S, van Akkooi ACJ, Suciu S, Robert C. Adjuvant Pembrolizumab versus Placebo in Resected Stage III Melanoma. N Engl J Med. 2018 May 10;378 (19):1789-1801. doi: 10.1056/NEJMoa1802357. Epub 2018 Apr 15. PubMed PMID: 29658430. Rudin CM, Awad MM, Navarro A, Gottfried M, Peters S, Csőszi T, Cheema PK, Rodriguez-Abreu D, Wollner M, Yang JC, Mazieres J, Orlandi FJ, Luft A, Gümüş M, Kato T, Kalemkerian GP, Luo Y, Ebiana V, Pietanza MC, Kim HR, . Pembrolizumab or Placebo Plus Etoposide and Platinum as First-Line Therapy for Extensive-Stage Small-Cell Lung Cancer: Randomized, Double-Blind, Phase III KEYNOTE-604 Study. J Clin Oncol. 2020 Jul 20;38(21):2369-2379. doi: 10.1200/JCO.20.00793. Epub 2020 Jul 29. PubMed PMID: 32468956. Sylvia Adams, Peter Schmid, Hope S. Rugo, Eric P. Winer, Delphine Loirat, Ahmad Awada, David W. Cescon, Hiroji Iwata, Mario Campone, Rita Nanda, Rina Hui, Giuseppe Curigliano, Deborah Toppmeyer, Joyce O'Shaughnessy, Sherene Loi, Shani Paluch-Shimon, Deborah Card, Jing Zhao, Vassiliki Karantza, Javier Cortes. Phase 2 study of pembrolizumab (pembro) monotherapy for previously treated metastatic triple-negative breast cancer (mTNBC): KEYNOTE-086 cohort A. DOI: 10.1200/JCO.2017.35.15_suppl.1008 Journal of Clinical Oncology 35, no. 15_suppl (May 20 2017) 1008-1008.
AVELUMAB	Powles T, Park SH, Voog E, Caserta C, Valderrama BP, Gurney H, Kalofonos H, Radulović S, Demey W, Ullén A, Loriot Y, Sridhar SS, Tsuchiya N, Kopyltsov E, Sternberg CN, Bellmunt J, Aragon-Ching JB, Petrylak DP, Laliberte R, Wang J, Huang B, Davis C, Fowst C, Costa N, Blake-Haskins JA, di Pietro A, Grivas P. Avelumab Maintenance Therapy for Advanced or Metastatic Urothelial Carcinoma. N Engl J Med. 2020 Sep 18;:. doi: 10.1056 /NEJMoa2002788. Epub 2020 Sep 18. PubMed PMID: 32945632. Andrea B. Apolo, John Allan Ellerton, Jeffrey R. Infante, Manish Agrawal, Michael S. Gordon, Raid Aljumaily, Carolyn D. Britten, Luc Yves Dirix, Keun-Wook Lee, Matthew H. Taylor, Patrick Schöffski, Ding Wang, Alain Ravaud, Arnold Gelb, Junyuan Xiong, Galit Rosen, Manish R. Patel. Updated efficacy and safety of avelumab in metastatic urothelial carcinoma (mUC): Pooled analysis from 2 cohorts of the phase 1b Javelin solid tumor study. Journal of Clinical Oncology 2017 35:15_suppl, 4528-4528. Morse CB, Elvin JA, Gay LM, Liao JB. Elevated tumor mutational burden and prolonged clinical response to anti-PD-L1 antibody in platinum-resistant recurrent ovarian cancer. Gynecol Oncol Rep. 2017 Jun 27;21:78-80. doi: 10.1016/j. gore.2017.06.013. eCollection 2017 Aug. PubMed PMID: 28736741; PubMed Central PMCID: PMC5510487. KONSTANTINOPOULOS, Panagiotis A., et al. Phase 2, two-group, two-stage study of avelumab in patients (pts) with microsatellite stable (MSS), microsatellite instable (MSI), and polymerase epsilon (POLE) mutated recurrent /persistent endometrial cancer (EC). 2019.
NIVOLUMAB	Kato K, Cho BC, Takahashi M, Okada M, Lin CY, Chin K, Kadowaki S, Ahn MJ, Hamamoto Y, Doki Y, Yen CC, Kubota Y, Kim SB, Hsu CH, Holtved E, Xynos I, Kodani M, Kitagawa Y. Nivolumab versus chemotherapy in patients with advanced oesophageal squamous cell carcinoma refractory or intolerant to previous chemotherapy (ATTRACTION-3): a multicentre, randomised, open-label, phase 3 trial. Lancet Oncol. 2019 11;20(11):1506-1517. doi: 10.1016/S1470-2045(19)30626-6. Epub 2019 Jul 30. PubMed PMID: 31582355. Hollebecque A, Meyer T, Moore KN, Machiels JPH, De Greve J, López-Picazo JM, Oaknin A, Kerger JN, Boni V, Evans TRJ, Kristeleit RS, Rao S, Soumaoro I, Cao ZA, Topalian SL. An open-label, multicohort, phase I/II study of nivolumab in patients with virus-associated tumors (CheckMate 358): Efficacy and safety in recurrent or metastatic (R/M) cervical, vaginal, and vulvar cancers. DOI: 10.1200/JCO.2017.35.15_suppl.5504 Journal of Clinical Oncology 35, no. 15_suppl (May 2017) 5504-5504. Janjigian YY, Bendell J, Calvo E, Kim JW, Ascierto PA, Sharma P, Ott PA, Peltola K, Jaeger D, Evans J, de Braud F, Chau I, Harbison CT, Dorange C, Tschaika M, Le DT. CheckMate-032 Study: Efficacy and Safety of Nivolumab and Nivolumab Plus Ipilimumab in Patients With Metastatic Esophagogastric Cancer. J Clin Oncol. 2018 Aug 15: JCO2017766212. doi: 10.1200/JCO.2017.76.6212. [Epub ahead of print] PubMed PMID: 30110194. Gettinger, S. et al. OA14.04 Five-Year Outcomes From the Randomized, Phase 3 Trials CheckMate 017/057: Nivolumab vs Docetaxel in Previously Treated NSCLC. Journal of Thoracic Oncology, Volume 14, Issue 10, S244 - S245. doi: 10.1016/j.jtho.2019.08.486 Kelly RJ et al., Adjuvant nivolumab in resected esophageal or gastroesophageal junction cancer (EC/GEJC) following neoadjuvant chemoradiation therapy (CRT): First results of the CheckMate 577 study. Annals of Oncology. 2020;31(suppl_4):S1142-S1215. doi: 10.1016/annonc/annonc325.
DOSTARLIMAB	OAKNIN, A., et al. Preliminary safety, efficacy, and pharmacokinetic/pharmacodynamic characterization from GARNET, a phase I/II clinical trial of the anti–PD-1 monoclonal antibody, TSR-042, in patients with recurrent or advanced MSI-h and MSS endometrial cancer. Gynecologic Oncology, 2019, 154: 17.
ENVAFOLIMAB	

Einsiedlerstrasse 23, 8834 Schindellegi, SWITZERLAND
E-mail: info@realtimeoncology.com **Web:** www.realtimeoncology.com

HATÓANYAG NEVE	REFERENCIA
	Lin Shen, Jian Li, Yanhong Deng, Weijie Zhang, Aiping Zhou, Weijian Guo, Jianwei Yang, Ying Yuan, Liangjun Zhu, Shukui Qin, Silong Xiang, Haolan Lu, John Gong, Ting Xu, David Liu. Envafolimab (KN035) in advanced tumors with mismatch-repair deficiency. DOI: 10.1200/JCO.2020.38.15_suppl.3021 Journal of Clinical Oncology 38, no. 15_suppl (May 20, 2020) 3021-3021.
camrelizumab	Qin S, Ren Z, Meng Z, Chen Z, Chai X, Xiong J, Bai Y, Yang L, Zhu H, Fang W, Lin X, Chen X, Li E, Wang L, Chen C, Zou J. Camrelizumab in patients with previously treated advanced hepatocellular carcinoma: a multicentre, open-label, parallel-group, randomised, phase 2 trial. Lancet Oncol. 2020 Apr;21(4):571-580. doi: 10.1016/S1470-2045(20)30011-5. Epub 2020 Feb 26. PubMed PMID: 32112738.
TISLELIZUMAB	Jie Wang, Xinmin Yu, Shun Lu, Yanping Hu, Yuping Sun, Zhijie Wang, Jun Zhao, Yan Yu, Chunhong Hu, Kunyu Yang, Guosheng Feng, Kejing Ying, Wu Zhuang, Jianying Zhou, Jingxun Wu, Yanjie Wu, Xiao Lin, Liang Liang, and Nong Yang. Phase III study of tislelizumab plus chemotherapy vs chemotherapy alone as first-line (1L) treatment for advanced squamous non-small cell lung cancer (sq NSCLC). Journal of Clinical Oncology 38, no. 15_suppl (May 20, 2020) 9554-9554. doi: 10.1200/JCO.2020.38.15_suppl.9554 Song Y, Gao Q, Zhang H, Fan L, Zhou J, Zou D, Li W, Yang H, Liu T, Wang Q, Lv F, Guo H, Yang L, Elstrom R, Huang J, Novotny W, Wei V, Zhu J. Treatment of relapsed or refractory classical Hodgkin lymphoma with the anti-PD-1, tislelizumab: results of a phase 2, single-arm, multicenter study. Leukemia. 2020 02;34(2):533-542. doi: 10.1038/s41375-019-0545-2. Epub 2019 Sep 13. PubMed PMID: 31520078; PubMed Central PMCID: PMC7214259.
SINTILIMAB	Yang Y, Wang Z, Fang J, Yu Q, Han B, Cang S, Chen G, Mei X, Yang Z, Ma R, Bi M, Ren X, Zhou J, Li B, Song Y, Feng J, Li J, He Z, Zhou R, Li W, Lu Y, Wang Y, Wang L, Yang N, Zhang Y, Yu Z, Zhao Y, Xie C, Cheng Y, Zhou H, Wang S, Zhu D, Zhang W, Zhang L. Efficacy and Safety of Sintilimab Plus Pemetrexed and Platinum as First-Line Treatment for Locally Advanced or Metastatic Nonsquamous NSCLC: a Randomized, Double-Blind, Phase 3 Study (Oncology pRogram by InnovENT anti-PD-1-11). J Thorac Oncol. 2020 Oct;15(10):1636-1646. doi: 10.1016/j.jtho.2020.07.014. Epub 2020 Oct 08. PubMed PMID: 32781263.
GEPTANOLIMAB	Yuankai Shi, Jianqiu Wu, Zhen Wang, Liling Zhang, Zhao Wang, Mingzhi Zhang, Hong Cen, Zhigang Peng, Yufu Li, Lei Fan, Ye Guo, Liping Ma, Jie Cui, Yuhuan Gao, Haiyan Yang, Hongyu Zhang, Lin Wang, Weihua Zhang, Huilai Zhang, Liping Xie, Ming Jiang, Hui Zhou, Yuerong Shuang, Hang Su, Xiaoyan Ke, Chuan Jin, Xin Du, Xin Du, Li Liu, Yaming Xi, Zheng Ge, Ru Feng, Yang Zhang, Shengyu Zhou, Fan Xie and Chao Gao. Abstract CT041: The efficacy and safety of Geptanolimab (GB226) in patients with relapsed/refractory peripheral T cell lymphoma (PTCL): A multicenter, open-label, single-arm, phase 2 trial. DOI: 10.1158/1538-7445.AM2020-CT041 Published August 2020
CEMIPLIMAB	A. Sezer, S. Kilickap, M. Gümüş, I. Bondarenko, M. Özgüroğlu, M. Gogishvili, H.M. Turk, İ. Çiçin, D. Bentsion, O. Gladkov, P. Clingan, V. Sriuranpong, N. Rizvi, S. Li, S. Lee, G. Gullo, I. Lowy, P. Rietschel. LBA52 EMPOWER-Lung 1: Phase III first-line (1L) cemiplimab monotherapy vs platinum-doublet chemotherapy (chemo) in advanced non-small cell lung cancer (NSCLC) with programmed cell death-ligand 1 (PD-L1) 50%. Annals of Oncology, Volume 31, S1182 - S1183. doi: 10.1016/j.annonc.2020.08.2285
TORIPALIMAB	Fu J, Wang F, Dong LH, Zhang J, Deng CL, Wang XL, Xie XY, Zhang J, Deng RX, Zhang LB, Wu H, Feng H, Chen B, Song HF. Preclinical evaluation of the efficacy, pharmacokinetics and immunogenicity of JS-001, a programmed cell death protein-1 (PD-1) monoclonal antibody. Acta Pharmacol Sin. 2017 May;38(5):710-718. doi: 10.1038/aps.2016.161. Epub 2017 Oct 20. PubMed PMID: 28317872; PubMed Central PMCID: PMC5457696.
ABBV-181	POWDERLY, J., et al. 438P Safety and efficacy of the PD-1 inhibitor ABBV-181 in patients with advanced solid tumors: Preliminary phase I results from study M15-891. Annals of Oncology, 2018, 29.suppl_8: mdy279. 425.
DURVALUMAB	Robin Kate Kelley, Bruno Sangro, William Proctor Harris, Masafumi Ikeda, Takuji Okusaka, Yoon-Koo Kang, Shukui Qin, Wai Meng David Tai, Ho Yeong Lim, Thomas Yau, Wei-Peng Yong, Ann-Lii Cheng, Antonio Gasbarrini, Filippo G. De Braud, Jordi Bruix, Mitesh J. Borad, Philip He, Alejandra Negro, Masatoshi Kudo, and Ghassan K. Abou-Alfa. Efficacy, tolerability, and biologic activity of a novel regimen of tremelimumab (T) in combination with durvalumab (D) for patients (pts) with advanced hepatocellular carcinoma (aHCC). Journal of Clinical Oncology 2020 38: 15_suppl, 4508-4508. doi: 10.1200/JCO.2020.38.15_suppl.4508 Patrick M. Forde, Zhuoxin Sun, Valsamo Anagnostou, Hedy L. Kindler, William T. Purcell, Bernardo H. L. Goulart, Arkadiusz Z. Dudek, Hossein Borghaei, Julie R. Brahmer, and Suresh S. Ramalingam. PrE0505: Phase II multicenter study of anti-PD-L1, durvalumab, in combination with cisplatin and pemetrexed for the first-line treatment of unresectable malignant pleural mesothelioma (MPM)—A PrECOG LLC study. Journal of Clinical Oncology. May 25, 2020;38(15_suppl):9003-9003. doi: 10.1200/JCO.2020.38.15_suppl.9003 Antonia SJ. Durvalumab after Chemoradiotherapy in Stage III Non-Small-Cell Lung Cancer. Reply. N Engl J Med. 2019 Mar 7;380(10):990. doi: 10.1056/NEJMc1900407. PubMed PMID: 30855761. BARVE, M., et al. Case Report: Immune Checkpoint Inhibitor Elicited Complete Response in a Heavily Pretreated Patient with Metastatic Endometrial Carcinoma with a High Tumor Mutation Burden (TMB). of, 2017, 4: 2.
ATEZOLIZUMAB	Mizugaki H, Yamamoto N, Murakami H, Kenmotsu H, Fujiwara Y, Ishida Y, Kawakami T, Takahashi T. Phase I dose-finding study of monotherapy with atezolizumab, an engineered immunoglobulin monoclonal antibody targeting PD-L1, in Japanese patients with advanced solid tumors. Invest New Drugs. 2016 Oct;34(5):596-603. doi: 10.1007/s10637-016-0371-6. Epub 2016 Jul 1. PubMed PMID: 27363843; PubMed Central PMCID: PMC5007272. West H, McCleod M, Hussein M, Morabito A, Rittmeyer A, Conter HJ, Kopp HG, Daniel D, McCune S, Mekhail T, Zer A, Reinmuth N, Sadiq A, Sandler A, Lin W, Ochi Lohmann T, Archer V, Wang L, Kowanetz M, Cappuzzo F. Atezolizumab in combination with carboplatin plus nab-paclitaxel chemotherapy compared with chemotherapy alone as first-line treatment for metastatic non-squamous non-small-cell lung cancer (IMpower130): a multicentre, randomised, open-label, phase 3 trial. Lancet Oncol. 2019 Jul;20(7):924-937. doi: 10.1016/S1470-2045(19)30167-6. Epub 2019 May 20. PubMed PMID: 31122901. Galsky MD, Arija JÁA, Bamias A, Davis ID, De Santis M, Kikuchi E, Garcia-Del-Muro X, De Giorgi U, Mencinger M, Izumi K, Panni S, Gumus M, Özgüroğlu M, Kalebasty AR, Park SH, Alekseev B, Schutz FA, Li JR, Ye D, Vogelzang NJ,

Einsiedlerstrasse 23, 8834 Schindellegi, SWITZERLAND
E-mail: info@realtimeoncology.com **Web:** www.realtimeoncology.com

HATÓANYAG NEVE	REFERENCIA
	Bernhard S, Tayama D, Mariathasan S, Mecke A, Thåström A, Grande E, . Atezolizumab with or without chemotherapy in metastatic urothelial cancer (IMvigor130): a multicentre, randomised, placebo-controlled phase 3 trial. Lancet. 2020 05 16;395(10236):1547-1557. doi: 10.1016/S0140-6736(20)30230-0. PubMed PMID: 32416780. Mittendorf EA, Zhang H, Barrios CH, Saji S, Jung KH, Hegg R, Koehler A, Sohn J, Iwata H, Telli ML, Ferrario C, Punie K, Penault-Llorca F, Patel S, Duc AN, Liste-Hermoso M, Maiya V, Molinero L, Chui SY, Harbeck N. Neoadjuvant atezolizumab in combination with sequential nab-paclitaxel and anthracycline-based chemotherapy versus placebo and chemotherapy in patients with early-stage triple-negative breast cancer (IMpassion031): a randomised, double-blind, phase 3 trial. Lancet. 2020 Sep 18;:. doi: 10.1016/S0140-6736(20)31953-X. Epub 2020 Sep 18. PubMed PMID: 32966830. Balar AV, Galsky MD, Rosenberg JE, Powles T, Petrylak DP, Bellmunt J, Loriot Y, Necchi A, Hoffman-Censits J, Perez-Gracia JL, Dawson NA, van der Heijden MS, Dreicer R, Srinivas S, Retz MM, Joseph RW, Drakaki A, Vaishampayan UN, Sridhar SS, Quinn DI, Durán I, Shaffer DR, Eigl BJ, Grivas PD, Yu EY, Li S, Kadel EE 3rd, Boyd Z, Bourgon R, Hegde PS, Mariathasan S, Thåström A, Abidoye OO, Fine GD, Bajorin DF; IMvigor210 Study Group. Atezolizumab as first-line treatment in cisplatin-ineligible patients with locally advanced and metastatic urothelial carcinoma: a single-arm, multicentre, phase 2 trial. Lancet. 2017 Jan 7;389(10064):67-76. doi: 10.1016/S0140-6736(16)32455-2. Epub 2016 Dec 8. PubMed PMID: 27939400; PubMed Central PMCID: PMC5568632.
CS1001	C. Zhou, Z. Wang, Y. Sun, L. Cao, Z. Ma, R. Wu, Y. Yu, W. Yao, J. Chang, J. Chen, W. Zhuang, J. Cui, X. Chen, Y. Lu, H. Shen, P. Li, J. Wang, B. Sun, D. Lu, J. Yang. LBA4 - GEMSTONE-302: A phase III study of platinum-based chemotherapy (chemo) with placebo or CS1001, an anti-PDL1 antibody, for first-line (1L) advanced non-small cell lung cancer (NSCLC). Annals of Oncology (2020) 31 (suppl_6): S1386-S1406. 10.1016/annonc/annonc367
BINTRAFUSP ALFA	Lan Y, Zhang D, Xu C, Hance KW, Marelli B, Qi J, Yu H, Qin G, Sircar A, Hernández VM, Jenkins MH, Fontana RE, Deshpande A, Locke G, Sabzevari H, Radvanyi L, Lo KM. Enhanced preclinical antitumor activity of M7824, a bifunctional fusion protein simultaneously targeting PD-L1 and TGF-. Sci Transl Med. 2018 01 17;10(424):. doi: 10.1126/scitranslmed.aan5488. PubMed PMID: 29343622.
PACMILIMAB	Fiona Thistlethwaite, Aung Naing, Marta Gil-Martin, Patricia LoRusso, Manreet Randhawa, Ferry Eskens, Rachel E. Sanborn, Nataliya Volodymyrivna Uboha, Daniel C. Cho, Alexander I. Spira, Igor Bondarenko, Elizabeth Ruth Plummer, Javier Garcia-Corbacho, Iván Victoria, Javier Lavernia, Ignacio Melero, Elisabeth De Vries, William Garner, Hendrik-Tobias Arkenau, Johanna C. Bendell. PROCLAIM-CX-072: Analysis of patients with advanced solid tumors receiving long-term treatment with CX-072, a PD-L1 probody therapeutic, as a single agent or in combination with ipilimumab. Journal of Clinical Oncology 38, no. 15_suppl (May 20, 2020) 3005-3005. doi: 10.1200/JCO.2020.38.15_suppl.3005
MDX-1105	Brahmer JR, Tykodi SS, Chow LQ, Hwu WJ, Topalian SL, Hwu P, Drake CG, Camacho LH, Kauh J, Odunsi K, Pitot HC, Hamid O, Bhatia S, Martins R, Eaton K, Chen S, Salay TM, Alaparthy S, Grosso JF, Korman AJ, Parker SM, Agrawal S, Goldberg SM, Pardoll DM, Gupta A, Wigginton JM. Safety and activity of anti-PD-L1 antibody in patients with advanced cancer. N Engl J Med. 2012 Jun 28;366(26):2455-65. doi: 10.1056/NEJMoa1200694. Epub 2012 Jun 2. PubMed PMID: 22658128; PubMed Central PMCID: PMC3563263.
IPILIMUMAB	Quinn DI, Shore ND, Egawa S, Gerritsen WR, Fizazi K. Immunotherapy for castration-resistant prostate cancer: Progress and new paradigms. Urol Oncol. 2015 May;33(5):245-60. doi: 10.1016/j.urolonc.2014.10.009. Epub 2015 Jan 7. Review. PubMed PMID: 25575714. Madan RA, Gulley JL, Kantoff PW. Demystifying immunotherapy in prostate cancer: understanding current and future treatment strategies. Cancer J. 2013 Jan-Feb;19(1):50-8. doi: 10.1097/PPO.0b013e31828160a9. PubMed PMID: 23337757; PubMed Central PMCID: PMC3556901. Slovin SF, Higano CS, Hamid O, Tejwani S, Harzstark A, Alumkal JJ, Scher HI, Chin K, Gagnier P, McHenry MB, Beer TM. Ipilimumab alone or in combination with radiotherapy in metastatic castration-resistant prostate cancer: results from an open-label, multicenter phase I/II study. Ann Oncol. 2013 Jul;24(7):1813-21. doi: 10.1093/annonc/mdt107. PubMed PMID: 23535954; PubMed Central PMCID: PMC3707423. Eggermont AM, Chiarion-Sileni V, Grob JJ, Dummer R, Wolchok JD, Schmidt H, Hamid O, Robert C, Ascierto PA, Richards JM, Lebbé C, Ferraresi V, Smylie M, Weber JS, Maio M, Konto C, Hoos A, de Pril V, Gurunath RK, de Schaetzen G, Suciu S, Testori A. Adjuvant ipilimumab versus placebo after complete resection of high-risk stage III melanoma (EORTC 18071): a randomised, double-blind, phase 3 trial. Lancet Oncol. 2015 May;16(5):522-30. doi: 10.1016/S1470-2045(15)70122-1. Epub 2015 Mar 31. Erratum in: Lancet Oncol. 2015 Jun;16(6):e262. Lancet Oncol. 2016 Jun;17 (6):e223. PubMed PMID: 25840693. Scherpereel A, Mazieres J, Greillier L, Lantuejoul S, Dô P, Bylicki O, Monnet I, Corre R, Audigier-Valette C, Locatelli-Sanchez M, Molinier O, Guisier F, Urban T, Ligeza-Poisson C, Planchard D, Amour E, Morin F, Moro-Sibilot D, Zalcman G, . Nivolumab or nivolumab plus ipilimumab in patients with relapsed malignant pleural mesothelioma (IFCT-1501 MAPS2): a multicentre, open-label, randomised, non-comparative, phase 2 trial. Lancet Oncol. 2019 02;20(2):239-253. doi: 10.1016/S1470-2045(18)30765-4. Epub 2019 Dec 16. PubMed PMID: 30660609.
ZALIFRELIMAB	D.M. O'Malley et al., LBA34 Single-agent anti-PD-1 balstilimab or in combination with anti-CTLA-4 zalifrelimab for recurrent/metastatic (R/M) cervical cancer (CC): Preliminary results of two independent phase II trials. Annals of Oncology (2020) 31 (suppl_4): S1142-S1215. 10.1016/annonc/annonc325.
TREMELIMUMAB	Robin Kate Kelley, Bruno Sangro, William Proctor Harris, Masafumi Ikeda, Takuji Okusaka, Yoon-Koo Kang, Shukui Qin, Wai Meng David Tai, Ho Yeong Lim, Thomas Yau, Wei-Peng Yong, Ann-Lii Cheng, Antonio Gasbarrini, Filippo G. De Braud, Jordi Bruix, Mitesh J. Borad, Philip He, Alejandra Negro, Masatoshi Kudo, and Ghassan K. Abou-Alfa. Efficacy, tolerability, and biologic activity of a novel regimen of tremelimumab (T) in combination with durvalumab (D) for patients (pts) with advanced hepatocellular carcinoma (aHCC). Journal of Clinical Oncology 2020 38: 15_suppl, 4508-4508. doi: 10.1200/JCO.2020.38.15_suppl.4508
EPACADOSTAT	Beatty GL, O'Dwyer PJ, Clark J, Shi JG, Bowman KJ, Scherle PA, Newton RC, Schaub R, Maleski J, Leopold L, Gajewski TF. First-in-Human Phase I Study of the Oral Inhibitor of Indoleamine 2,3-Dioxygenase-1 Epacadostat (INCB024360) in Patients with Advanced Solid Malignancies. Clin Cancer Res. 2017 07 01;23(13):3269-3276. doi:

Einsiedlerstrasse 23, 8834 Schindellegi, SWITZERLAND
E-mail: info@realtimeoncology.com **Web:** www.realtimeoncology.com

HATÓANYAG NEVE	REFERENCIA
	10.1158/1078-0432.CCR-16-2272. Epub 2017 Jun 04. PubMed PMID: 28053021; PubMed Central PMCID: PMC5496788.
PALBOCICLIB	Fry DW, Harvey PJ, Keller PR, Elliott WL, Meade M, Trachet E, Albassam M, Zheng X, Leopold WR, Pryer NK, Toogood PL. Specific inhibition of cyclin-dependent kinase 4/6 by PD 0332991 and associated antitumor activity in human tumor xenografts. Mol Cancer Ther. 2004 Nov;3(11):1427-38. PubMed PMID: 15542782.
	LEONARD, John P., et al. Selective CDK4/6 inhibition with tumor responses by PD0332991 in patients with mantle cell lymphoma. Blood, 2012, 119.20: 4597-4607.
	Kollmann K, Briand C, Bellutti F, Schicher N, Blunder S, Zojer M, Hoeller C. The interplay of CDK4 and CDK6 in melanoma. Oncotarget. 2019 Feb 15;10(14):1346-1359. doi: 10.18632/oncotarget.26515. eCollection 2019 Feb 15. PubMed PMID: 30858922; PubMed Central PMCID: PMC6402717.
	Konecny GE, Wahner Hendrickson AE, Jatoi A, Burton JK, Paroly J, Glaspy JA, et al. A multicenter open-label phase II study of the efficacy and safety of palbociclib a cyclin-dependent kinases 4 and 6 inhibitor in patients with recurrent ovarian cancer. JCO. 2016 May 20;34(15_suppl):5557–5557.
	Karasic TB, et al. Phase II trial of palbociclib in patients with advanced esophageal or gastric cancer. 2018.
LETROZOLE	Yokoyama Y, Mizunuma H. Recurrent epithelial ovarian cancer and hormone therapy. World J Clin Cases. 2013 Sep 16;1(6):187-90. doi: 10.12998/wjcc.v1.i6.187. PubMed PMID: 24303498; PubMed Central PMCID: PMC3845958.
	Ramirez PT, Schmeler KM, Milam MR, Slomovitz BM, Smith JA, Kavanagh JJ, Deavers M, Levenback C, Coleman RL, Gershenson DM. Efficacy of letrozole in the treatment of recurrent platinum- and taxane-resistant high-grade cancer of the ovary or peritoneum. Gynecol Oncol. 2008 Jul;110(1):56-9. doi: 10.1016/j.ygyno.2008.03.014. Epub 2008 May 5. PubMed PMID: 18457865.
	Bowman A, Gabra H, Langdon SP, Lessells A, Stewart M, Young A, Smyth JF. CA125 response is associated with estrogen receptor expression in a phase II trial of letrozole in ovarian cancer: identification of an endocrine-sensitive subgroup. Clin Cancer Res. 2002 Jul;8(7):2233-9. PubMed PMID: 12114425.
	Smyth JF, Gourley C, Walker G, MacKean MJ, Stevenson A, Williams AR, Nafussi AA, Rye T, Rye R, Stewart M, McCurdy J, Mano M, Reed N, McMahon T, Vasey P, Gabra H, Langdon SP. Antiestrogen therapy is active in selected ovarian cancer cases: the use of letrozole in estrogen receptor-positive patients. Clin Cancer Res. 2007 Jun 15;13(12):3617-22. PubMed PMID: 17575226.
	Baselga J, Semiglazov V, van Dam P, Manikhas A, Bellet M, Mayordomo J, Campone M, Kubista E, Greil R, Bianchi G, Steinseifer J, Molloy B, Tokaji E, Gardner H, Phillips P, Stumm M, Lane HA, Dixon JM, Jonat W, Rugo HS. Phase II randomized study of neoadjuvant everolimus plus letrozole compared with placebo plus letrozole in patients with estrogen receptor-positive breast cancer. J Clin Oncol. 2009 Jun 1;27(16):2630-7. doi: 10.1200/JCO.2008.18.8391. Epub 2009 Apr 20. PubMed PMID: 19380449.
RIBOCICLIB	Condorelli R, Spring L, O'Shaughnessy J, Lacroix L, Bailleux C, Scott V, Dubois J, Nagy RJ, Lanman RB, Iafrate AJ, Andre F, Bardia A. Polyclonal RB1 mutations and acquired resistance to CDK 4/6 inhibitors in patients with metastatic breast cancer. Ann Oncol. 2018 Mar 1;29(3):640-645. doi: 10.1093/annonc/mdx784. PubMed PMID: 29236940.
	SLAMON, Dennis J., et al. Ribociclib (RIB)+ fulvestrant (FUL) in postmenopausal women with hormone receptor-positive (HR+), HER2-negative (HER2–) advanced breast cancer (ABC): Results from MONALEESA-3. 2018.
	Slamon DJ, Neven P, Chia S, Fasching PA, De Laurentiis M, Im SA, Petrakova K, Bianchi GV, Esteva FJ, Martín M, Nusch A, Sonke GS, De la Cruz-Merino L, Beck JT, Pivot X, Sondhi M, Wang Y, Chakravartty A, Rodriguez-Lorenc K, Taran T, Jerusalem G. Overall Survival with Ribociclib plus Fulvestrant in Advanced Breast Cancer. N Engl J Med. 2020 02 06;382(6):514-524. doi: 10.1056/NEJMoa1911149. Epub 2019 Jul 11. PubMed PMID: 31826360.
	Hortobagyi GN, Stemmer SM, Burris HA, Yap YS, Sonke GS, Paluch-Shimon S, Campone M, Blackwell KL, André F, Winer EP, Janni W, Verma S, Conte P, Arteaga CL, Cameron DA, Petrakova K, Hart LL, Villanueva C, Chan A, Jakobsen E, Nusch A, Burdaeva O, Grischke EM, Alba E, Wist E, Marschner N, Favret AM, Yardley D, Bachelot T, Tseng LM, Blau S, Xuan F, Souami F, Miller M, Germa C, Hirawat S, O'Shaughnessy J. Ribociclib as First-Line Therapy for HR-Positive, Advanced Breast Cancer. N Engl J Med. 2016 Nov 3;375(18):1738-1748. Epub 2016 Oct 7. PubMed PMID: 27717303.
ABEMACICLIB	Raub TJ, Wishart GN, Kulanthaivel P, Staton BA, Ajamie RT, Sawada GA, Gelbert LM, Shannon HE, Sanchez-Martinez C, De Dios A. Brain Exposure of Two Selective Dual CDK4 and CDK6 Inhibitors and the Antitumor Activity of CDK4 and CDK6 Inhibition in Combination with Temozolomide in an Intracranial Glioblastoma Xenograft. Drug Metab Dispos. 2015 Sep;43(9):1360-71. doi: 10.1124/dmd.114.062745. Epub 2015 Jan 06. PubMed PMID: 26149830.
	http://ascopubs.org/doi/abs/10.1200/JCO.2017.35.15_suppl.TPS4150
	MORSCHHAUSER, Franck, et al. Clinical activity of abemaciclib (LY2835219), a cell cycle inhibitor selective for CDK4 and CDK6, in patients with relapsed or refractory mantle cell lymphoma. 2014.
	Dickler MN, Tolaney SM, Rugo HS, Cortés J, Diéras V, Patt D, Wildiers H, Hudis CA, O'Shaughnessy J, Zamora E, Yardley DA, Frenzel M, Koustenis A, Baselga J. MONARCH 1, A Phase II Study of Abemaciclib, a CDK4 and CDK6 Inhibitor, as a Single Agent, in Patients with Refractory HR(+)/HER2(-) Metastatic Breast Cancer. Clin Cancer Res. 2017 Sep 1;23(17):5218-5224. doi: 10.1158/1078-0432.CCR-17-0754. Epub 2017 May 22. PubMed PMID: 28533223; PubMed Central PMCID: PMC5581697.

Einsiedlerstrasse 23, 8834 Schindellegi, SWITZERLAND
E-mail: info@realtimeoncology.com **Web:** www.realtimeoncology.com

HATÓANYAG NEVE	REFERENCIA
	Johnston S, Martin M, Di Leo A, Im SA, Awada A, Forrester T, Frenzel M, Hardebeck MC, Cox J, Barriga S, Toi M, Iwata H, Goetz MP. MONARCH 3 final PFS: a randomized study of abemaciclib as initial therapy for advanced breast cancer. NPJ Breast Cancer. 2019 Jan 17;5:5. doi: 10.1038/s41523-018-0097-z. eCollection 2019. PubMed PMID: 30675515; PubMed Central PMCID: PMC6336880.
TAMOXIFEN	Lee WL, Yen MS, Chao KC, Yuan CC, Ng HT, Chao HT, Lee FK, Wang PH. Hormone therapy for patients with advanced or recurrent endometrial cancer. J Chin Med Assoc. 2014 May;77(5):221-6. doi: 10.1016/j.jcma.2014.02.007. Epub 2014 Mar 30. Review. PubMed PMID: 24694672.
	McCubrey JA, Sokolosky ML, Lehmann BD, Taylor JR, Navolanic PM, Chappell WH, Abrams SL, Stadelman KM, Wong EW, Misaghian N, Horn S, Bäsecke J, Libra M, Stivala F, Ligresti G, Tafuri A, Milella M, Zarzycki M, Dzugaj A, Chiarini F, Evangelisti C, Martelli AM, Terrian DM, Franklin RA, Steelman LS. Alteration of Akt activity increases chemotherapeutic drug and hormonal resistance in breast cancer yet confers an achilles heel by sensitization to targeted therapy. Adv Enzyme Regul. 2008;48:113-35. doi: 10.1016/j.advenzreg.2008.02.006. Epub 2008 Feb 21. PubMed PMID: 18423407; PubMed Central PMCID: PMC2583357.
	Tropé C, Marth C, Kaern J. Tamoxifen in the treatment of recurrent ovarian carcinoma. Eur J Cancer. 2000 Sep;36 Suppl 4:S59-61. PubMed PMID: 11056321.
	Musgrove EA, Sutherland RL. Biological determinants of endocrine resistance in breast cancer. Nat Rev Cancer. 2009 Sep;9(9):631-43. doi: 10.1038/nrc2713. Review. PubMed PMID: 19701242.
	Yokoyama Y, Mizunuma H. Recurrent epithelial ovarian cancer and hormone therapy. World J Clin Cases. 2013 Sep 16;1(6):187-90. doi: 10.12998/wjcc.v1.i6.187. PubMed PMID: 24303498; PubMed Central PMCID: PMC3845958.
FULVESTRANT	Argenta PA, Thomas SG, Judson PL, Downs LS Jr, Geller MA, Carson LF, Jonson AL, Ghebre R. A phase II study of fulvestrant in the treatment of multiply-recurrent epithelial ovarian cancer. Gynecol Oncol. 2009 May;113(2):205-9. doi: 10.1016/j.ygyno.2009.01.012. Epub 2009 Feb 23. PubMed PMID: 19239974.
	Chung SH, Lambert PF. Prevention and treatment of cervical cancer in mice using estrogen receptor antagonists. Proc Natl Acad Sci U S A. 2009 Nov 17;106(46):19467-72. doi: 10.1073/pnas.0911436106. Epub 2009 Sep 09. PubMed PMID: 19901334; PubMed Central PMCID: PMC2780740.
	Sledge GW Jr, Toi M, Neven P, Sohn J, Inoue K, Pivot X, Burdaeva O, Okera M, Masuda N, Kaufman PA, Koh H, Grischke EM, Frenzel M, Lin Y, Barriga S, Smith IC, Bourayou N, Llombart-Cussac A. MONARCH 2: Abemaciclib in Combination With Fulvestrant in Women With HR+/HER2- Advanced Breast Cancer Who Had Progressed While Receiving Endocrine Therapy. J Clin Oncol. 2017 Sep 1;35(25):2875-2884. doi: 10.1200/JCO.2017.73.7585. Epub 2017 Jun 3. PubMed PMID: 28580882.
	Cristofanilli M, Turner NC, Bondarenko I, Ro J, Im SA, Masuda N, Colleoni M, DeMichele A, Loi S, Verma S, Iwata H, Harbeck N, Zhang K, Theall KP, Jiang Y, Bartlett CH, Koehler M, Slamon D. Fulvestrant plus palbociclib versus fulvestrant plus placebo for treatment of hormone-receptor-positive, HER2-negative metastatic breast cancer that progressed on previous endocrine therapy (PALOMA-3): final analysis of the multicentre, double-blind, phase 3 randomised controlled trial. Lancet Oncol. 2016 Apr;17(4):425-39. doi: 10.1016/S1470-2045(15)00613-0. Epub 2016 Mar 3. PubMed PMID: 26947331.
EVEROLIMUS	Pachow D, Andrae N, Kliese N, Angenstein F, Stork O, Wilisch-Neumann A, Kirches E, Mawrin C. mTORC1 inhibitors suppress meningioma growth in mouse models. Clin Cancer Res. 2013 Mar 1;19(5):1180-9. doi: 10.1158/1078-0432.CCR-12-1904. Epub 2013 Feb 13. PubMed PMID: 23406776.
	Ng K, Tabernero J, Hwang J, Bajetta E, Sharma S, Del Prete SA, Arrowsmith ER, Ryan DP, Sedova M, Jin J, Malek K, Fuchs CS. Phase II study of everolimus in patients with metastatic colorectal adenocarcinoma previously treated with bevacizumab-, fluoropyrimidine-, oxaliplatin-, and irinotecan-based regimens. Clin Cancer Res. 2013 Jul 15;19(14):3987-95. doi: 10.1158/1078-0432.CCR-13-0027. Epub 2013 Jun 6. PubMed PMID: 23743569; PubMed Central PMCID: PMC3725595.
	Singh J, Novik Y, Stein S, Volm M, Meyers M, Smith J, Omene C, Speyer J, Schneider R, Jhaveri K, Formenti S, Kyriakou V, Joseph B, Goldberg JD, Li X, Adams S, Tiersten A. Phase 2 trial of everolimus and carboplatin combination in patients with triple negative metastatic breast cancer. Breast Cancer Res. 2014 Mar 31;16(2):R32. doi: 10.1186/bcr3634. PubMed PMID: 24684785; PubMed Central PMCID: PMC4053575.
	Yao JC, Fazio N, Singh S, Buzzoni R, Carnaghi C, Wolin E, Tomasek J, Raderer M, Lahner H, Voi M, Pacaud LB, Rouyrre N, Sachs C, Valle JW, Fave GD, Van Cutsem E, Tesselaar M, Shimada Y, Oh DY, Strosberg J, Kulke MH, Pavel ME; RAD001 in Advanced Neuroendocrine Tumours, Fourth Trial (RADIANT-4) Study Group. Everolimus for the treatment of advanced, non-functional neuroendocrine tumours of the lung or gastrointestinal tract (RADIANT-4): a randomised, placebo-controlled, phase 3 study. Lancet. 2016 Mar 5;387(10022):968-977. doi: 10.1016/S0140-6736(15)00817-X. Epub 2015 Dec 17. PubMed PMID: 26703889.
	Ray-Coquard I, Favier L, Weber B, Roemer-Becuwe C, Bougnoux P, Fabbro M, Floquet A, Joly F, Plantade A, Paraiso D, Pujade-Lauraine E. Everolimus as second- or third-line treatment of advanced endometrial cancer: ENDORAD, a phase II trial of GINECO. Br J Cancer. 2013 May 14;108(9):1771-7. doi: 10.1038/bjc.2013.183. Epub 2013 Apr 23. PubMed PMID: 23612453; PubMed Central PMCID: PMC3658508.
OMIPALISIB	Thorpe LM, Yuzugullu H, Zhao JJ. PI3K in cancer: divergent roles of isoforms, modes of activation and therapeutic targeting. Nat Rev Cancer. 2015 Jan;15(1):7-24. doi: 10.1038/nrc3860. Review. PubMed PMID: 25533673; PubMed Central PMCID: PMC4384662.
	Hassett M, Sternberg A, Roepe PD. Inhibition of Human Class I vs Class III Phosphatidylinositol 3'-Kinases. Biochemistry. 2017 Jul 18. doi: 10.1021/acs.biochem.7b00413. [Epub ahead of print] PubMed PMID: 28719179.

Einsiedlerstrasse 23, 8834 Schindellegi, SWITZERLAND
E-mail: info@realtimeoncology.com **Web:** www.realtimeoncology.com

HATÓANYAG NEVE	REFERENCIA
	Albawardi A, Al Ayyan M, Al Bashir M, Souid AK, Almarzooqi S. In vitro assessment of antitumor activities of the PI3K /mTOR inhibitor GSK2126458. Cancer Cell Int. 2014 Sep 24;14(1):90. doi: 10.1186/s12935-014-0090-z. eCollection 2014. PubMed PMID: 25298748; PubMed Central PMCID: PMC4189195. Rewcastle GW, Kolekar S, Buchanan CM, Gamage SA, Giddens AC, Tsang KY, Kendall JD, Singh R, Lee WJ, Smith GC, Han W, Matthews DJ, Denny WA, Shepherd PR, Jamieson SMF. Biological characterization of SN32976, a selective inhibitor of PI3K and mTOR with preferential activity to PI3K, in comparison to established pan PI3K inhibitors. Oncotarget. 2017 May 9. doi: 10.18632/oncotarget.17730. [Epub ahead of print] PubMed PMID: 28537878. PI3K kinase inhibitor GSK2126458 (GSK458): clinical activity in select patient (pt) populations defined by predictive markers (study P3K112826) [Internet] Available from: http://abstracts.webges.com/viewing/view.php?congress=esmo2012&congress_id=370&publication_id=1500.
DACTOLISIB	Gan ZY, Fitter S, Vandyke K, To LB, Zannettino AC, Martin SK. The effect of the dual PI3K and mTOR inhibitor BEZ235 on tumour growth and osteolytic bone disease in multiple myeloma. Eur J Haematol. 2014 Sep 2. doi: 10.1111/ejh.12436. [Epub ahead of print] PubMed PMID: 25179233. Serra V, Markman B, Scaltriti M, Eichhorn PJ, Valero V, Guzman M, Botero ML, Llonch E, Atzori F, Di Cosimo S, Maira M, Garcia-Echeverria C, Parra JL, Arribas J, Baselga J. NVP-BEZ235, a dual PI3K/mTOR inhibitor, prevents PI3K signaling and inhibits the growth of cancer cells with activating PI3K mutations. Cancer Res. 2008 Oct 01;68(19):8022-30. doi: 10.1158/0008-5472.CAN-08-1385. PubMed PMID: 18829560. Thorpe LM, Yuzugullu H, Zhao JJ. PI3K in cancer: divergent roles of isoforms, modes of activation and therapeutic targeting. Nat Rev Cancer. 2015 Jan;15(1):7-24. doi: 10.1038/nrc3860. Review. PubMed PMID: 25533673; PubMed Central PMCID: PMC4384662. Chen D, Lin X, Zhang C, Liu Z, Chen Z, Li Z, Wang J, Li B, Hu Y, Dong B, Shen L, Ji J, Gao J, Zhang X. Dual PI3K /mTOR inhibitor BEZ235 as a promising therapeutic strategy against paclitaxel-resistant gastric cancer via targeting PI3K/Akt/mTOR pathway. Cell Death Dis. 2018 Jan 26;9(2):123. doi: 10.1038/s41419-017-0132-2. PubMed PMID: 29374144. Engelman JA, Chen L, Tan X, Crosby K, Guimaraes AR, Upadhyay R, Maira M, McNamara K, Perera SA, Song Y, Chirieac LR, Kaur R, Lightbown A, Simendinger J, Li T, Padera RF, García-Echeverría C, Weissleder R, Mahmood U, Cantley LC, Wong KK. Effective use of PI3K and MEK inhibitors to treat mutant Kras G12D and PIK3CA H1047R murine lung cancers. Nat Med. 2008 Dec;14(12):1351-6. doi: 10.1038/nm.1890. Epub 2008 Nov 30. PubMed PMID: 19029981; PubMed Central PMCID: PMC2683415.
VOXTALISIB	Thorpe LM, Yuzugullu H, Zhao JJ. PI3K in cancer: divergent roles of isoforms, modes of activation and therapeutic targeting. Nat Rev Cancer. 2015 Jan;15(1):7-24. doi: 10.1038/nrc3860. Review. PubMed PMID: 25533673; PubMed Central PMCID: PMC4384662. Papadopoulos KP, Egile C, Ruiz-Soto R, Jiang J, Shi W, Bentzien F, Rasco D, Abrisqueta P, Vose JM, Tabernero J. Efficacy, safety, pharmacokinetics and pharmacodynamics of SAR245409 (XL765), an orally administered PI3K /mTOR inhibitor: a phase 1 expansion cohort in patients with relapsed or refractory lymphoma. Leuk Lymphoma. 2014 Oct 10:1-32. [Epub ahead of print] PubMed PMID: 25300944.
PWT33597	Thorpe LM, Yuzugullu H, Zhao JJ. PI3K in cancer: divergent roles of isoforms, modes of activation and therapeutic targeting. Nat Rev Cancer. 2015 Jan;15(1):7-24. doi: 10.1038/nrc3860. Review. PubMed PMID: 25533673; PubMed Central PMCID: PMC4384662.
SF1126	Thorpe LM, Yuzugullu H, Zhao JJ. PI3K in cancer: divergent roles of isoforms, modes of activation and therapeutic targeting. Nat Rev Cancer. 2015 Jan;15(1):7-24. doi: 10.1038/nrc3860. Review. PubMed PMID: 25533673; PubMed Central PMCID: PMC4384662. Singh AR, Joshi S, Burgoyne AM, Sicklick JK, Ikeda S, Kono Y, Garlich JR, Morales GA, Durden DL. Single Agent and Synergistic Activity of the "First-in-Class" Dual PI3K/BRD4 Inhibitor SF1126 with Sorafenib in Hepatocellular Carcinoma. Mol Cancer Ther. 2016 Nov;15(11):2553-2562. Epub 2016 Aug 5. PubMed PMID: 27496136; PubMed Central PMCID: PMC5278767.
GEDATOLISIB	Thorpe LM, Yuzugullu H, Zhao JJ. PI3K in cancer: divergent roles of isoforms, modes of activation and therapeutic targeting. Nat Rev Cancer. 2015 Jan;15(1):7-24. doi: 10.1038/nrc3860. Review. PubMed PMID: 25533673; PubMed Central PMCID: PMC4384662. Del Campo JM, Birrer M, Davis C, Fujiwara K, Gollerkeri A, Gore M, Houk B, Lau S, Poveda A, González-Martín A, Muller C, Muro K, Pierce K, Suzuki M, Vermette J, Oza A. A randomized phase II non-comparative study of PF-04691502 and gedatolisib (PF-05212384) in patients with recurrent endometrial cancer. Gynecol Oncol. 2016 Jul;142(1):62-9. doi: 10.1016/j.ygyno.2016.04.019. Epub 2016 Apr 24. PubMed PMID: 27103175. Zhu Y, Shah K. Multiple lesions in receptor tyrosine kinase pathway determine glioblastoma response to pan-ERBB inhibitor PF-00299804 and PI3K/mTOR dual inhibitor PF-05212384. Cancer Biol Ther. 2014 Jun 1;15(6):815-22. doi: 10.4161/cbt.28585. Epub 2014 Mar 21. PubMed PMID: 24658109; PubMed Central PMCID: PMC4049797.
PF-04691502	Britten CD, Adjei AA, Millham R, Houk BE, Borzillo G, Pierce K, Wainberg ZA, LoRusso PM. Phase I study of PF-04691502, a small-molecule, oral, dual inhibitor of PI3K and mTOR, in patients with advanced cancer. Invest New Drugs. 2014 Jun;32(3):510-7. doi: 10.1007/s10637-013-0062-5. Epub 2014 Jan 7. Erratum in: Invest New Drugs. 2014 Jun;32(3):575. PubMed PMID: 24395457. Thorpe LM, Yuzugullu H, Zhao JJ. PI3K in cancer: divergent roles of isoforms, modes of activation and therapeutic targeting. Nat Rev Cancer. 2015 Jan;15(1):7-24. doi: 10.1038/nrc3860. Review. PubMed PMID: 25533673; PubMed Central PMCID: PMC4384662.

Einsiedlerstrasse 23, 8834 Schindellegi, SWITZERLAND
E-mail: info@realtimeoncology.com **Web:** www.realtimeoncology.com

HATÓANYAG NEVE	REFERENCIA
	Fang DD, Zhang CC, Gu Y, Jani JP, Cao J, Tsaparikos K, Yuan J, Thiel M, Jackson-Fisher A, Zong Q, Lappin PB, Hayashi T, Schwab RB, Wong A, John-Baptiste A, Bagrodia S, Los G, Bender S, Christensen J, Vanarsdale T. Antitumor Efficacy of the Dual PI3K/mTOR Inhibitor PF-04691502 in a Human Xenograft Tumor Model Derived from Colorectal Cancer Stem Cells Harboring a PIK3CA Mutation. PLoS One. 2013 Jun 27;8(6):e67258. Print 2013. PubMed PMID: 23826249; PubMed Central PMCID: PMC3695076. Del Campo JM, Birrer M, Davis C, Fujiwara K, Gollerkeri A, Gore M, Houk B, Lau S, Poveda A, González-Martín A, Muller C, Muro K, Pierce K, Suzuki M, Vermette J, Oza A. A randomized phase II non-comparative study of PF-04691502 and gedatolisib (PF-05212384) in patients with recurrent endometrial cancer. Gynecol Oncol. 2016 Jul; 142(1):62-9. doi: 10.1016/j.ygyno.2016.04.019. Epub 2016 Apr 24. PubMed PMID: 27103175.
APITOLISIB	Thorpe LM, Yuzugullu H, Zhao JJ. PI3K in cancer: divergent roles of isoforms, modes of activation and therapeutic targeting. Nat Rev Cancer. 2015 Jan;15(1):7-24. doi: 10.1038/nrc3860. Review. PubMed PMID: 25533673; PubMed Central PMCID: PMC4384662. Makker V, Recio FO, Ma L, Matulonis UA, Lauchle JO, Parmar H, Gilbert HN, Ware JA, Zhu R, Lu S, Huw LY, Wang Y, Koeppen H, Spoerke JM, Lackner MR, Aghajanian CA. A multicenter, single-arm, open-label, phase 2 study of apitolisib (GDC-0980) for the treatment of recurrent or persistent endometrial carcinoma (MAGGIE study). Cancer. 2016 Sep 7. doi: 10.1002/cncr.30286. [Epub ahead of print] PubMed PMID: 27603005. Powles T, Lackner MR, Oudard S, Escudier B, Ralph C, Brown JE, Hawkins RE, Castellano D, Rini BI, Staehler MD, Ravaud A, Lin W, O'Keeffe B, Wang Y, Lu S, Spoerke JM, Huw LY, Byrtek M, Zhu R, Ware JA, Motzer RJ. Randomized Open-Label Phase II Trial of Apitolisib (GDC-0980), a Novel Inhibitor of the PI3K/Mammalian Target of Rapamycin Pathway, Versus Everolimus in Patients With Metastatic Renal Cell Carcinoma. J Clin Oncol. 2016 May 10;34(14):1660-8. doi: 10.1200/JCO.2015.64.8808. Epub 2016 Mar 7. PubMed PMID: 26951309. Tang JY, Tu D, Zhang H, Xiong WJ, Xu MZ, Wang XJ, Tang QH, Chen B, Xu M. GDC-0980-induced apoptosis is enhanced by autophagy inhibition in human pancreatic cancer cells. Biochem Biophys Res Commun. 2014 Oct 5. pii: S0006-291X(14)01752-5. doi: 10.1016/j.bbrc.2014.09.115. [Epub ahead of print] PubMed PMID: 25285629.
DS-7423	Kashiyama T, Oda K, Ikeda Y, Shiose Y, Hirota Y, Inaba K, Makii C, Kurikawa R, Miyasaka A, Koso T, Fukuda T, Tanikawa M, Shoji K, Sone K, Arimoto T, Wada-Hiraike O, Kawana K, Nakagawa S, Matsuda K, McCormick F, Aburatani H, Yano T, Osuga Y, Fujii T. Antitumor activity and induction of TP53-dependent apoptosis toward ovarian clear cell adenocarcinoma by the dual PI3K/mTOR inhibitor DS-7423. PLoS One. 2014 Feb 4;9(2):e87220. doi: 10.1371/journal.pone.0087220. eCollection 2014. PubMed PMID: 24504419; PubMed Central PMCID: PMC3913610. Thorpe LM, Yuzugullu H, Zhao JJ. PI3K in cancer: divergent roles of isoforms, modes of activation and therapeutic targeting. Nat Rev Cancer. 2015 Jan;15(1):7-24. doi: 10.1038/nrc3860. Review. PubMed PMID: 25533673; PubMed Central PMCID: PMC4384662. Oda K, Ikeda Y, Kashiyama T, Miyasaka A, Inaba K, Fukuda T, Asada K, Sone K, Wada-Hiraike O, Kawana K, Osuga Y, Fujii T. Characterization of TP53 and PI3K signaling pathways as molecular targets in gynecologic malignancies. J Obstet Gynaecol Res. 2016 Jul;42(7):757-62. doi: 10.1111/jog.13018. Epub 2016 Apr 20. Review. PubMed PMID: 27094348.
BGT226	Thorpe LM, Yuzugullu H, Zhao JJ. PI3K in cancer: divergent roles of isoforms, modes of activation and therapeutic targeting. Nat Rev Cancer. 2015 Jan;15(1):7-24. doi: 10.1038/nrc3860. Review. PubMed PMID: 25533673; PubMed Central PMCID: PMC4384662. Chang KY, Tsai SY, Wu CM, Yen CJ, Chuang BF, Chang JY. Novel phosphoinositide 3-kinase/mTOR dual inhibitor, NVP-BGT226, displays potent growth-inhibitory activity against human head and neck cancer cells in vitro and in vivo. Clin Cancer Res. 2011 Nov 15;17(22):7116-26. doi: 10.1158/1078-0432.CCR-11-0796. Epub 2011 Oct 5. PubMed PMID: 21976531. Simioni C, Cani A, Martelli AM, Zauli G, Alameen AA, Ultimo S, Tabellini G, McCubrey JA, Capitani S, Neri LM. The novel dual PI3K/mTOR inhibitor NVP-BGT226 displays cytotoxic activity in both normoxic and hypoxic hepatocarcinoma cells. Oncotarget. 2015 Jul 10;6(19):17147-60. PubMed PMID: 26003166; PubMed Central PMCID: PMC4627298.
PANULISIB	Veena R. Agarwal, Asavari Joshi, Magesh Venkataraman, Dimple Bhatia, Julie Bose, Lakshmi Sireesha Kolla, Parkash Gill, and Somesh Sharma. P7170, a novel inhibitor of phosphoinositide 3-kinase (PI3K)-mammalian target of Rapamycin (mTOR) and activin receptor-like kinase 1 (ALK1) as a new therapeutic option for Kras mutated non small cell lung cancer (NSCLC). Proceedings of the 103rd Annual Meeting of the American Association for Cancer Research; 2012 Mar 31-Apr 4; Chicago, IL. Philadelphia (PA): AACR; Cancer Res 2012;72(8 Suppl):Abstract nr 3759. doi:1538-7445.AM2012-3759 Jalota-Badhwar A, Bhatia DR, Boreddy S, Joshi A, Venkatraman M, Desai N, Chaudhari S, Bose J, Kolla LS, Deore V, Yewalkar N, Kumar S, Sharma R, Damre A, More A, Sharma S, Agarwal VR. P7170: A Novel Molecule with Unique Profile of mTORC1/C2 and Activin Receptor-like Kinase 1 Inhibition Leading to Antitumor and Antiangiogenic Activity. Mol Cancer Ther. 2015 May;14(5):1095-106. doi: 10.1158/1535-7163.MCT-14-0486. Epub 2015 Feb 19. PubMed PMID: 25700704.
AZD9496	Weir HM, Bradbury RH, Lawson M, Rabow AA, Buttar D, Callis RJ, Curwen JO, de Almeida C, Ballard P, Hulse M, Donald CS, Feron LJ, Karoutchi G, MacFaul P, Moss T, Norman RA, Pearson SE, Tonge M, Davies G, Walker GE, Wilson Z, Rowlinson R, Powell S, Sadler C, Richmond G, Ladd B, Pazolli E, Mazzola AM, D'Cruz C, De Savi C. AZD9496: An Oral Estrogen Receptor Inhibitor That Blocks the Growth of ER-Positive and ESR1-Mutant Breast Tumors in Preclinical Models. Cancer Res. 2016 Jun 1;76(11):3307-18. doi: 10.1158/0008-5472.CAN-15-2357. Epub 2016 Mar 28. PubMed PMID: 27020862.

Einsiedlerstrasse 23, 8834 Schindellegi, SWITZERLAND
E-mail: info@realtimeoncology.com **Web:** www.realtimeoncology.com

HATÓANYAG NEVE	REFERENCIA
	Hamilton EP, Patel MR, Armstrong AC, Baird RD, Jhaveri K, Hoch M, Klinowska T, Lindemann JPO, Morgan SR, Schiavon G, Weir HM, Im SA. A First-in-Human Study of the New Oral Selective Estrogen Receptor Degrader AZD9496 for ER(+)/HER2(-) Advanced Breast Cancer. Clin Cancer Res. 2018 Aug 1;24(15):3510-3518. doi: 10.1158/1078-0432.CCR-17-3102. Epub 2018 Feb 13. PubMed PMID: 29440181.
PI-103	Bagci-Onder T, Wakimoto H, Anderegg M, Cameron C, Shah K. A dual PI3K/mTOR inhibitor, PI-103, cooperates with stem cell-delivered TRAIL in experimental glioma models. Cancer Res. 2011 Jan 1;71(1):154-63. doi: 10.1158/0008-5472.CAN-10-1601. Epub 2010 Nov 17. PubMed PMID: 21084267.
VS-5584	Hart S, Novotny-Diermayr V, Goh KC, Williams M, Tan YC, Ong LC, Cheong A, Ng BK, Amalini C, Madan B, Nagaraj H, Jayaraman R, Pasha KM, Ethirajulu K, Chng WJ, Mustafa N, Goh BC, Benes C, McDermott U, Garnett M, Dymock B, Wood JM. VS-5584, a novel and highly selective PI3K/mTOR kinase inhibitor for the treatment of cancer. Mol Cancer Ther. 2013 Feb;12(2):151-61. doi: 10.1158/1535-7163.MCT-12-0466. Epub 2012 Dec 27. PubMed PMID: 23270925; PubMed Central PMCID: PMC3588144. Ning C, Liang M, Liu S, Wang G, Edwards H, Xia Y, Polin L, Dyson G, Taub JW, Mohammad RM, Azmi AS, Zhao L, Ge Y. Targeting ERK enhances the cytotoxic effect of the novel PI3K and mTOR dual inhibitor VS-5584 in preclinical models of pancreatic cancer. Oncotarget. 2017 Jul 4;8(27):44295-44311. doi: 10.18632/oncotarget.17869. PubMed PMID: 28574828.
PKI179	Venkatesan AM, Chen Z, dos Santos O, Dehnhardt C, Santos ED, Ayral-Kaloustian S, Mallon R, Hollander I, Feldberg L, Lucas J, Yu K, Chaudhary I, Mansour TS. PKI-179: an orally efficacious dual phosphatidylinositol-3-kinase (PI3K)/mammalian target of rapamycin (mTOR) inhibitor. Bioorg Med Chem Lett. 2010 Oct 1;20(19):5869-73. doi: 10.1016/j.bmcl.2010.07.104. Epub 2010 Jul 30. PubMed PMID: 20797855.
BRILANESTRANT	Maura Dickler, Aditya Bardia, Ingrid Mayer, Eric Winer, Peter Rix, Jeff Hager, Meng Chen, Iris Chan, Edna Chow-Maneval, Carlos Arteaga, Jose Baselga. A first-in-human phase I study to evaluate the oral selective estrogen receptor degrader GDC-0810 (ARN-810) in postmenopausal women with estrogen receptor+ HER2-, advanced /metastatic breast cancer. [abstract]. In: Proceedings of the 106th Annual Meeting of the American Association for Cancer Research; 2015 Apr 18-22; Philadelphia, PA. Philadelphia (PA): AACR; Cancer Res 2015;75(15 Suppl):Abstract nr CT231. doi:10.1158/1538-7445.AM2015-CT231
ELACESTRANT	Bihani T, Patel HK, Arlt H, Tao N, Jiang H, Brown JL, Purandare DM, Hattersley G, Garner F. Elacestrant (RAD1901), a Selective Estrogen Receptor Degrader (SERD), Has Antitumor Activity in Multiple ER(+) Breast Cancer Patient-derived Xenograft Models. Clin Cancer Res. 2017 Aug 15;23(16):4793-4804. doi: 10.1158/1078-0432.CCR-16-2561. Epub 2017 May 4. PubMed PMID: 28473534.
EXEMESTANE	Yardley DA, Noguchi S, Pritchard KI, Burris HA 3rd, Baselga J, Gnant M, Hortobagyi GN, Campone M, Pistilli B, Piccart M, Melichar B, Petrakova K, Arena FP, Erdkamp F, Harb WA, Feng W, Cahana A, Taran T, Lebwohl D, Rugo HS. Everolimus plus exemestane in postmenopausal patients with HR(+) breast cancer: BOLERO-2 final progression-free survival analysis. Adv Ther. 2013 Oct;30(10):870-84. doi: 10.1007/s12325-013-0060-1. Epub 2013 Oct 25. Erratum in: Adv Ther. 2014 Sep;31(9):1008-9. PubMed PMID: 24158787; PubMed Central PMCID: PMC3898123.
CAPIVASERTIB	Sa JK, Hong JY, Lee IK, Kim JS, Sim MH, Kim HJ, An JY, Sohn TS, Lee JH, Bae JM, Kim S, Kim KM, Kim ST, Park SH, Park JO, Lim HY, Kang WK, Her NG, Lee Y, Cho HJ, Shin YJ, Kim M, Koo H, Kim M, Seo YJ, Kim JY, Choi MG, Nam DH, Lee J. Comprehensive pharmacogenomic characterization of gastric cancer. Genome Med. 2020 02 18;12(1):17. doi: 10.1186/s13073-020-0717-8. Epub 2020 Feb 18. PubMed PMID: 32070411; PubMed Central PMCID: PMC7029441. Toren P, Kim S, Cordonnier T, Crafter C, Davies BR, Fazli L, Gleave ME, Zoubeidi A. Combination AZD5363 with Enzalutamide Significantly Delays Enzalutamide-resistant Prostate Cancer in Preclinical Models. Eur Urol. 2014 Aug 20. pii: S0302-2838(14)00748-9. doi: 10.1016/j.eururo.2014.08.006. [Epub ahead of print] PubMed PMID: 25151012. Jones RH, Casbard A, Carucci M, Cox C, Butler R, Alchami F, Madden TA, Bale C, Bezecny P, Joffe J, Moon S, Twelves C, Venkitaraman R, Waters S, Foxley A, Howell SJ. Fulvestrant plus capivasertib versus placebo after relapse or progression on an aromatase inhibitor in metastatic, oestrogen receptor-positive breast cancer (FAKTION): a multicentre, randomised, controlled, phase 2 trial. Lancet Oncol. 2020 03;21(3):345-357. doi: 10.1016/S1470-2045(19)30817-4. Epub 2020 Jul 05. PubMed PMID: 32035020; PubMed Central PMCID: PMC7052734.
TASELISIB	Juric D, Krop I, Ramanathan RK, Wilson TR, Ware JA, Sanabria Bohorquez SM, Savage HM, Sampath D, Salphati L, Lin RS, Jin H, Parmar H, Hsu JY, Von Hoff DD, Baselga J. Phase I Dose-Escalation Study of Taselisib, an Oral PI3K Inhibitor, in Patients with Advanced Solid Tumors. Cancer Discov. 2017 Jul;7(7):704-715. doi: 10.1158/2159-8290.CD-16-1080. Epub 2017 Mar 22. PubMed PMID: 28331003; PubMed Central PMCID: PMC5501742. Lopez S, Schwab CL, Cocco E, Bellone S, Bonazzoli E, English DP, Schwartz PE, Rutherford T, Angioli R, Santin AD. Taselisib, a selective inhibitor of PIK3CA, is highly effective on PIK3CA-mutated and HER2/neu amplified uterine serous carcinoma in vitro and in vivo. Gynecol Oncol. 2014 Nov;135(2):312-7. doi: 10.1016/j.ygyno.2014.08.024. Epub 2014 Aug 27. PubMed PMID: 25172762; PubMed Central PMCID: PMC4270135. Thorpe LM, Yuzugullu H, Zhao JJ. PI3K in cancer: divergent roles of isoforms, modes of activation and therapeutic targeting. Nat Rev Cancer. 2015 Jan;15(1):7-24. doi: 10.1038/nrc3860. Review. PubMed PMID: 25533673; PubMed Central PMCID: PMC4384662. SAURA, C., et al. LBA10_PRPrimary results of LORELEI: A phase II randomized, double-blind study of neoadjuvant letrozole (LET) plus taselisib versus LET plus placebo (PLA) in postmenopausal patients (pts) with ER+/HER2-negative early breast cancer (EBC). Annals of Oncology, 2017, 28.suppl_5. BASELGA, Jose, et al. Phase III study of taselisib (GDC-0032)+ fulvestrant (FULV) v FULV in patients (pts) with estrogen receptor (ER)-positive, PIK3CA-mutant (MUT), locally advanced or metastatic breast cancer (MBC): Primary analysis from SANDPIPER. 2018.
ALPELISIB	

Einsiedlerstrasse 23, 8834 Schindellegi, SWITZERLAND
E-mail: info@realtimeoncology.com **Web:** www.realtimeoncology.com

HATÓANYAG NEVE	REFERENCIA
	Mayer IA, Abramson VG, Formisano L, Balko JM, Estrada MV, Sanders ME, Juric D, Solit D, Berger MF, Won HH, Li Y, Cantley LC, Winer E, Arteaga CL. A Phase Ib Study of Alpelisib (BYL719), a PI3K-Specific Inhibitor, with Letrozole in ER+/HER2- Metastatic Breast Cancer. Clin Cancer Res. 2017 Jan 01;23(1):26-34. doi: 10.1158/1078-0432.CCR-16-0134. Epub 2016 Jul 28. PubMed PMID: 27126994; PubMed Central PMCID: PMC5085926. Juric D, Rodon J, Tabernero J, Janku F, Burris HA, Schellens JHM, Middleton MR, Berlin J, Schuler M, Gil-Martin M, Rugo HS, Seggewiss-Bernhardt R, Huang A, Bootle D, Demanse D, Blumenstein L, Coughlin C, Quadt C, Baselga J. Phosphatidylinositol 3-Kinase -Selective Inhibition With Alpelisib (BYL719) in PIK3CA-Altered Solid Tumors: Results From the First-in-Human Study. J Clin Oncol. 2018 May 1;36(13):1291-1299. doi: 10.1200/JCO.2017.72.7107. Epub 2018 Feb 5. Erratum in: J Clin Oncol. 2019 Feb 1;37(4):361. J Clin Oncol. 2019 Feb 1;37(4):361. PubMed PMID: 29401002; PubMed Central PMCID: PMC5920739. Gobin B, Huin MB, Lamoureux F, Ory B, Charrier C, Lanel R, Battaglia S, Redini F, Lezot F, Blanchard F, Heymann D. BYL719, a new -specific PI3K inhibitor: Single administration and in combination with conventional chemotherapy for the treatment of osteosarcoma. Int J Cancer. 2014 Jun 24. doi: 10.1002/ijc.29040. [Epub ahead of print] PubMed PMID: 24961790. Juric D, Castel P, Griffith M, Griffith OL, Won HH, Ellis H, Ebbesen SH, Ainscough BJ, Ramu A, Iyer G, Shah RH, Huynh T, Mino-Kenudson M, Sgroi D, Isakoff S, Thabet A, Elamine L, Solit DB, Lowe SW, Quadt C, Peters M, Derti A, Schegel R, Huang A, Mardis ER, Berger MF, Baselga J, Scaltriti M. Convergent loss of PTEN leads to clinical resistance to a PI(3)K inhibitor. Nature. 2015 Feb 12;518(7538):240-4. doi: 10.1038/nature13948. Epub 2014 Jul 17. PubMed PMID: 25409150; PubMed Central PMCID: PMC4326538. Schwartz S, Wongvipat J, Trigwell CB, Hancox U, Carver BS, Rodrik-Outmezguine V, Will M, Yellen P, de Stanchina E, Baselga J, Scher HI, Barry ST, Sawyers CL, Chandarlapaty S, Rosen N. Feedback suppression of PI3K signaling in PTEN-mutated tumors is relieved by selective inhibition of PI3K. Cancer Cell. 2015 Jan 12;27(1):109-22. doi: 10.1016/j.ccell.2014.11.008. Epub 2014 Aug 24. PubMed PMID: 25544636; PubMed Central PMCID: PMC4293347.
RONICICLIB	Siemeister G, Lücking U, Wengner AM, Lienau P, Steinke W, Schatz C, Mumberg D, Ziegelbauer K. BAY 1000394, a novel cyclin-dependent kinase inhibitor, with potent antitumor activity in mono- and in combination treatment upon oral application. Mol Cancer Ther. 2012 Oct;11(10):2265-73. doi: 10.1158/1535-7163.MCT-12-0286. Epub 2012 Jul 19. PubMed PMID: 22821149. Ayaz P, Andres D, Kwiatkowski DA, Kolbe CC, Lienau P, Siemeister G, Lücking U, Stegmann CM. Conformational Adaption May Explain the Slow Dissociation Kinetics of Roniciclib (BAY 1000394), a Type I CDK Inhibitor with Kinetic Selectivity for CDK2 and CDK9. ACS Chem Biol. 2016 Jun 17;11(6):1710-9. doi: 10.1021/acschembio.6b00074. Epub 2016 Apr 19. PubMed PMID: 27090615.
PICTILISIB	Thorpe LM, Yuzugullu H, Zhao JJ. PI3K in cancer: divergent roles of isoforms, modes of activation and therapeutic targeting. Nat Rev Cancer. 2015 Jan;15(1):7-24. doi: 10.1038/nrc3860. Review. PubMed PMID: 25533673; PubMed Central PMCID: PMC4384662. Weigelt B, Warne PH, Lambros MB, Reis-Filho JS, Downward J. PI3K pathway dependencies in endometrioid endometrial cancer cell lines. Clin Cancer Res. 2013 Jul 1;19(13):3533-44. doi: 10.1158/1078-0432.CCR-12-3815. Epub 2013 May 14. PubMed PMID: 23674493; PubMed Central PMCID: PMC3700760. Dogan T, Gnad F, Chan J, Phu L, Young A, Chen MJ, Doll S, Stokes MP, Belvin M, Friedman LS, Kirkpatrick DS, Hoeflich KP, Hatzivassiliou G. Role of the E3 ubiquitin ligase RNF157 as a novel downstream effector linking PI3K and MAPK signaling to the cell cycle. J Biol Chem. 2017 Jun 27. pii: jbc.M117.792754. doi: 10.1074/jbc.M117.792754. [Epub ahead of print] PubMed PMID: 28655764. Nakanishi Y, Walter K, Spoerke JM, O'Brien C, Huw LY, Hampton GM, Lackner MR. Activating Mutations in PIK3CB Confer Resistance to PI3K Inhibition and Define a Novel Oncogenic Role for p110. Cancer Res. 2016 Mar 1;76(5):1193-203. doi: 10.1158/0008-5472.CAN-15-2201. Epub 2016 Jan 12. PubMed PMID: 26759240. Spoerke JM, O'Brien C, Huw L, Koeppen H, Fridlyand J, Brachmann RK, Haverty PM, Pandita A, Mohan S, Sampath D, Friedman LS, Ross L, Hampton GM, Amler LC, Shames DS, Lackner MR. Phosphoinositide 3-kinase (PI3K) pathway alterations are associated with histologic subtypes and are predictive of sensitivity to PI3K inhibitors in lung cancer preclinical models. Clin Cancer Res. 2012 Dec 15;18(24):6771-83. doi: 10.1158/1078-0432.CCR-12-2347. Epub 2012 Nov 7. PubMed PMID: 23136191.
COPANLISIB	Thorpe LM, Yuzugullu H, Zhao JJ. PI3K in cancer: divergent roles of isoforms, modes of activation and therapeutic targeting. Nat Rev Cancer. 2015 Jan;15(1):7-24. doi: 10.1038/nrc3860. Review. PubMed PMID: 25533673; PubMed Central PMCID: PMC4384662. Liu N, Rowley BR, Bull CO, Schneider C, Haegebarth A, Schatz CA, Fracasso PR, Wilkie DP, Hentemann M, Wilhelm SM, Scott WJ, Mumberg D, Ziegelbauer K. BAY 80-6946 is a highly selective intravenous PI3K inhibitor with potent p110 and p110 activities in tumor cell lines and xenograft models. Mol Cancer Ther. 2013 Nov;12(11):2319-30. doi: 10.1158/1535-7163.MCT-12-0993-T. Epub 2013 Oct 29. PubMed PMID: 24170767. Gerisch M, Schwarz T, Lang D, Rohde G, Reif S, Genvresse I, Reschke S, van der Mey D, Granvil C. Pharmacokinetics of intravenous pan-class I phosphatidylinositol 3-kinase (PI3K) inhibitor [(14)C]copanlisib (BAY 80-6946) in a mass balance study in healthy male volunteers. Cancer Chemother Pharmacol. 2017 Jul 11. doi: 10.1007/s00280-017-3383-9. [Epub ahead of print] PubMed PMID: 28714036. Dreyling M, Morschhauser F, Bouabdallah K, Bron D, Cunningham D, Assouline SE, Verhoef G, Linton K, Thieblemont C, Vitolo U, Hiemeyer F, Giurescu M, Garcia-Vargas J, Gorbatchevsky I, Liu L, Koechert K, Peña C, Neves M, Childs BH, Zinzani PL. Phase II study of copanlisib, a PI3K inhibitor, in relapsed or refractory, indolent or

Einsiedlerstrasse 23, 8834 Schindellegi, SWITZERLAND
E-mail: info@realtimeoncology.com **Web:** www.realtimeoncology.com

HATÓANYAG NEVE	REFERENCIA
	aggressive lymphoma. Ann Oncol. 2017 Sep 01;28(9):2169-2178. doi: 10.1093/annonc/mdx289. PubMed PMID: 28633365; PubMed Central PMCID: PMC5834070.
PILARALISIB	Thorpe LM, Yuzugullu H, Zhao JJ. PI3K in cancer: divergent roles of isoforms, modes of activation and therapeutic targeting. Nat Rev Cancer. 2015 Jan;15(1):7-24. doi: 10.1038/nrc3860. Review. PubMed PMID: 25533673; PubMed Central PMCID: PMC4384662. Reynolds CP, Kang MH, Carol H, Lock R, Gorlick R, Kolb EA, Kurmasheva RT, Keir ST, Maris JM, Billups CA, Houghton PJ, Smith MA. Initial testing (stage 1) of the phosphatidylinositol 3' kinase inhibitor, SAR245408 (XL147) by the pediatric preclinical testing program. Pediatr Blood Cancer. 2013 May;60(5):791-8. doi: 10.1002/pbc.24301. Epub 2012 Sep 21. PubMed PMID: 23002019. http://www.ncbi.nlm.nih.gov/pubmed/25528496 Janku F, Tsimberidou AM, Garrido-Laguna I, Wang X, Luthra R, Hong DS, Naing A, Falchook GS, Moroney JW, Piha-Paul SA, Wheler JJ, Moulder SL, Fu S, Kurzrock R. PIK3CA mutations in patients with advanced cancers treated with PI3K/AKT/mTOR axis inhibitors. Mol Cancer Ther. 2011 Mar;10(3):558-65. doi: 10.1158/1535-7163.MCT-10-0994. Epub 2011 Jan 7. PubMed PMID: 21216929; PubMed Central PMCID: PMC3072168.
BUPARLISIB	Thorpe LM, Yuzugullu H, Zhao JJ. PI3K in cancer: divergent roles of isoforms, modes of activation and therapeutic targeting. Nat Rev Cancer. 2015 Jan;15(1):7-24. doi: 10.1038/nrc3860. Review. PubMed PMID: 25533673; PubMed Central PMCID: PMC4384662. Chen L, Yang L, Yao L, Kuang XY, Zuo WJ, Li S, Qiao F, Liu YR, Cao ZG, Zhou SL, Zhou XY, Yang WT, Shi JX, Huang W, Hu X, Shao ZM. Characterization of PIK3CA and PIK3R1 somatic mutations in Chinese breast cancer patients. Nat Commun. 2018 Apr 10;9(1):1357. doi: 10.1038/s41467-018-03867-9. PubMed PMID: 29636477; PubMed Central PMCID: PMC5893593. Kirstein MM, Boukouris AE, Pothiraju D, Buitrago-Molina LE, Marhenke S, Schütt J, Orlik J, Kühnel F, Hegermann J, Manns MP, Vogel A. Activity of the mTOR inhibitor RAD001, the dual mTOR and PI3-kinase inhibitor BEZ235 and the PI3-kinase inhibitor BKM120 in hepatocellular carcinoma. Liver Int. 2013 May;33(5):780-93. doi: 10.1111/liv.12126. Epub 2013 Mar 15. PubMed PMID: 23489999. Mueller A, Bachmann E, Linnig M, Khillimberger K, Schimanski CC, Galle PR, Moehler M. Selective PI3K inhibition by BKM120 and BEZ235 alone or in combination with chemotherapy in wild-type and mutated human gastrointestinal cancer cell lines. Cancer Chemother Pharmacol. 2012 Jun;69(6):1601-15. doi: 10.1007/s00280-012-1869-z. Epub 2012 Apr 29. PubMed PMID: 22543857.
CH 5132799	Blagden S, Omlin A, Josephs D, Stavraka C, Zivi A, Pinato DJ, Anthoney A, Decordova S, Swales K, Riisnaes R, Pope L, Noguchi K, Shiokawa R, Inatani M, Prince J, Jones K, Twelves C, Spicer J, Banerji U. First-in-human study of CH5132799, an oral class I PI3K inhibitor, studying toxicity, pharmacokinetics, and pharmacodynamics, in patients with metastatic cancer. Clin Cancer Res. 2014 Dec 1;20(23):5908-17. doi: 10.1158/1078-0432.CCR-14-1315. Epub 2014 Sep 17. Erratum in: Clin Cancer Res. 2015 Feb 1;21(3):660. Olmin, Aurelius [corrected to Omlin, Aurelius]. PubMed PMID: 25231405; PubMed Central PMCID: PMC4254850. Thorpe LM, Yuzugullu H, Zhao JJ. PI3K in cancer: divergent roles of isoforms, modes of activation and therapeutic targeting. Nat Rev Cancer. 2015 Jan;15(1):7-24. doi: 10.1038/nrc3860. Review. PubMed PMID: 25533673; PubMed Central PMCID: PMC4384662.
SIROLIMUS	Bergamo F, Maruzzo M, Basso U, Montesco MC, Zagonel V, Gringeri E, Cillo U. Neoadjuvant sirolimus for a large hepatic perivascular epithelioid cell tumor (PEComa). World J Surg Oncol. 2014 Feb 27;12:46. doi: 10.1186/1477-7819-12-46. PubMed PMID: 24575738; PubMed Central PMCID: PMC3943801. Kang S, Bader AG, Vogt PK. Phosphatidylinositol 3-kinase mutations identified in human cancer are oncogenic. Proc Natl Acad Sci U S A. 2005 Jan 18;102(3):802-7. Epub 2005 Jan 12. PubMed PMID: 15647370; PubMed Central PMCID: PMC545580. Rouanne M, Loriot Y, Lebret T, Soria JC. Novel therapeutic targets in advanced urothelial carcinoma. Crit Rev Oncol Hematol. 2016 Feb;98:106-15. doi: 10.1016/j.critrevonc.2015.10.021. Epub 2015 Nov 9. Review. PubMed PMID: 26589398. Benson C, Vitfell-Rasmussen J, Maruzzo M, Fisher C, Tunariu N, Mitchell S, Al-Muderis O, Thway K, Larkin J, Judson I. A retrospective study of patients with malignant PEComa receiving treatment with sirolimus or temsirolimus: the Royal Marsden Hospital experience. Anticancer Res. 2014 Jul;34(7):3663-8. PMID: 24982384. Rizell M, Andersson M, Cahlin C, Hafström L, Olausson M, Lindnér P. Effects of the mTOR inhibitor sirolimus in patients with hepatocellular and cholangiocellular cancer. Int J Clin Oncol. 2008 Feb;13(1):66-70. doi: 10.1007/s10147-007-0733-3. Epub 2008 Feb 29. PubMed PMID: 18307022.
BAZEDOXIFENE	Wardell SE, Ellis MJ, Alley HM, Eisele K, VanArsdale T, Dann SG, Arndt KT, Primeau T, Griffin E, Shao J, Crowder R, Lai JP, Norris JD, McDonnell DP, Li S. Efficacy of SERD/SERM Hybrid-CDK4/6 Inhibitor Combinations in Models of Endocrine Therapy-Resistant Breast Cancer. Clin Cancer Res. 2015 Nov 15;21(22):5121-5130. doi: 10.1158/1078-0432.CCR-15-0360. Epub 2015 May 19. PubMed PMID: 25991817; PubMed Central PMCID: PMC4644714.
SRN-927	Dickler MN, Villanueva R, Perez Fidalgo JA, Mayer IA, Boni V, Winer EP, Hamilton EP, Bellet M, Urruticoechea A, Gonzalez-Martin A, Cortes J, Martin M, Giltnane J, Gates M, Cheeti S, Fredrickson J, Wang X, Friedman LS, Spoerke JM, Metcalfe C, Liu L, Li R, Morley R, McCurry U, Chan IT, Mueller L, Milan S, Lauchle J, Humke EW, Bardia A. A first-in-human phase I study to evaluate the oral selective estrogen receptor degrader (SERD), GDC-0927, in postmenopausal women with estrogen receptor positive (ER+) HER2-negative metastatic breast cancer (BC) [abstract]. In: Proceedings of the 2017 San Antonio Breast Cancer Symposium; 2017 Dec 5-9; San Antonio, TX. Philadelphia (PA): AACR; Cancer Res 2018;78(4 Suppl):Abstract nr PD5-10.

Einsiedlerstrasse 23, 8834 Schindellegi, SWITZERLAND
E-mail: info@realtimeoncology.com **Web:** www.realtimeoncology.com

HATÓANYAG NEVE	REFERENCIA
TEMSIROLIMUS	Liu W, Huang S, Chen Z, Wang H, Wu H, Zhang D. Temsirolimus, the mTOR inhibitor, induces autophagy in adenoid cystic carcinoma: In vitro and in vivo. Pathol Res Pract. 2014 Mar 30. pii: S0344-0338(14)00095-8. doi: 10.1016/j.prp.2014.03.008. [Epub ahead of print] PubMed PMID: 24767255. Mounier N, Vignot S, Spano JP. [Update on clinical activity of CCI779 (temsirolimus), mTOR inhibitor]. Bull Cancer. 2006 Nov;93(11):1139-43. Review. French. PubMed PMID: 17145584. Takano M, Kikuchi Y, Kudoh K, Goto T, Furuya K, Kikuchi R, Kita T, Fujiwara K, Shiozawa T, Aoki D. Weekly administration of temsirolimus for heavily pretreated patients with clear cell carcinoma of the ovary: a report of six cases. Int J Clin Oncol. 2011 Oct;16(5):605-9. doi: 10.1007/s10147-010-0177-z. Epub 2011 Jan 18. PubMed PMID: 21243393. Villaruz LC, Socinski MA. Temsirolimus therapy in a patient with lung adenocarcinoma harboring an FBXW7 mutation. Lung Cancer. 2014 Feb;83(2):300-1. doi: 10.1016/j.lungcan.2013.11.018. PubMed PMID: 24360397; PubMed Central PMCID: PMC4836187. Pachow D, Andrae N, Kliese N, Angenstein F, Stork O, Wilisch-Neumann A, Kirches E, Mawrin C. mTORC1 inhibitors suppress meningioma growth in mouse models. Clin Cancer Res. 2013 Mar 1;19(5):1180-9. doi: 10.1158/1078-0432.CCR-12-1904. Epub 2013 Feb 13. PubMed PMID: 23406776.
SONOLISIB	Hong DS, Bowles DW, Falchook GS, Messersmith WA, George GC, O'Bryant CL, Vo AC, Klucher K, Herbst RS, Eckhardt SG, Peterson S, Hausman DF, Kurzrock R, Jimeno A. A multicenter phase I trial of PX-866, an oral irreversible phosphatidylinositol 3-kinase inhibitor, in patients with advanced solid tumors. Clin Cancer Res. 2012 Aug 1;18(15):4173-82. doi: 10.1158/1078-0432.CCR-12-0714. Epub 2012 Jun 12. PubMed PMID: 22693357. Thorpe LM, Yuzugullu H, Zhao JJ. PI3K in cancer: divergent roles of isoforms, modes of activation and therapeutic targeting. Nat Rev Cancer. 2015 Jan;15(1):7-24. doi: 10.1038/nrc3860. Review. PubMed PMID: 25533673; PubMed Central PMCID: PMC4384662.
ZSTK474	Thorpe LM, Yuzugullu H, Zhao JJ. PI3K in cancer: divergent roles of isoforms, modes of activation and therapeutic targeting. Nat Rev Cancer. 2015 Jan;15(1):7-24. doi: 10.1038/nrc3860. Review. PubMed PMID: 25533673; PubMed Central PMCID: PMC4384662. Zhao W, Guo W, Zhou Q, Ma SN, Wang R, Qiu Y, Jin M, Duan HQ, Kong D. In Vitro Antimetastatic Effect of Phosphatidylinositol 3-Kinase Inhibitor ZSTK474 on Prostate Cancer PC3 Cells. Int J Mol Sci. 2013 Jun 28;14(7):13577-91. doi: 10.3390/ijms140713577. PubMed PMID: 23812078; PubMed Central PMCID: PMC3742204.
FIMEPINOSTAT	Qian C, Lai CJ, Bao R, Wang DG, Wang J, Xu GX, Atoyan R, Qu H, Yin L, Samson M, Zifcak B, Ma AW, DellaRocca S, Borek M, Zhai HX, Cai X, Voi M. Cancer network disruption by a single molecule inhibitor targeting both histone deacetylase activity and phosphatidylinositol 3-kinase signaling. Clin Cancer Res. 2012 Aug 01;18(15):4104-13. doi: 10.1158/1078-0432.CCR-12-0055. Epub 2012 Sep 12. PubMed PMID: 22693356.
IPATASERTIB	Lin J, Sampath D, Nannini MA, Lee BB, Degtyarev M, Oeh J, Savage H, Guan Z, Hong R, Kassees R, Lee LB, Risom T, Gross S, Liederer BM, Koeppen H, Skelton NJ, Wallin JJ, Belvin M, Punnoose E, Friedman LS, Lin K. Targeting activated Akt with GDC-0068, a novel selective Akt inhibitor that is efficacious in multiple tumor models. Clin Cancer Res. 2013 Apr 1;19(7):1760-72. doi: 10.1158/1078-0432.CCR-12-3072. Epub 2013 Jan 3. PubMed PMID: 23287563. Yan Y, Serra V, Prudkin L, Scaltriti M, Murli S, Rodríguez O, Guzman M, Sampath D, Nannini M, Xiao Y, Wagle MC, Wu JQ, Wongchenko M, Hampton G, Ramakrishnan V, Lackner MR, Saura C, Roda D, Cervantes A, Tabernero J, Patel P, Baselga J. Evaluation and clinical analyses of downstream targets of the Akt inhibitor GDC-0068. Clin Cancer Res. 2013 Dec 15;19(24):6976-86. doi: 10.1158/1078-0432.CCR-13-0978. Epub 2013 Oct 18. PubMed PMID: 24141624. Kim SB, Dent R, Im SA, Espié M, Blau S, Tan AR, Isakoff SJ, Oliveira M, Saura C, Wongchenko MJ, Kapp AV, Chan WY, Singel SM, Maslyar DJ, Baselga J; LOTUS investigators. Ipatasertib plus paclitaxel versus placebo plus paclitaxel as first-line therapy for metastatic triple-negative breast cancer (LOTUS): a multicentre, randomised, double-blind, placebo-controlled, phase 2 trial. Lancet Oncol. 2017 Oct;18(10):1360-1372. doi: 10.1016/S1470-2045(17)30450-3. Epub 2017 Aug 8. PubMed PMID: 28800861; PubMed Central PMCID: PMC5626630. de Bono JS, De Giorgi U, Rodrigues DN, Massard C, Bracarda S, Font A, Arranz Arija JA, Shih KC, Radavoi GD, Xu N, Chan WY, Ma H, Gendreau S, Riisnaes R, Patel PH, Maslyar DJ, Jinga V. Randomized Phase II Study Evaluating Akt Blockade with Ipatasertib, in Combination with Abiraterone, in Patients with Metastatic Prostate Cancer with and without PTEN Loss. Clin Cancer Res. 2019 Feb 1;25(3):928-936. doi: 10.1158/1078-0432.CCR-18-0981. Epub 2018 Jul 23. PubMed PMID: 30037818.
METFORMIN	Zi FM, He JS, Li Y, Wu C, Yang L, Yang Y, Wang LJ, He DH, Zhao Y, Wu WJ, Zheng GF, Han XY, Huang H, Yi Q, Cai Z. Metformin displays anti-myeloma activity and synergistic effect with dexamethasone in vitro and in xenograft models. Cancer Lett. 2014 Oct 8. pii: S0304-3835(14)00591-6. doi: 10.1016/j.canlet.2014.09.050. [Epub ahead of print] PubMed PMID: 25305450. El-Benhawy SA, El-Sheredy HG. Metformin and survival in diabetic patients with breast cancer. J Egypt Public Health Assoc. 2014 Dec;89(3):148-53. doi: 10.1097/01.EPX.0000456620.00173.c0. PubMed PMID: 25534180. Tan XL, Bhattacharyya KK, Dutta SK, Bamlet WR, Rabe KG, Wang E, Smyrk TC, Oberg AL, Petersen GM, Mukhopadhyay D. Metformin suppresses pancreatic tumor growth with inhibition of NFB/STAT3 inflammatory signaling. Pancreas. 2015 May;44(4):636-47. doi: 10.1097/MPA.0000000000000308. PubMed PMID: 25875801; PubMed Central PMCID: PMC4399019.

Einsiedlerstrasse 23, 8834 Schindellegi, SWITZERLAND
E-mail: info@realtimeoncology.com **Web:** www.realtimeoncology.com

HATÓANYAG NEVE	REFERENCIA
	Cao X, Wen ZS, Wang XD, Li Y, Liu KY, Wang X. The Clinical Effect of Metformin on the Survival of Lung Cancer Patients with Diabetes: A Comprehensive Systematic Review and Meta-analysis of Retrospective Studies. J Cancer. 2017 Aug 2;8(13):2532-2541. doi: 10.7150/jca.19750. eCollection 2017. PubMed PMID: 28900491; PubMed Central PMCID: PMC5595083. Kato K, Gong J, Iwama H, Kitanaka A, Tani J, Miyoshi H, Nomura K, Mimura S, Kobayashi M, Aritomo Y, Kobara H, Mori H, Himoto T, Okano K, Suzuki Y, Murao K, Masaki T. The antidiabetic drug metformin inhibits gastric cancer cell proliferation in vitro and in vivo. Mol Cancer Ther. 2012 Mar;11(3):549-60. doi: 10.1158/1535-7163.MCT-11-0594. Epub 2012 Jan 5. PubMed PMID: 22222629.
RIDAFOROLIMUS	Gozgit JM, Squillace RM, Wongchenko MJ, Miller D, Wardwell S, Mohemmad Q, Narasimhan NI, Wang F, Clackson T, Rivera VM. Combined targeting of FGFR2 and mTOR by ponatinib and ridaforolimus results in synergistic antitumor activity in FGFR2 mutant endometrial cancer models. Cancer Chemother Pharmacol. 2013 May;71(5):1315-23. doi: 10.1007/s00280-013-2131-z. Epub 2013 Mar 7. PubMed PMID: 23468082. Tsoref D, Welch S, Lau S, Biagi J, Tonkin K, Martin LA, Ellard S, Ghatage P, Elit L, Mackay HJ, Allo G, Tsao MS, Kamel-Reid S, Eisenhauer EA, Oza AM. Phase II study of oral ridaforolimus in women with recurrent or metastatic endometrial cancer. Gynecol Oncol. 2014 Aug 28. pii: S0090-8258(14)01074-9. doi: 10.1016/j.ygyno.2014.06.033. [Epub ahead of print] PubMed PMID: 25173583. http://www.ncbi.nlm.nih.gov/pubmed/26077241
AZD8055	Jin ZZ, Wang W, Fang DL, Jin YJ. mTOR inhibition sensitizes ONC201-induced anti-colorectal cancer cell activity. Biochem Biophys Res Commun. 2016 Sep 30;478(4):1515-20. doi: 10.1016/j.bbrc.2016.08.126. Epub 2016 Aug 24. PubMed PMID: 27565731. Xu DQ, Toyoda H, Yuan XJ, Qi L, Chelakkot VS, Morimoto M, Hanaki R, Kihira K, Hori H, Komada Y, Hirayama M. Anti-tumor effect of AZD8055 against neuroblastoma cells in vitro and in vivo. Exp Cell Res. 2018 04 15;365(2):177-184. doi: 10.1016/j.yexcr.2018.02.032. Epub 2018 Jun 28. PubMed PMID: 29499203.
RES 529	Weinberg MA. RES-529: a PI3K/AKT/mTOR pathway inhibitor that dissociates the mTORC1 and mTORC2 complexes. Anticancer Drugs. 2016 Jul;27(6):475-87. doi: 10.1097/CAD.0000000000000354. PubMed PMID: 26918392; PubMed Central PMCID: PMC4881730.
GDC 0349	Pei Z, Blackwood E, Liu L, Malek S, Belvin M, Koehler MF, Ortwine DF, Chen H, Cohen F, Kenny JR, Bergeron P, Lau K, Ly C, Zhao X, Estrada AA, Truong T, Epler JA, Nonomiya J, Trinh L, Sideris S, Lesnick J, Bao L, Vijapurkar U, Mukadam S, Tay S, Deshmukh G, Chen YH, Ding X, Friedman LS, Lyssikatos JP. Discovery and Biological Profiling of Potent and Selective mTOR Inhibitor GDC-0349. ACS Med Chem Lett. 2012 Nov 29;4(1):103-7. doi: 10.1021/ml3003132. eCollection 2013 Jan 10. PubMed PMID: 24900569; PubMed Central PMCID: PMC4027466.
CC-115	Mortensen DS, Perrin-Ninkovic SM, Shevlin G, Elsner J, Zhao J, Whitefield B, Tehrani L, Sapienza J, Riggs JR, Parnes JS, Papa P, Packard G, Lee BG, Harris R, Correa M, Bahmanyar S, Richardson SJ, Peng SX, Leisten J, Khambatta G, Hickman M, Gamez JC, Bisonette RR, Apuy J, Cathers BE, Canan SS, Moghaddam MF, Raymon HK, Worland P, Narla RK, Fultz KE, Sankar S. Optimization of a Series of Triazole Containing Mammalian Target of Rapamycin (mTOR) Kinase Inhibitors and the Discovery of CC-115. J Med Chem. 2015 Jul 23;58(14):5599-608. doi: 10.1021/acs.jmedchem.5b00627. Epub 2015 Jul 8. PubMed PMID: 26102506.
MLN0128	Rubens JA, Wang SZ, Price A, Weingart MF, Allen SJ, Orr BA, Eberhart CG, Raabe EH. The TORC1/2 inhibitor TAK228 sensitizes atypical teratoid rhabdoid tumors to cisplatin-induced cytotoxicity. Neuro Oncol. 2017 Jun 3. doi: 10.1093/neuonc/nox067. [Epub ahead of print] PubMed PMID: 28582547.
OSI-027	Bhagwat SV, Gokhale PC, Crew AP, Cooke A, Yao Y, Mantis C, Kahler J, Workman J, Bittner M, Dudkin L, Epstein DM, Gibson NW, Wild R, Arnold LD, Houghton PJ, Pachter JA. Preclinical characterization of OSI-027, a potent and selective inhibitor of mTORC1 and mTORC2: distinct from rapamycin. Mol Cancer Ther. 2011 Aug;10(8):1394-406. doi: 10.1158/1535-7163.MCT-10-1099. Epub 2011 Jun 14. PubMed PMID: 21673091.
ONATASERTIB	Rama Krishna Narla, Sophie Peng, Jim Gamez, Jason Katz, Julius Apuy, Mehran Moghaddam, Kimberly E. Fultz, Sabita Sankar, Deborah S. Mortensen, Heather K. Raymon. Antitumor activity of mTOR kinase inhibitor CC-223 in a mouse model of prostate cancer. [abstract]. In: Proceedings of the AACR-NCI-EORTC International Conference: Molecular Targets and Cancer Therapeutics; 2013 Oct 19-23; Boston, MA. Philadelphia (PA): AACR; Mol Cancer Ther 2013;12(11 Suppl):Abstract nr A165.
VISTUSERTIB	Zheng B, Mao JH, Qian L, Zhu H, Gu DH, Pan XD, Yi F, Ji DM. Pre-clinical evaluation of AZD-2014, a novel mTORC1/2 dual inhibitor, against renal cell carcinoma. Cancer Lett. 2015 Feb 28;357(2):468-75. doi: 10.1016/j.canlet.2014.11.012. Epub 2014 Nov 12. PubMed PMID: 25444920. Ezell SA, Mayo M, Bihani T, Tepsuporn S, Wang S, Passino M, Grosskurth SE, Collins M, Parmentier J, Reimer C, Byth KF. Synergistic induction of apoptosis by combination of BTK and dual mTORC1/2 inhibitors in diffuse large B cell lymphoma. Oncotarget. 2014 Jul 15;5(13):4990-5001. PubMed PMID: 24970801; PubMed Central PMCID: PMC4148116.
INAVOLISIB	STABEN, Steven T. Abstract DDT02-01: Discovery of GDC-0077, a highly isoform selective inhibitor of PI3K that promotes selective loss of mutant-p110. 2017. JHAVERI, Komal, et al. Abstract P1-19-46: A phase Ib dose escalation study evaluating the mutant selective PI3K-alpha inhibitor GDC-0077 (G) in combination with letrozole (L) with and without palbociclib (P) in patients with PIK3CA-mutant HR+/HER2-breast cancer. 2020. HONG, R., et al. Abstract PD4-14: GDC-0077 is a selective PI3Kalpha inhibitor that demonstrates robust efficacy in PIK3CA mutant breast cancer models as a single agent and in combination with standard of care therapies. 2018.

Einsiedlerstrasse 23, 8834 Schindellegi, SWITZERLAND
E-mail: info@realtimeoncology.com **Web:** www.realtimeoncology.com

HATÓANYAG NEVE	REFERENCIA
	JURIC, Dejan, et al. Abstract OT1-08-04: A first-in-human phase Ia dose escalation study of GDC-0077, a p110a-selective and mutant-degrading PI3K inhibitor, in patients with PIK3CA-mutant solid tumors. 2020.
	EDGAR, Kyle, et al. Abstract P3-11-23: GDC-0077 is a selective PI3K alpha inhibitor with robust efficacy in PIK3CA mutant hormone-positive breast cancer models. 2020.
PAXALISIB	Salphati L, Alicke B, Heffron TP, Shahidi-Latham S, Nishimura M, Cao T, Carano RA, Cheong J, Greve J, Koeppen H, Lau S, Lee LB, Nannini-Pepe M, Pang J, Plise EG, Quiason C, Rangell L, Zhang X, Gould SE, Phillips HS, Olivero AG. Brain Distribution and Efficacy of the Brain Penetrant PI3K Inhibitor GDC-0084 in Orthotopic Mouse Models of Human Glioblastoma. Drug Metab Dispos. 2016 Dec;44(12):1881-1889. Epub 2016 Sep 16. PubMed PMID: 27638506.
	Ippen FM, Alvarez-Breckenridge CA, Kuter BM, Fink AL, Bihun IV, Lastrapes M, Penson T, Schmidt SP, Wojtkiewicz GR, Ning J, Subramanian M, Giobbie-Hurder A, Martinez-Lage M, Carter SL, Cahill DP, Wakimoto H, Brastianos PK. The Dual PI3K/mTOR Pathway Inhibitor GDC-0084 Achieves Antitumor Activity in PIK3CA-Mutant Breast Cancer Brain Metastases. Clin Cancer Res. 2019 Jun 1;25(11):3374-3383. doi: 10.1158/1078-0432.CCR-18-3049. Epub 2019 Feb 22. PubMed PMID: 30796030; PubMed Central PMCID: PMC6685218.
WX 037	Haagensen EJ, Thomas HD, Schmalix WA, Payne AC, Kevorkian L, Allen RA, Bevan P, Maxwell RJ, Newell DR. Enhanced anti-tumour activity of the combination of the novel MEK inhibitor WX-554 and the novel PI3K inhibitor WX-037. Cancer Chemother Pharmacol. 2016 Dec;78(6):1269-1281. Epub 2016 Nov 11. PubMed PMID: 27837257; PubMed Central PMCID: PMC5114336.
MLN1117	Thorpe LM, Yuzugullu H, Zhao JJ. PI3K in cancer: divergent roles of isoforms, modes of activation and therapeutic targeting. Nat Rev Cancer. 2015 Jan;15(1):7-24. doi: 10.1038/nrc3860. Review. PubMed PMID: 25533673; PubMed Central PMCID: PMC4384662.
GSK1059615	Joel Greshock, Kurtis Bachman, Kurt Auger, Christopher Moy, Jeffrey Jackson, Barbara Weber, and Richard Wooster. In vitro sensitivity data suggests targeting several tumor types and molecular subtypes with the PI3K inhibitor GSK1059615 could maximize response rates in early clinical trials. AACR International Conference: Molecular Diagnostics in Cancer Therapeutic Development-- Sep 22-25, 2008; Philadelphia, PA. Clin Cancer Res October 1, 2008 14; B37.
	Carnero A. Novel inhibitors of the PI3K family. Expert Opin Investig Drugs. 2009 Sep;18(9):1265-77. doi: 10.1517/13543780903066798. Review. PubMed PMID: 19589091.
TRICIRIBINE	Evangelisti C, Ricci F, Tazzari P, Chiarini F, Battistelli M, Falcieri E, Ognibene A, Pagliaro P, Cocco L, McCubrey JA, Martelli AM. Preclinical testing of the Akt inhibitor triciribine in T-cell acute lymphoblastic leukemia. J Cell Physiol. 2011 Mar;226(3):822-31. doi: 10.1002/jcp.22407. PubMed PMID: 20857426.
	Shibata T, Kokubu A, Tsuta K, Hirohashi S. Oncogenic mutation of PIK3CA in small cell lung carcinoma: a potential therapeutic target pathway for chemotherapy-resistant lung cancer. Cancer Lett. 2009 Oct 08;283(2):203-11. doi: 10.1016/j.canlet.2009.03.038. Epub 2009 Mar 25. PubMed PMID: 19394761.
DANUSERTIB	Calvo, et al. First-in-human phase I study of LY2780301, an oral P70S6K/AKT inhibitor, in patients with refractory solid tumors. J Clin Oncol. 2012;30(Suppl):Abstr 3005.
	Meulenbeld HJ, Mathijssen RH, Verweij J, de Wit R, de Jonge MJ. Danusertib, an aurora kinase inhibitor. Expert Opin Investig Drugs. 2012 Mar;21(3):383-93. doi: 10.1517/13543784.2012.652303. Epub 2012 Jan 13. Review. PubMed PMID: 22242557.
MK2206	Yap TA, Yan L, Patnaik A, Fearen I, Olmos D, Papadopoulos K, Baird RD, Delgado L, Taylor A, Lupinacci L, Riisnaes R, Pope LL, Heaton SP, Thomas G, Garrett MD, Sullivan DM, de Bono JS, Tolcher AW. First-in-man clinical trial of the oral pan-AKT inhibitor MK-2206 in patients with advanced solid tumors. J Clin Oncol. 2011 Dec 10;29(35):4688-95. doi: 10.1200/JCO.2011.35.5263. Epub 2011 Oct 24. PubMed PMID: 22025163.
	Molife LR, Yan L, Vitfell-Rasmussen J, Zernhelt AM, Sullivan DM, Cassier PA, Chen E, Biondo A, Tetteh E, Siu LL, Patnaik A, Papadopoulos KP, de Bono JS, Tolcher AW, Minton S. Phase 1 trial of the oral AKT inhibitor MK-2206 plus carboplatin/paclitaxel, docetaxel, or erlotinib in patients with advanced solid tumors. J Hematol Oncol. 2014 Jan 3;7:1. doi: 10.1186/1756-8722-7-1. PubMed PMID: 24387695; PubMed Central PMCID: PMC3884022.
	Shouse G, de Necochea-Campion R, Mirshahidi S, Liu X, Chen CS. Novel B55-PP2A mutations in AML promote AKT T308 phosphorylation and sensitivity to AKT inhibitor-induced growth arrest. Oncotarget. 2016 Sep 20;7(38):61081-61092. doi: 10.18632/oncotarget.11209. PubMed PMID: 27531894; PubMed Central PMCID: PMC5308637.
	Samartzis EP, Gutsche K, Dedes KJ, Fink D, Stucki M, Imesch P. Loss of ARID1A expression sensitizes cancer cells to PI3K- and AKT-inhibition. Oncotarget. 2014 Jul 30;5(14):5295-303. PubMed PMID: 24979463; PubMed Central PMCID: PMC4170604.
MSC 2363318A	Mundi PS, Sachdev J, McCourt C, Kalinsky K. AKT in cancer: new molecular insights and advances in drug development. Br J Clin Pharmacol. 2016 Oct;82(4):943-56. doi: 10.1111/bcp.13021. Epub 2016 Jun 27. Review. PubMed PMID: 27232857; PubMed Central PMCID: PMC5137819.
	Machl A, Wilker EW, Tian H, Liu X, Schroeder P, Clark A, Huck BR. M2698 is a potent dual-inhibitor of p70S6K and Akt that affects tumor growth in mouse models of cancer and crosses the blood-brain barrier. Am J Cancer Res. 2016;6(4):806-18. Epub 2016 Feb 15. PubMed PMID: 27186432; PubMed Central PMCID: PMC4859885.
SR13668	Kummar S, Doroshow JH. Phase 0 trials: expediting the development of chemoprevention agents. Cancer Prev Res (Phila). 2011 Mar;4(3):288-92. doi: 10.1158/1940-6207.CAPR-11-0013. PubMed PMID: 21372025; PubMed Central PMCID: PMC3077921.

Einsiedlerstrasse 23, 8834 Schindellegi, SWITZERLAND
E-mail: info@realtimeoncology.com **Web:** www.realtimeoncology.com

HATÓANYAG NEVE	REFERENCIA
	Jong L, Chao W-R, Amin K, et al. SR13668: a novel indole derived inhibitor of phospho-Akt potently suppresses tumor growth in various murine xenograft models [abstract 3684]. Proc Amer Assoc Cancer Res 2004;45.
GSK2141795	Lassen A, Atefi M, Robert L, Wong DJ, Cerniglia M, Comin-Anduix B, Ribas A. Effects of AKT inhibitor therapy in response and resistance to BRAF inhibition in melanoma. Mol Cancer. 2014 Apr 16;13:83. doi: 10.1186/1476-4598-13-83. PubMed PMID: 24735930; PubMed Central PMCID: PMC4021505.
AFURESERTIB	Spencer A, Yoon SS, Harrison SJ, Morris SR, Smith DA, Brigandi RA, Gauvin J, Kumar R, Opalinska JB, Chen C. Novel AKT inhibitor afuresertib shows favorable safety, pharmacokinetics, and clinical activity in multiple myeloma: Phase 1 study results. Blood. 2014 Jul 29. pii: blood-2014-03-559963. [Epub ahead of print] PubMed PMID: 25075128.
BAY1125976	Politz O, Siegel F, Bärfacker L, Bömer U, Hägebarth A, Scott WJ, Michels M, Ince S, Neuhaus R, Meyer K, Fernández-Montalván AE, Liu N, von Nussbaum F, Mumberg D, Ziegelbauer K. BAY 1125976, a selective allosteric AKT1/2 inhibitor, exhibits high efficacy on AKT signaling-dependent tumor growth in mouse models. Int J Cancer. 2017 Jan 15;140(2):449-459. doi: 10.1002/ijc.30457. Epub 2016 Oct 20. PubMed PMID: 27699769.
AT13148	Yap TA, Walton MI, Grimshaw KM, Te Poele RH, Eve PD, Valenti MR, de Haven Brandon AK, Martins V, Zetterlund A, Heaton SP, Heinzmann K, Jones PS, Feltell RE, Reule M, Woodhead SJ, Davies TG, Lyons JF, Raynaud FI, Eccles SA, Workman P, Thompson NT, Garrett MD. AT13148 is a novel, oral multi-AGC kinase inhibitor with potent pharmacodynamic and antitumor activity. Clin Cancer Res. 2012 Jul 15;18(14):3912-23. doi: 10.1158/1078-0432.CCR-11-3313. Epub 2012 Jul 10. PubMed PMID: 22781553.
ARQ 092	Slomovitz BM, Coleman RL. The PI3K/AKT/mTOR pathway as a therapeutic target in endometrial cancer. Clin Cancer Res. 2012 Nov 1;18(21):5856-64. doi: 10.1158/1078-0432.CCR-12-0662. Epub 2012 Oct 18. Review. PubMed PMID: 23082003.
SC-66	Rashmi R, DeSelm C, Helms C, Bowcock A, Rogers BE, Rader J, Grigsby PW, Schwarz JK. AKT inhibitors promote cell death in cervical cancer through disruption of mTOR signaling and glucose uptake. PLoS One. 2014 Apr 4;9(4):e92948. doi: 10.1371/journal.pone.0092948. eCollection 2014. PubMed PMID: 24705275; PubMed Central PMCID: PMC3976291.
GSK690693	Dana S. Levy, Jason A. Kahana, Rakesh Kumar. AKT inhibitor, GSK690693, induces growth inhibition and apoptosis in acute lymphoblastic leukemia cell lines. BloodFeb 2009,113(8)1723-1729;DOI: 10.1182/blood-2008-02-137737
RALOXIFENE HYDROCHLORIDE	Chung SH, Lambert PF. Prevention and treatment of cervical cancer in mice using estrogen receptor antagonists. Proc Natl Acad Sci U S A. 2009 Nov 17;106(46):19467-72. doi: 10.1073/pnas.0911436106. Epub 2009 Sep 09. PubMed PMID: 19901334; PubMed Central PMCID: PMC2780740.
MILCICLIB	Weiss GJ, Hidalgo M, Borad MJ, Laheru D, Tibes R, Ramanathan RK, Blaydorn L, Jameson G, Jimeno A, Isaacs JD, Scaburri A, Pacciarini MA, Fiorentini F, Ciomei M, Von Hoff DD. Phase I study of the safety, tolerability and pharmacokinetics of PHA-848125AC, a dual tropomyosin receptor kinase A and cyclin-dependent kinase inhibitor, in patients with advanced solid malignancies. Invest New Drugs. 2012 Dec;30(6):2334-43. doi: 10.1007/s10637-011-9774-6. Epub 2011 Dec 9. PubMed PMID: 22160853; PubMed Central PMCID: PMC3561458.
RIVICICLIB	Mariaule G, Belmont P. Cyclin-dependent kinase inhibitors as marketed anticancer drugs: where are we now? A short survey. Molecules. 2014 Sep 11;19(9):14366-82. doi: 10.3390/molecules190914366. Review. PubMed PMID: 25215591.
RGB-286638	Mariaule G, Belmont P. Cyclin-dependent kinase inhibitors as marketed anticancer drugs: where are we now? A short survey. Molecules. 2014 Sep 11;19(9):14366-82. doi: 10.3390/molecules190914366. Review. PubMed PMID: 25215591.
ALVOCIDIB	Senderowicz AM. Flavopiridol: the first cyclin-dependent kinase inhibitor in human clinical trials. Invest New Drugs. 1999;17(3):313-20. Review. PubMed PMID: 10665481.
OLAPARIB	Murai J, Huang SY, Das BB, Renaud A, Zhang Y, Doroshow JH, Ji J, Takeda S, Pommier Y. Trapping of PARP1 and PARP2 by Clinical PARP Inhibitors. Cancer Res. 2012 Nov 1;72(21):5588-99. doi: 10.1158/0008-5472.CAN-12-2753. PubMed PMID: 23118055; PubMed Central PMCID: PMC3528345. Hiroyuki Yasojima, Harukaze Yamamoto, Norikazu Masuda, Kenjiro Aogi, Masato Takahashi, Kan Yonemori, Masahiro Takeuchi, Akinobu Hamada, Kenji Tamura, Tamie Sukigara, Ritsuko Nagasaka, Rie Nakano, Yukie Tsujimoto, Yuka Morioka, Kiyomi Higuchi, Yasuhiro Fujiwara. A phase I/II trial of olaparib in combination with eribulin in patients with advanced or metastatic triple negative breast cancer (TNBC) previously treated with anthracyclines and taxanes: First results from phase I. DOI: 10.1200/jco.2015.33.15_suppl.1038 Journal of Clinical Oncology 33, no. 15_suppl (May 20 2015) 1038-1038. Choy E, Butrynski JE, Harmon DC, Morgan JA, George S, Wagner AJ, D'Adamo D, Cote GM, Flamand Y, Benes CH, Haber DA, Baselga JM, Demetri GD. Phase II study of olaparib in patients with refractory Ewing sarcoma following failure of standard chemotherapy. BMC Cancer. 2014 Nov 5;14:813. doi: 10.1186/1471-2407-14-813. PubMed PMID: 25374341; PubMed Central PMCID: PMC4230717. Leichman L, Groshen S, O'Neil BH, Messersmith W, Berlin J, Chan E, Leichman CG, Cohen SJ, Cohen D, Lenz HJ, Gold P, Boman B, Fielding A, Locker G, Cason RC, Hamilton SR, Hochster HS. Phase II Study of Olaparib (AZD-2281) After Standard Systemic Therapies for Disseminated Colorectal Cancer. Oncologist. 2016 Feb;21(2):172-7. doi: 10.1634/theoncologist.2015-0319. Epub 2016 Jan 19. PubMed PMID: 26786262; PubMed Central PMCID: PMC4746089. Camero S, Ceccarelli S, De Felice F, Marampon F, Mannarino O, Camicia L, Vescarelli E, Pontecorvi P, Pizer B, Shukla R, Schiavetti A, Mollace MG, Pizzuti A, Tombolini V, Marchese C, Megiorni F, Dominici C. PARP inhibitors affect growth, survival and radiation susceptibility of human alveolar and embryonal rhabdomyosarcoma cell lines. J Cancer Res Clin Oncol. 2019 Jan;145(1):137-152. doi: 10.1007/s00432-018-2774-6. Epub 2018 Oct 24. PubMed PMID: 30357520; PubMed Central PMCID: PMC6326011.
LAPATINIB	Johnston SR, Leary A. Lapatinib: a novel EGFR/HER2 tyrosine kinase inhibitor for cancer. Drugs Today (Barc). 2006 Jul;42(7):441-53. Review. PubMed PMID: 16894399.

Einsiedlerstrasse 23, 8834 Schindellegi, SWITZERLAND
E-mail: info@realtimeoncology.com **Web:** www.realtimeoncology.com

HATÓANYAG NEVE	REFERENCIA
	Jeck WR, Parker J, Carson CC, Shields JM, Sambade MJ, Peters EC, Burd CE, Thomas NE, Chiang DY, Liu W, Eberhard DA, Ollila D, Grilley-Olson J, Moschos S, Neil Hayes D, Sharpless NE. Targeted next generation sequencing identifies clinically actionable mutations in patients with melanoma. Pigment Cell Melanoma Res. 2014 Jul;27(4):653-63. doi: 10.1111/pcmr.12238. Epub 2014 Apr 7. PubMed PMID: 24628946; PubMed Central PMCID: PMC4121659. Xia W, Husain I, Liu L, Bacus S, Saini S, Spohn J, Pry K, Westlund R, Stein SH, Spector NL. Lapatinib antitumor activity is not dependent upon phosphatase and tensin homologue deleted on chromosome 10 in ErbB2-overexpressing breast cancers. Cancer Res. 2007 Feb 1;67(3):1170-5. PubMed PMID: 17283152. Bello M, Saldaña-Rivero L, Correa-Basurto J, García B, Sánchez-Espinosa VA. Structural and energetic basis for the molecular recognition of dual synthetic vs. natural inhibitors of EGFR/HER2. Int J Biol Macromol. 2018 Jan 9;111:569-586. doi: 10.1016/j.ijbiomac.2017.12.162. [Epub ahead of print] PubMed PMID: 29329808. Wang H. Lapatinib for the treatment of breast cancer in the People's Republic of China. Onco Targets Ther. 2014 Jul 31;7:1367-73. doi: 10.2147/OTT.S60586. eCollection 2014. Review. PubMed PMID: 25114575; PubMed Central PMCID: PMC4125370.
GSK2636771	Thorpe LM, Yuzugullu H, Zhao JJ. PI3K in cancer: divergent roles of isoforms, modes of activation and therapeutic targeting. Nat Rev Cancer. 2015 Jan;15(1):7-24. doi: 10.1038/nrc3860. Review. PubMed PMID: 25533673; PubMed Central PMCID: PMC4384662. Greshock J. Abstract IA17: Exploiting the synthetic lethal properties of selective PI3K- inhibition in PTEN deficient cells with GSK2636771. Mol Cancer Ther. 2013 May 1;12(5 Supplement):IA17–IA17. Mateo J, Ganji G, Lemech C, Burris HA, Han SW, Swales K, Decordova S, DeYoung MP, Smith DA, Kalyana-Sundaram S, Wu J, Motwani M, Kumar R, Tolson JM, Rha SY, Chung HC, Eder JP, Sharma S, Bang YJ, Infante JR, Yan L, de Bono JS, Arkenau HT. A First-Time-in-Human Study of GSK2636771, a Phosphoinositide 3 Kinase Beta-Selective Inhibitor, in Patients with Advanced Solid Tumors. Clin Cancer Res. 2017 Oct 1;23(19):5981-5992. doi: 10.1158/1078-0432.CCR-17-0725. Epub 2017 Jun 23. PubMed PMID: 28645941.
AZD6482	Costa HA, Leitner MG, Sos ML, Mavrantoni A, Rychkova A, Johnson JR, Newton BW, Yee MC, De La Vega FM, Ford JM, Krogan NJ, Shokat KM, Oliver D, Halaszovich CR, Bustamante CD. Discovery and functional characterization of a neomorphic PTEN mutation. Proc Natl Acad Sci U S A. 2015 Nov 10;112(45):13976-81. doi: 10.1073/pnas.1422504112. Epub 2015 Oct 26. PubMed PMID: 26504226; PubMed Central PMCID: PMC4653168. Kumar DT, Doss CG. Investigating the Inhibitory Effect of Wortmannin in the Hotspot Mutation at Codon 1047 of PIK3CA Kinase Domain: A Molecular Docking and Molecular Dynamics Approach. Adv Protein Chem Struct Biol. 2016;102:267-97. doi: 10.1016/bs.apcsb.2015.09.008. Epub 2015 Oct 29. Review. PubMed PMID: 26827608. Xu PF, Yang JA, Liu JH, Yang X, Liao JM, Yuan FE, Liu BH, Chen QX. PI3K inhibitor AZD6482 exerts antiproliferative activity and induces apoptosis in human glioblastoma cells. Oncol Rep. 2019 Jan;41(1):125-132. doi: 10.3892/or.2018.6845. Epub 2018 Nov 02. PubMed PMID: 30542720; PubMed Central PMCID: PMC6278584.
RUCAPARIB	Hunter JE, Willmore E, Irving JA, Hostomsky Z, Veuger SJ, Durkacz BW. NF-B mediates radio-sensitization by the PARP-1 inhibitor, AG-014699. Oncogene. 2012 Jan 12;31(2):251-64. doi: 10.1038/onc.2011.229. Epub 2011 Jun 27. PubMed PMID: 21706052; PubMed Central PMCID: PMC3191117. Morgan RD, Clamp AR, Evans DGR, Edmondson RJ, Jayson GC. PARP inhibitors in platinum-sensitive high-grade serous ovarian cancer. Cancer Chemother Pharmacol. 2018 Apr;81(4):647-658. doi: 10.1007/s00280-018-3532-9. Epub 2018 Feb 20. Review. PubMed PMID: 29464354; PubMed Central PMCID: PMC5854713. Coleman RL, Oza AM, Lorusso D, Aghajanian C, Oaknin A, Dean A, Colombo N, Weberpals JI, Clamp A, Scambia G, Leary A, Holloway RW, Gancedo MA, Fong PC, Goh JC, O'Malley DM, Armstrong DK, Garcia-Donas J, Swisher EM, Floquet A, Konecny GE, McNeish IA, Scott CL, Cameron T, Maloney L, Isaacson J, Goble S, Grace C, Harding TC, Raponi M, Sun J, Lin KK, Giordano H, Ledermann JA; ARIEL3 investigators. Rucaparib maintenance treatment for recurrent ovarian carcinoma after response to platinum therapy (ARIEL3): a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet. 2017 Oct 28;390(10106):1949-1961. doi: 10.1016/S0140-6736(17)32440-6. Epub 2017 Sep 12. Erratum in: Lancet. 2017 Oct 28;390(10106):1948. PubMed PMID: 28916367; PubMed Central PMCID: PMC5901715. Swisher EM, Lin KK, Oza AM, Scott CL, Giordano H, Sun J, Konecny GE, Coleman RL, Tinker AV, O'Malley DM, Kristeleit RS, Ma L, Bell-McGuinn KM, Brenton JD, Cragun JM, Oaknin A, Ray-Coquard I, Harrell MI, Mann E, Kaufmann SH, Floquet A, Leary A, Harding TC, Goble S, Maloney L, Isaacson J, Allen AR, Rolfe L, Yelensky R, Raponi M, McNeish IA. Rucaparib in relapsed, platinum-sensitive high-grade ovarian carcinoma (ARIEL2 Part 1): an international, multicentre, open-label, phase 2 trial. Lancet Oncol. 2017 Jan;18(1):75-87. doi: 10.1016/S1470-2045(16)30559-9. Epub 2016 Nov 29. PubMed PMID: 27908594.
AZD1480	Gudernova I, Balek L, Varecha M, Kucerova JF, Kunova Bosakova M, Fafilek B, Palusova V, Uldrijan S, Trantirek L, Krejci P. Inhibitor repurposing reveals ALK, LTK, FGFR, RET and TRK kinases as the targets of AZD1480. Oncotarget. 2017 12 12;8(65):109319-109331. doi: 10.18632/oncotarget.22674. Epub 2017 Dec 27. PubMed PMID: 29312610; PubMed Central PMCID: PMC5752523. Yan S, Li Z, Thiele CJ. Inhibition of STAT3 with orally active JAK inhibitor, AZD1480, decreases tumor growth in Neuroblastoma and Pediatric Sarcomas In vitro and In vivo. Oncotarget. 2013 Mar;4(3):433-45. doi: 10.18632/oncotarget.930. PubMed PMID: 23531921; PubMed Central PMCID: PMC3717306. Wang SW, Hu J, Guo QH, Zhao Y, Cheng JJ, Zhang DS, Fei Q, Li J, Sun YM. AZD1480, a JAK inhibitor, inhibits cell growth and survival of colorectal cancer via modulating the JAK2/STAT3 signaling pathway. Oncol Rep. 2014 Sep 10. doi: 10.3892/or.2014.3477. [Epub ahead of print] PubMed PMID: 25216185.

Einsiedlerstrasse 23, 8834 Schindellegi, SWITZERLAND
E-mail: info@realtimeoncology.com **Web:** www.realtimeoncology.com

HATÓANYAG NEVE	REFERENCIA
NIRAPARIB	Bridges KA, Toniatti C, Buser CA, Liu H, Buchholz TA, Meyn RE. Niraparib (MK-4827), a novel poly(ADP-Ribose) polymerase inhibitor, radiosensitizes human lung and breast cancer cells. Oncotarget. 2014 Jul 15;5(13):5076-86. PubMed PMID: 24970803; PubMed Central PMCID: PMC4148123. X. Wu, J. Zhu, R. Yin, J. Yang, J. Liu, J. Wang, L. Wu, Z. Liu, Y. Gao, D. Wang, G. Lou, H. Yang, Q. Zhou, B. Kong, Y. Huang, L. Chen, G. Li, R. An, K. Wang, Y. Zhang. Individualized starting dose of niraparib in Chinese patients with platinum-sensitive recurrent ovarian cancer (PSROC): A randomized, double-blind, placebo-controlled, phase III trial (NORA). DOI:https://doi.org/10.1016/j.annonc.2020.08.2259 Moore KN, Secord AA, Geller MA, Miller DS, Cloven N, Fleming GF, Wahner Hendrickson AE, Azodi M, DiSilvestro P, Oza AM, Cristea M, Berek JS, Chan JK, Rimel BJ, Matei DE, Li Y, Sun K, Luptakova K, Matulonis UA, Monk BJ. Niraparib monotherapy for late-line treatment of ovarian cancer (QUADRA): a multicentre, open-label, single-arm, phase 2 trial. Lancet Oncol. 2019 May;20(5):636-648. doi: 10.1016/S1470-2045(19)30029-4. Epub 2019 Apr 1. Erratum in: Lancet Oncol. 2019 May;20(5):e242. PubMed PMID: 30948273. Mirza MR, Monk BJ, Herrstedt J, Oza AM, Mahner S, Redondo A, Fabbro M, Ledermann JA, Lorusso D, Vergote I, Ben-Baruch NE, Marth C, Mądry R, Christensen RD, Berek JS, Dørum A, Tinker AV, du Bois A, González-Martín A, Follana P, Benigno B, Rosenberg P, Gilbert L, Rimel BJ, Buscema J, Balser JP, Agarwal S, Matulonis UA; ENGOT-OV16/NOVA Investigators. Niraparib Maintenance Therapy in Platinum-Sensitive, Recurrent Ovarian Cancer. N Engl J Med. 2016 Dec 1;375(22):2154-2164. Epub 2016 Oct 7. PubMed PMID: 27717299.
SITRAVATINIB	Patwardhan PP, Ivy KS, Musi E, de Stanchina E, Schwartz GK. Significant blockade of multiple receptor tyrosine kinases by MGCD516 (Sitravatinib), a novel small molecule inhibitor, shows potent anti-tumor activity in preclinical models of sarcoma. Oncotarget. 2016 Jan 26;7(4):4093-109. doi: 10.18632/oncotarget.6547. PubMed PMID: 26675259; PubMed Central PMCID: PMC4826192.
VELIPARIB	Donawho CK, Luo Y, Luo Y, Penning TD, Bauch JL, Bouska JJ, Bontcheva-Diaz VD, Cox BF, DeWeese TL, Dillehay LE, Ferguson DC, Ghoreishi-Haack NS, Grimm DR, Guan R, Han EK, Holley-Shanks RR, Hristov B, Idler KB, Jarvis K, Johnson EF, Kleinberg LR, Klinghofer V, Lasko LM, Liu X, Marsh KC, McGonigal TP, Meulbroek JA, Olson AM, Palma JP, Rodriguez LE, Shi Y, Stavropoulos JA, Tsurutani AC, Zhu GD, Rosenberg SH, Giranda VL, Frost DJ. ABT-888, an orally active poly(ADP-ribose) polymerase inhibitor that potentiates DNA-damaging agents in preclinical tumor models. Clin Cancer Res. 2007 May 1;13(9):2728-37. PubMed PMID: 17473206. Joshi PM, Sutor SL, Huntoon CJ, Karnitz LM. Ovarian cancer-associated mutations disable catalytic activity of CDK12, a kinase that promotes homologous recombination repair and resistance to cisplatin and poly(ADP-ribose) polymerase inhibitors. J Biol Chem. 2014 Mar 28;289(13):9247-53. doi: 10.1074/jbc.M114.551143. Epub 2014 Feb 19. PubMed PMID: 24554720; PubMed Central PMCID: PMC3979363. Moreno T et al., ARID2 deficiency promotes tumor progression and is associated with higher sensitivity to PARP inhibition in lung cancer. bioRxiv 2020.01.10.898726; doi: https://doi.org/10.1101/2020.01.10.898726
2X-121	Kurnit KC, Coleman RL, Westin SN. Using PARP Inhibitors in the Treatment of Patients With Ovarian Cancer. Curr Treat Options Oncol. 2018 Nov 15;19(12):1. doi: 10.1007/s11864-018-0572-7. Review. PubMed PMID: 30535808. R. Plummer, D. Dua, N. Cresti, A. Suder, Y. Drew, V. Prathapan, P. Stephens, J. Thornton, B.D.L. Heras, B. Ink, L. Lee, M. Matijevic, S. McGrath and D. Sarker. PHASE 1 STUDY OF THE PARP INHIBITOR E7449 AS A SINGLE AGENT IN PATIENTS WITH ADVANCED SOLID TUMORS OR B-CELL LYMPHOMA. Ann Oncol (2014) 25 (suppl 4): iv151. doi: 10.1093/annonc/mdu331.13
AZD 2461	Oplustil O'Connor L, Rulten SL, Cranston AN, Odedra R, Brown H, Jaspers JE, Jones L, Knights C, Evers B, Ting A, Bradbury RH, Pajic M, Rottenberg S, Jonkers J, Rudge D, Martin NM, Caldecott KW, Lau A, O'Connor MJ. The PARP Inhibitor AZD2461 Provides Insights into the Role of PARP3 Inhibition for Both Synthetic Lethality and Tolerability with Chemotherapy in Preclinical Models. Cancer Res. 2016 Oct 15;76(20):6084-6094. Epub 2016 Aug 22. PubMed PMID: 27550455.
INO-1001	Bedikian AY, Papadopoulos NE, Kim KB, Hwu WJ, Homsi J, Glass MR, Cain S, Rudewicz P, Vernillet L, Hwu P. A phase IB trial of intravenous INO-1001 plus oral temozolomide in subjects with unresectable stage-III or IV melanoma. Cancer Invest. 2009 Aug;27(7):756-63. doi: 10.1080/07357900802709159. PubMed PMID: 19440934.
FLUZOPARIB	Yuan Z, Chen J, Li W, Li D, Chen C, Gao C, Jiang Y. PARP inhibitors as antitumor agents: a patent update (2013-2015). Expert Opin Ther Pat. 2017 Mar;27(3):363-382. doi: 10.1080/13543776.2017.1259413. Epub 2016 Nov 21. Review. PubMed PMID: 27841036.
PAMIPARIB	Tang Z, Liu Y, Zhen Q, Ren B, Wang H, Shi Z, et al. Abstract 1653: BGB-290: A highly potent and specific PARP1/2 inhibitor potentiates anti-tumor activity of chemotherapeutics in patient biopsy derived SCLC models. Cancer Res. 2015 Aug 1;75(15 Supplement):1653–1653.
E7016	Russo AL, Kwon HC, Burgan WE, Carter D, Beam K, Weizheng X, Zhang J, Slusher BS, Chakravarti A, Tofilon PJ, Camphausen K. In vitro and in vivo radiosensitization of glioblastoma cells by the poly (ADP-ribose) polymerase inhibitor E7016. Clin Cancer Res. 2009 Jan 15;15(2):607-12. doi: 10.1158/1078-0432.CCR-08-2079. PubMed PMID: 19147766.
CEP-9722	Miknyoczki S, Chang H, Grobelny J, Pritchard S, Worrell C, McGann N, Ator M, Husten J, Deibold J, Hudkins R, Zulli A, Parchment R, Ruggeri B. The selective poly(ADP-ribose) polymerase-1(2) inhibitor, CEP-8983, increases the sensitivity of chemoresistant tumor cells to temozolomide and irinotecan but does not potentiate myelotoxicity. Mol Cancer Ther. 2007 Aug;6(8):2290-302. PubMed PMID: 17699724.
INIPARIB	Liang H, Tan AR. Iniparib, a PARP1 inhibitor for the potential treatment of cancer, including triple-negative breast cancer. IDrugs. 2010 Sep;13(9):646-56. Review. PubMed PMID: 20799148.
TALAZOPARIB	Aoyagi-Scharber M, Gardberg AS, Yip BK, Wang B, Shen Y, Fitzpatrick PA. Structural basis for the inhibition of poly (ADP-ribose) polymerases 1 and 2 by BMN 673, a potent inhibitor derived from dihydropyridophthalazinone. Acta Crystallogr F Struct Biol Commun. 2014 Sep 1;70(Pt 9):1143-9. doi: 10.1107/S2053230X14015088. Epub 2014 Aug 29. PubMed PMID: 25195882.

Einsiedlerstrasse 23, 8834 Schindellegi, SWITZERLAND
E-mail: info@realtimeoncology.com **Web:** www.realtimeoncology.com

HATÓANYAG NEVE	REFERENCIA
ABT767	M.J.A. de Jonge, C. van Herpen, J.A. Gietema, S. Shepherd, R. Koornstra, A. Jager, M. Den Hollander, M. Dunbar, R. Hetman, C. Serpenti, H. Xiong, M. Zhu and V.L. Giranda. A STUDY OF ABT-767 IN ADVANCED SOLID TUMORS WITH BRCA 1 AND BRCA 2 MUTATIONS AND HIGH GRADE SEROUS OVARIAN, FALLOPIAN TUBE, OR PRIMARY PERITONEAL CANCER. Ann Oncol (2014) 25 (suppl 4): iv150. doi: 10.1093/annonc/mdu331.12
TALETRECTINIB	Katayama R, Gong B, Togashi N, Miyamoto M, Kiga M, Iwasaki S, Kamai Y, Tominaga Y, Takeda Y, Kagoshima Y, Shimizu Y, Seto Y, Oh-Hara T, Koike S, Nakao N, Hanzawa H, Watanabe K, Yoda S, Yanagitani N, Hata AN, Shaw AT, Nishio M, Fujita N, Isoyama T. The new-generation selective ROS1/NTRK inhibitor DS-6051b overcomes crizotinib resistant ROS1-G2032R mutation in preclinical models. Nat Commun. 2019 08 09;10(1):3604. doi: 10.1038/s41467-019-11496-z. Epub 2019 Jan 09. PubMed PMID: 31399568; PubMed Central PMCID: PMC6688997.
CRIZOTINIB	Forde PM, Rudin CM. Crizotinib in the treatment of non-small-cell lung cancer. Expert Opin Pharmacother. 2012 Jun;13(8):1195-201. doi: 10.1517/14656566.2012.688029. Review. PubMed PMID: 22594847. Chand D, Yamazaki Y, Ruuth K, Schönherr C, Martinsson T, Kogner P, Attiyeh EF, Maris J, Morozova O, Marra MA, Ohira M, Nakagawara A, Sandström PE, Palmer RH, Hallberg B. Cell culture and Drosophila model systems define three classes of anaplastic lymphoma kinase mutations in neuroblastoma. Dis Model Mech. 2013 Mar;6(2):373-82. doi: 10.1242/dmm.010348. Epub 2012 Jun 25. PubMed PMID: 23104988; PubMed Central PMCID: PMC3597019. Zou HY, Li Q, Lee JH, Arango ME, McDonnell SR, Yamazaki S, Koudriakova TB, Alton G, Cui JJ, Kung PP, Nambu MD, Los G, Bender SL, Mroczkowski B, Christensen JG. An orally available small-molecule inhibitor of c-Met, PF-2341066, exhibits cytoreductive antitumor efficacy through antiproliferative and antiangiogenic mechanisms. Cancer Res. 2007 May 1;67(9):4408-17. PubMed PMID: 17483355. Fontana D, Ceccon M, Gambacorti-Passerini C, Mologni L. Activity of second-generation ALK inhibitors against crizotinib-resistant mutants in an NPM-ALK model compared to EML4-ALK. Cancer Med. 2015 Jul;4(7):953-65. doi: 10.1002/cam4.413. Epub 2015 Feb 26. PubMed PMID: 25727400; PubMed Central PMCID: PMC4529334. Sasaki T, Okuda K, Zheng W, Butrynski J, Capelletti M, Wang L, Gray NS, Wilner K, Christensen JG, Demetri G, Shapiro GI, Rodig SJ, Eck MJ, Jänne PA. The neuroblastoma-associated F1174L ALK mutation causes resistance to an ALK kinase inhibitor in ALK-translocated cancers. Cancer Res. 2010 Dec 15;70(24):10038-43. doi: 10.1158/0008-5472.CAN-10-2956. Epub 2010 Oct 28. PubMed PMID: 21030459; PubMed Central PMCID: PMC3045808.
ACALISIB	Thorpe LM, Yuzugullu H, Zhao JJ. PI3K in cancer: divergent roles of isoforms, modes of activation and therapeutic targeting. Nat Rev Cancer. 2015 Jan;15(1):7-24. doi: 10.1038/nrc3860. Review. PubMed PMID: 25533673; PubMed Central PMCID: PMC4384662.
ASPIRIN	Verdoodt F, Friis S, Dehlendorff C, Albieri V, Kjaer SK. Non-steroidal anti-inflammatory drug use and risk of endometrial cancer: A systematic review and meta-analysis of observational studies. Gynecol Oncol. 2016 Feb;140(2):352-8. doi: 10.1016/j.ygyno.2015.12.009. Epub 2015 Dec 14. Review. PubMed PMID: 26701413. Ng K, Meyerhardt JA, Chan AT, Sato K, Chan JA, Niedzwiecki D, Saltz LB, Mayer RJ, Benson AB 3rd, Schaefer PL, Whittom R, Hantel A, Goldberg RM, Venook AP, Ogino S, Giovannucci EL, Fuchs CS. Aspirin and COX-2 inhibitor use in patients with stage III colon cancer. J Natl Cancer Inst. 2014 Nov 27;107(1):345. doi: 10.1093/jnci/dju345. Print 2015 Jan. PubMed PMID: 25432409; PubMed Central PMCID: PMC4271076. Gu M, Nishihara R, Chen Y, Li W, Shi Y, Masugi Y, Hamada T, Kosumi K, Liu L, da Silva A, Nowak JA, Twombly T, Du C, Koh H, Li W, Meyerhardt JA, Wolpin BM, Giannakis M, Aguirre AJ, Bass AJ, Drew DA, Chan AT, Fuchs CS, Qian ZR, Ogino S. Aspirin exerts high anti-cancer activity in PIK3CA-mutant colon cancer cells. Oncotarget. 2017 Sep 18;8(50):87379-87389. doi: 10.18632/oncotarget.20972. eCollection 2017 Oct 20. PubMed PMID: 29152088; PubMed Central PMCID: PMC5675640. Liao X, Lochhead P, Nishihara R, Morikawa T, Kuchiba A, Yamauchi M, Imamura Y, Qian ZR, Baba Y, Shima K, Sun R, Nosho K, Meyerhardt JA, Giovannucci E, Fuchs CS, Chan AT, Ogino S. Aspirin use, tumor PIK3CA mutation, and colorectal-cancer survival. N Engl J Med. 2012 Oct 25;367(17):1596-606. doi: 10.1056/NEJMoa1207756. PubMed PMID: 23094721; PubMed Central PMCID: PMC3532946.
SAR260301	Thorpe LM, Yuzugullu H, Zhao JJ. PI3K in cancer: divergent roles of isoforms, modes of activation and therapeutic targeting. Nat Rev Cancer. 2015 Jan;15(1):7-24. doi: 10.1038/nrc3860. Review. PubMed PMID: 25533673; PubMed Central PMCID: PMC4384662.
AZD8186	Thorpe LM, Yuzugullu H, Zhao JJ. PI3K in cancer: divergent roles of isoforms, modes of activation and therapeutic targeting. Nat Rev Cancer. 2015 Jan;15(1):7-24. doi: 10.1038/nrc3860. Review. PubMed PMID: 25533673; PubMed Central PMCID: PMC4384662.
LORLATINIB	Yoda S, Lin JJ, Lawrence MS, Burke BJ, Friboulet L, Langenbucher A, Dardaei L, Prutisto-Chang K, Dagogo-Jack I, Timofeevski S, Hubbeling H, Gainor JF, Ferris LA, Riley AK, Kattermann KE, Timonina D, Heist RS, Iafrate AJ, Benes CH, Lennerz JK, Mino-Kenudson M, Engelman JA, Johnson TW, Hata AN, Shaw AT. Sequential ALK Inhibitors Can Select for Lorlatinib-Resistant Compound ALK Mutations in ALK-Positive Lung Cancer. Cancer Discov. 2018 Jun;8(6):714-729. doi: 10.1158/2159-8290.CD-17-1256. Epub 2018 Apr 12. PubMed PMID: 29650534; PubMed Central PMCID: PMC5984716. Okada K, Araki M, Sakashita T, Ma B, Kanada R, Yanagitani N, Horiike A, Koike S, Oh-Hara T, Watanabe K, Tamai K, Maemondo M, Nishio M, Ishikawa T, Okuno Y, Fujita N, Katayama R. Prediction of ALK mutations mediating ALK-TKIs resistance and drug re-purposing to overcome the resistance. EBioMedicine. 2019 Mar;41:105-119. doi: 10.1016/j.ebiom.2019.01.019. Epub 2019 Jan 17. PubMed PMID: 30662002; PubMed Central PMCID: PMC6441848. Guan J, Tucker ER, Wan H, Chand D, Danielson LS, Ruuth K, El Wakil A, Witek B, Jamin Y, Umapathy G, Robinson SP, Johnson TW, Smeal T, Martinsson T, Chesler L, Palmer RH, Hallberg B. The ALK inhibitor PF-06463922 is effective as a single agent in neuroblastoma driven by expression of ALK and MYCN. Dis Model Mech. 2016 Sep 1;9(9):941-52. doi: 10.1242/dmm.024448. Epub 2016 Jul 7. PubMed PMID: 27483357; PubMed Central PMCID: PMC5047689.

Einsiedlerstrasse 23, 8834 Schindellegi, SWITZERLAND
E-mail: info@realtimeoncology.com **Web:** www.realtimeoncology.com

HATÓANYAG NEVE	REFERENCIA
	Johnson TW, Richardson PF, Bailey S, Brooun A, Burke BJ, Collins MR, Cui JJ, Deal JG, Deng YL, Dinh D, Engstrom LD, He M, Hoffman J, Hoffman RL, Huang Q, Kania RS, Kath JC, Lam H, Lam JL, Le PT, Lingardo L, Liu W, McTigue M, Palmer CL, Sach NW, Smeal T, Smith GL, Stewart AE, Timofeevski S, Zhu H, Zhu J, Zou HY, Edwards MP. Discovery of (10R)-7-amino-12-fluoro-2,10,16-trimethyl-15-oxo-10,15,16,17-tetrahydro-2H-8,4-(m etheno)pyrazolo[4,3-h][2,5,11]-benzoxadiazacyclotetradecine-3-carbonitrile (PF-06463922), a macrocyclic inhibitor of anaplastic lymphoma kinase (ALK) and c-ros oncogene 1 (ROS1) with preclinical brain exposure and broad-spectrum potency against ALK-resistant mutations. J Med Chem. 2014 Jun 12;57(11):4720-44. doi: 10.1021/jm500261q. Epub 2014 Jun 3. PubMed PMID: 24819116. Mologni L, Ceccon M, Pirola A, Chiriano G, Piazza R, Scapozza L, Gambacorti-Passerini C. NPM/ALK mutants resistant to ASP3026 display variable sensitivity to alternative ALK inhibitors but succumb to the novel compound PF-06463922. Oncotarget. 2015 Mar 20;6(8):5720-34. PubMed PMID: 25749034; PubMed Central PMCID: PMC4467397.
REPOTRECTINIB	O'donohue T et al. TPX-0005 (Repotrectinib), a next-generation ALK/ROS1/NTRK1–3 inhibitor, has potent antiproliferative and anti-tumor activity as monotherapy and in combination with chemotherapy in neuroblastoma cell lines and pediatric patient derived xenograft models. VOLUME 138, SUPPLEMENT 2, S16-S17, OCTOBER 01, 2020
ALECTINIB	Zdzalik D, Dymek B, Grygielewicz P, Gunerka P, Bujak A, Lamparska-Przybysz M, Wieczorek M, Dzwonek K. Activating mutations in ALK kinase domain confer resistance to structurally unrelated ALK inhibitors in NPM-ALK-positive anaplastic large-cell lymphoma. J Cancer Res Clin Oncol. 2014 Apr;140(4):589-98. doi: 10.1007/s00432-014-1589-3. Epub 2014 Feb 8. PubMed PMID: 24509625; PubMed Central PMCID: PMC3949014. Fontana D, Ceccon M, Gambacorti-Passerini C, Mologni L. Activity of second-generation ALK inhibitors against crizotinib-resistant mutants in an NPM-ALK model compared to EML4-ALK. Cancer Med. 2015 Jul;4(7):953-65. doi: 10.1002/cam4.413. Epub 2015 Feb 26. PubMed PMID: 25727400; PubMed Central PMCID: PMC4529334. Sakamoto H, Tsukaguchi T, Hiroshima S, Kodama T, Kobayashi T, Fukami TA, Oikawa N, Tsukuda T, Ishii N, Aoki Y. CH5424802, a selective ALK inhibitor capable of blocking the resistant gatekeeper mutant. Cancer Cell. 2011 May 17;19(5):679-90. doi: 10.1016/j.ccr.2011.04.004. PubMed PMID: 21575866. Gadgeel SM, Gandhi L, Riely GJ, Chiappori AA, West HL, Azada MC, Morcos PN, Lee RM, Garcia L, Yu L, Boisserie F, Di Laurenzio L, Golding S, Sato J, Yokoyama S, Tanaka T, Ou SH. Safety and activity of alectinib against systemic disease and brain metastases in patients with crizotinib-resistant ALK-rearranged non-small-cell lung cancer (AF-002JG): results from the dose-finding portion of a phase 1/2 study. Lancet Oncol. 2014 Sep;15(10):1119-28. doi: 10.1016/S1470-2045(14)70362-6. Epub 2014 Aug 18. PubMed PMID: 25153538. Lu J, Guan S, Zhao Y, Yu Y, Woodfield SE, Zhang H, Yang KL, Bieerkehazhi S, Qi L, Li X, Gu J, Xu X, Jin J, Muscal JA, Yang T, Xu GT, Yang J. The second-generation ALK inhibitor alectinib effectively induces apoptosis in human neuroblastoma cells and inhibits tumor growth in a TH-MYCN transgenic neuroblastoma mouse model. Cancer Lett. 2017 Aug 1;400:61-68. doi: 10.1016/j.canlet.2017.04.022. Epub 2017 Apr 26. PubMed PMID: 28455243; PubMed Central PMCID: PMC5502736.
BRIGATINIB	Fontana D, Ceccon M, Gambacorti-Passerini C, Mologni L. Activity of second-generation ALK inhibitors against crizotinib-resistant mutants in an NPM-ALK model compared to EML4-ALK. Cancer Med. 2015 Jul;4(7):953-65. doi: 10.1002/cam4.413. Epub 2015 Feb 26. PubMed PMID: 25727400; PubMed Central PMCID: PMC4529334. Katayama R, Khan TM, Benes C, Lifshits E, Ebi H, Rivera VM, Shakespeare WC, Iafrate AJ, Engelman JA, Shaw AT. Therapeutic strategies to overcome crizotinib resistance in non-small cell lung cancers harboring the fusion oncogene EML4-ALK. Proc Natl Acad Sci U S A. 2011 May 3;108(18):7535-40. doi: 10.1073/pnas.1019559108. Epub 2011 Apr 18. PubMed PMID: 21502504; PubMed Central PMCID: PMC3088626. Zhang S, Anjum R, Squillace R, Nadworny S, Zhou T, Keats J, Ning Y, Wardwell SD, Miller D, Song Y, Eichinger L, Moran L, Huang WS, Liu S, Zou D, Wang Y, Mohemmad Q, Jang HG, Ye E, Narasimhan N, Wang F, Miret J, Zhu X, Clackson T, Dalgarno D, Shakespeare WC, Rivera VM. The Potent ALK Inhibitor Brigatinib (AP26113) Overcomes Mechanisms of Resistance to First- and Second-Generation ALK Inhibitors in Preclinical Models. Clin Cancer Res. 2016 Nov 15;22(22):5527-5538. doi: 10.1158/1078-0432.CCR-16-0569. Epub 2016 Oct 25. PubMed PMID: 27780853. Lin JJ, Zhu VW, Schoenfeld AJ, Yeap BY, Saxena A, Ferris LA, Dagogo-Jack I, Farago AF, Taber A, Traynor A, Menon S, Gainor JF, Lennerz JK, Plodkowski AJ, Digumarthy SR, Ou SI, Shaw AT, Riely GJ. Brigatinib in Patients With Alectinib-Refractory ALK-Positive NSCLC. J Thorac Oncol. 2018 Oct;13(10):1530-1538. doi: 10.1016/j.jtho.2018.06.005. Epub 2018 Jun 20. PubMed PMID: 29935304; PubMed Central PMCID: PMC6341982. Siaw JT, Wan H, Pfeifer K, Rivera VM, Guan J, Palmer RH, Hallberg B. Brigatinib, an anaplastic lymphoma kinase inhibitor, abrogates activity and growth in ALK-positive neuroblastoma cells, Drosophila and mice. Oncotarget. 2016 May 17;7(20):29011-22. doi: 10.18632/oncotarget.8508. PubMed PMID: 27049722; PubMed Central PMCID: PMC5045374.
TAE684	Zdzalik D, Dymek B, Grygielewicz P, Gunerka P, Bujak A, Lamparska-Przybysz M, Wieczorek M, Dzwonek K. Activating mutations in ALK kinase domain confer resistance to structurally unrelated ALK inhibitors in NPM-ALK-positive anaplastic large-cell lymphoma. J Cancer Res Clin Oncol. 2014 Apr;140(4):589-98. doi: 10.1007/s00432-014-1589-3. Epub 2014 Feb 8. PubMed PMID: 24509625; PubMed Central PMCID: PMC3949014. Sasaki T, Okuda K, Zheng W, Butrynski J, Capelletti M, Wang L, Gray NS, Wilner K, Christensen JG, Demetri G, Shapiro GI, Rodig SJ, Eck MJ, Jänne PA. The neuroblastoma-associated F1174L ALK mutation causes resistance to an ALK kinase inhibitor in ALK-translocated cancers. Cancer Res. 2010 Dec 15;70(24):10038-43. doi: 10.1158/0008-5472.CAN-10-2956. Epub 2010 Oct 28. PubMed PMID: 21030459; PubMed Central PMCID: PMC3045808.
CEP-37440	

Einsiedlerstrasse 23, 8834 Schindellegi, SWITZERLAND
E-mail: info@realtimeoncology.com **Web:** www.realtimeoncology.com

HATÓANYAG NEVE	REFERENCIA
	Iragavarapu C, Mustafa M, Akinleye A, Furqan M, Mittal V, Cang S, Liu D. Novel ALK inhibitors in clinical use and development. J Hematol Oncol. 2015 Feb 27;8:17. doi: 10.1186/s13045-015-0122-8. Review. PubMed PMID: 25888090; PubMed Central PMCID: PMC4349797.
ENSARTINIB	Lovly CM, Heuckmann JM, de Stanchina E, Chen H, Thomas RK, Liang C, Pao W. Insights into ALK-driven cancers revealed through development of novel ALK tyrosine kinase inhibitors. Cancer Res. 2011 Jul 15;71(14):4920-31. doi: 10.1158/0008-5472.CAN-10-3879. Epub 2011 May 25. PubMed PMID: 21613408; PubMed Central PMCID: PMC3138877.
GSK1838705A	Sabbatini P, Korenchuk S, Rowand JL, Groy A, Liu Q, Leperi D, Atkins C, Dumble M, Yang J, Anderson K, Kruger RG, Gontarek RR, Maksimchuk KR, Suravajjala S, Lapierre RR, Shotwell JB, Wilson JW, Chamberlain SD, Rabindran SK, Kumar R. GSK1838705A inhibits the insulin-like growth factor-1 receptor and anaplastic lymphoma kinase and shows antitumor activity in experimental models of human cancers. Mol Cancer Ther. 2009 Oct;8(10):2811-20. doi: 10.1158/1535-7163.MCT-09-0423. PubMed PMID: 19825801.
IMATINIB	Saini M, Jha AN, Abrari A, Ali S. Expression of proto-oncogene KIT is up-regulated in subset of human meningiomas. BMC Cancer. 2012 Jun 6;12:212. doi: 10.1186/1471-2407-12-212. PubMed PMID: 22672386; PubMed Central PMCID: PMC3443037. Malavaki CJ, Roussidis AE, Gialeli C, Kletsas D, Tsegenidis T, Theocharis AD, Tzanakakis GN, Karamanos NK. Imatinib as a key inhibitor of the platelet-derived growth factor receptor mediated expression of cell surface heparan sulfate proteoglycans and functional properties of breast cancer cells. FEBS J. 2013 May;280(10):2477-89. doi: 10.1111/febs.12163. Epub 2013 Feb 27. PubMed PMID: 23374223. Olshen A, Tang M, Cortes J, Gonen M, Hughes T, Branford S, Quintás-Cardama A, Michor F. Dynamics of chronic myeloid leukemia response to dasatinib, nilotinib, and high-dose imatinib. Haematologica. 2014 Sep 12. pii: haematol.2013.085977. [Epub ahead of print] PubMed PMID: 25216683. Redaelli S, Piazza R, Rostagno R, Magistroni V, Perini P, Marega M, Gambacorti-Passerini C, Boschelli F. Activity of bosutinib, dasatinib, and nilotinib against 18 imatinib-resistant BCR/ABL mutants. J Clin Oncol. 2009 Jan 20;27(3):469-71. doi: 10.1200/JCO.2008.19.8853. Epub 2008 Dec 15. PubMed PMID: 19075254. Cho J, Kim SY, Kim YJ, Sim MH, Kim ST, Kim NKD, Kim K, Park W, Kim JH, Jang KT, Lee J. Emergence of CTNNB1 mutation at acquired resistance to KIT inhibitor in metastatic melanoma. Clin Transl Oncol. 2017 Oct;19(10):1247-1252. doi: 10.1007/s12094-017-1662-x. Epub 2017 Apr 18. PubMed PMID: 28421416.
E7386	YAMADA, Kazuhiko, et al. E7386: First-in-class orally active CBP/beta-catenin modulator as an anticancer agent. 2017.
PRI-724	Lenz HJ, Kahn M. Safely targeting cancer stem cells via selective catenin coactivator antagonism. Cancer Sci. 2014 Sep;105(9):1087-92. doi: 10.1111/cas.12471. Epub 2014 Sep 6. PubMed PMID: 24975284; PubMed Central PMCID: PMC4175086.
AZD1390	Durant ST, Zheng L, Wang Y, Chen K, Zhang L, Zhang T, Yang Z, Riches L, Trinidad AG, Fok JHL, Hunt T, Pike KG, Wilson J, Smith A, Colclough N, Reddy VP, Sykes A, Janefeldt A, Johnström P, Varnäs K, Takano A, Ling S, Orme J, Stott J, Roberts C, Barrett I, Jones G, Roudier M, Pierce A, Allen J, Kahn J, Sule A, Karlin J, Cronin A, Chapman M, Valerie K, Illingworth R, Pass M. The brain-penetrant clinical ATM inhibitor AZD1390 radiosensitizes and improves survival of preclinical brain tumor models. Sci Adv. 2018 06;4(6):eaat1719. doi: 10.1126/sciadv.aat1719. Epub 2018 Nov 20. PubMed PMID: 29938225; PubMed Central PMCID: PMC6010333.
KU 55933	Li Y, Yang DQ. The ATM inhibitor KU-55933 suppresses cell proliferation and induces apoptosis by blocking Akt in cancer cells with overactivated Akt. Mol Cancer Ther. 2010 Jan;9(1):113-25. doi: 10.1158/1535-7163.MCT-08-1189. Epub 2010 Jan 6. PubMed PMID: 20053781.
PONATINIB	Gozgit JM, Squillace RM, Wongchenko MJ, Miller D, Wardwell S, Mohemmad Q, Narasimhan NI, Wang F, Clackson T, Rivera VM. Combined targeting of FGFR2 and mTOR by ponatinib and ridaforolimus results in synergistic antitumor activity in FGFR2 mutant endometrial cancer models. Cancer Chemother Pharmacol. 2013 May;71(5):1315-23. doi: 10.1007/s00280-013-2131-z. Epub 2013 Mar 7. PubMed PMID: 23468082. Sadovnik I, Lierman E, Peter B, Herrmann H, Suppan V, Stefanzl G, Haas O, Lion T, Pickl W, Cools J, Vandenberghe P, Valent P. Identification of Ponatinib as a potent inhibitor of growth, migration, and activation of neoplastic eosinophils carrying FIP1L1-PDGFRA. Exp Hematol. 2014 Apr;42(4):282-293.e4. doi: 10.1016/j.exphem.2013.12.007. Epub 2014 Jan 6. PubMed PMID: 24407160. Borad MJ, Champion MD, Egan JB, Liang WS, Fonseca R, Bryce AH, McCullough AE, Barrett MT, Hunt K, Patel MD, Young SW, Collins JM, Silva AC, Condjella RM, Block M, McWilliams RR, Lazaridis KN, Klee EW, Bible KC, Harris P, Oliver GR, Bhavsar JD, Nair AA, Middha S, Asmann Y, Kocher JP, Schahl K, Kipp BR, Barr Fritcher EG, Baker A, Aldrich J, Kurdoglu A, Izatt T, Christoforides A, Cherni I, Nasser S, Reiman R, Phillips L, McDonald J, Adkins J, Mastrian SD, Placek P, Watanabe AT, Lobello J, Han H, Von Hoff D, Craig DW, Stewart AK, Carpten JD. Integrated genomic characterization reveals novel, therapeutically relevant drug targets in FGFR and EGFR pathways in sporadic intrahepatic cholangiocarcinoma. PLoS Genet. 2014 Feb 13;10(2):e1004135. doi: 10.1371/journal.pgen.1004135. eCollection 2014 Feb. PubMed PMID: 24550739; PubMed Central PMCID: PMC3923676. O'Hare T, Shakespeare WC, Zhu X, Eide CA, Rivera VM, Wang F, Adrian LT, Zhou T, Huang WS, Xu Q, Metcalf CA 3rd, Tyner JW, Loriaux MM, Corbin AS, Wardwell S, Ning Y, Keats JA, Wang Y, Sundaramoorthi R, Thomas M, Zhou D, Snodgrass J, Commodore L, Sawyer TK, Dalgarno DC, Deininger MW, Druker BJ, Clackson T. AP24534, a pan-BCR-ABL inhibitor for chronic myeloid leukemia, potently inhibits the T315I mutant and overcomes mutation-based resistance. Cancer Cell. 2009 Nov 6;16(5):401-12. doi: 10.1016/j.ccr.2009.09.028. PubMed PMID: 19878872; PubMed Central PMCID: PMC2804470.

Einsiedlerstrasse 23, 8834 Schindellegi, SWITZERLAND
E-mail: info@realtimeoncology.com **Web:** www.realtimeoncology.com

HATÓANYAG NEVE	REFERENCIA
	Gibbons DL, Pricl S, Posocco P, Laurini E, Fermeglia M, Sun H, Talpaz M, Donato N, Quintás-Cardama A. Molecular dynamics reveal BCR-ABL1 polymutants as a unique mechanism of resistance to PAN-BCR-ABL1 kinase inhibitor therapy. Proc Natl Acad Sci U S A. 2014 Mar 4;111(9):3550-5. doi: 10.1073/pnas.1321173111. Epub 2014 Feb 18. PubMed PMID: 24550512; PubMed Central PMCID: PMC3948238.
NINTEDANIB	Hilberg F, Roth GJ, Krssak M, Kautschitsch S, Sommergruber W, Tontsch-Grunt U, Garin-Chesa P, Bader G, Zoephel A, Quant J, Heckel A, Rettig WJ. BIBF 1120: triple angiokinase inhibitor with sustained receptor blockade and good antitumor efficacy. Cancer Res. 2008 Jun 15;68(12):4774-82. doi: 10.1158/0008-5472.CAN-07-6307. PubMed PMID: 18559524. Capdevila J, Carrato A, Tabernero J, Grande E. What could Nintedanib (BIBF 1120), a triple inhibitor of VEGFR, PDGFR, and FGFR, add to the current treatment options for patients with metastatic colorectal cancer? Crit Rev Oncol Hematol. 2014 May 14. pii: S1040-8428(14)00083-3. doi: 10.1016/j.critrevonc.2014.05.004. [Epub ahead of print] Review. PubMed PMID: 24924525. Mulligan LM. RET revisited: expanding the oncogenic portfolio. Nat Rev Cancer. 2014 Mar;14(3):173-86. doi: 10.1038/nrc3680. Review. PubMed PMID: 24561444. Kim Y, Lee SJ, Lee JY, Lee SH, Sun JM, Park K, An HJ, Cho JY, Kang EJ, Lee HY, Kim J, Keam B, Kim HR, Lee KE, Choi MY, Lee KH, Ahn MJ. Clinical trial of nintedanib in patients with recurrent or metastatic salivary gland cancer of the head and neck: A multicenter phase 2 study (Korean Cancer Study Group HN14-01). Cancer. 2017 Jun 1;123(11):1958-1964. doi: 10.1002/cncr.30537. Epub 2017 Jan 19. PubMed PMID: 28102887. du Bois A, Kristensen G, Ray-Coquard I, Reuss A, Pignata S, Colombo N, Denison U, Vergote I, Del Campo JM, Ottevanger P, Heubner M, Minarik T, Sevin E, de Gregorio N, Bidziński M, Pfisterer J, Malander S, Hilpert F, Mirza MR, Scambia G, Meier W, Nicoletto MO, Bjørge L, Lortholary A, Sailer MO, Merger M, Harter P; AGO Study Group led Gynecologic Cancer Intergroup/European Network of Gynaecologic Oncology Trials Groups Intergroup Consortium. Standard first-line chemotherapy with or without nintedanib for advanced ovarian cancer (AGO-OVAR 12): a randomised, double-blind, placebo-controlled phase 3 trial. Lancet Oncol. 2016 Jan;17(1):78-89. doi: 10.1016/S1470-2045(15)00366-6. Epub 2015 Nov 16. PubMed PMID: 26590673.
SUNITINIB	Schueneman AJ, Himmelfarb E, Geng L, Tan J, Donnelly E, Mendel D, McMahon G, Hallahan DE. SU11248 maintenance therapy prevents tumor regrowth after fractionated irradiation of murine tumor models. Cancer Res. 2003 Jul 15;63(14):4009-16. PubMed PMID: 12873999. Broutin S, Ameur N, Lacroix L, Robert T, Petit B, Oumata N, Talbot M, Caillou B, Schlumberger M, Dupuy C, Bidart JM. Identification of soluble candidate biomarkers of therapeutic response to sunitinib in medullary thyroid carcinoma in preclinical models. Clin Cancer Res. 2011 Apr 1;17(7):2044-54. doi: 10.1158/1078-0432.CCR-10-2041. Epub 2011 Feb 15. PubMed PMID: 21325074. Zimmermann K, Schmittel A, Steiner U, Asemissen AM, Knoedler M, Thiel E, Miller K, Keilholz U. Sunitinib treatment for patients with advanced clear-cell renal-cell carcinoma after progression on sorafenib. Oncology. 2009;76(5):350-4. doi: 10.1159/000209961. Epub 2009 Mar 24. PubMed PMID: 19321976. O'Farrell AM, Foran JM, Fiedler W, Serve H, Paquette RL, Cooper MA, Yuen HA, Louie SG, Kim H, Nicholas S, Heinrich MC, Berdel WE, Bello C, Jacobs M, Scigalla P, Manning WC, Kelsey S, Cherrington JM. An innovative phase I clinical study demonstrates inhibition of FLT3 phosphorylation by SU11248 in acute myeloid leukemia patients. Clin Cancer Res. 2003 Nov 15;9(15):5465-76. PubMed PMID: 14654525. Roskoski R Jr. Sunitinib: a VEGF and PDGF receptor protein kinase and angiogenesis inhibitor. Biochem Biophys Res Commun. 2007 May 4;356(2):323-8. Epub 2007 Mar 7. PubMed PMID: 17367763.
LY3039478	EVEN, Caroline, et al. Notch pathway inhibition with LY3039478 in adenoid cystic carcinoma (ACC). 2017.
BMS-906024	Gavai AV, Quesnelle C, Norris D, Han WC, Gill P, Shan W, Balog A, Chen K, Tebben A, Rampulla R, Wu DR, Zhang Y, Mathur A, White R, Rose A, Wang H, Yang Z, Ranasinghe A, D'Arienzo C, Guarino V, Xiao L, Su C, Everlof G, Arora V, Shen DR, Cvijic ME, Menard K, Wen ML, Meredith J, Trainor G, Lombardo LJ, Olson R, Baran PS, Hunt JT, Vite GD, Fischer BS, Westhouse RA, Lee FY. Discovery of Clinical Candidate BMS-906024: A Potent Pan-Notch Inhibitor for the Treatment of Leukemia and Solid Tumors. ACS Med Chem Lett. 2015 May 14;6(5):523-7. doi: 10.1021/acsmedchemlett.5b00001. Epub 2015 Aug 11. PubMed PMID: 26005526; PubMed Central PMCID: PMC4434460. Morgan KM, Fischer BS, Lee FY, Shah JJ, Bertino JR, Rosenfeld J, Singh A, Khiabanian H, Pine SR. Gamma Secretase Inhibition by BMS-906024 Enhances Efficacy of Paclitaxel in Lung Adenocarcinoma. Mol Cancer Ther. 2017 Dec;16(12):2759-2769. doi: 10.1158/1535-7163.MCT-17-0439. Epub 2017 Aug 04. PubMed PMID: 28978720; PubMed Central PMCID: PMC5716926.
NIROGACESTAT	Wei P, Walls M, Qiu M, Ding R, Denlinger RH, Wong A, Tsaparikos K, Jani JP, Hosea N, Sands M, Randolph S, Smeal T. Evaluation of selective gamma-secretase inhibitor PF-03084014 for its antitumor efficacy and gastrointestinal safety to guide optimal clinical trial design. Mol Cancer Ther. 2010 Jun;9(6):1618-28. doi: 10.1158/1535-7163.MCT-10-0034. Epub 2010 Jun 8. PubMed PMID: 20530712.
DEMCIZUMAB	Smith DC, Eisenberg PD, Manikhas GM, Chugh R, Gubens MA, Stagg RJ, Kapoun AM, Xu L, Dupont J, Sikic BI. A Phase 1 Dose Escalation and Expansion Study of the Anti-Cancer Stem Cell Agent Demcizumab (Anti-DLL4) in Patients with Previously Treated Solid Tumors. Clin Cancer Res. 2014 Oct 16. pii: clincanres.1373.2014. [Epub ahead of print] PubMed PMID: 25324140.
MK-0752	Schott AF, Landis MD, Dontu G, Griffith KA, Layman RM, Krop I, Paskett LA, Wong H, Dobrolecki LE, Lewis MT, Froehlich AM, Paranilam J, Hayes DF, Wicha MS, Chang JC. Preclinical and clinical studies of gamma secretase inhibitors with docetaxel on human breast tumors. Clin Cancer Res. 2013 Mar 15;19(6):1512-24. doi: 10.1158/1078-0432.CCR-11-3326. Epub 2013 Jan 22. PubMed PMID: 23340294; PubMed Central PMCID: PMC3602220.
AMG 397	

Einsiedlerstrasse 23, 8834 Schindellegi, SWITZERLAND
E-mail: info@realtimeoncology.com **Web:** www.realtimeoncology.com

HATÓANYAG NEVE	REFERENCIA
	WEI, AndrewH, et al. Targeting MCL-1 in hematologic malignancies: Rationale and progress. Blood Reviews, 2020, 100672.
S64315	WEI, AndrewH, et al. Targeting MCL-1 in hematologic malignancies: Rationale and progress. Blood Reviews, 2020, 100672.
AZD5991	WEI, AndrewH, et al. Targeting MCL-1 in hematologic malignancies: Rationale and progress. Blood Reviews, 2020, 100672. Tron AE, Belmonte MA, Adam A, Aquila BM, Boise LH, Chiarparin E, Cidado J, Embrey KJ, Gangl E, Gibbons FD, Gregory GP, Hargreaves D, Hendricks JA, Johannes JW, Johnstone RW, Kazmirski SL, Kettle JG, Lamb ML, Matulis SM, Nooka AK, Packer MJ, Peng B, Rawlins PB, Robbins DW, Schuller AG, Su N, Yang W, Ye Q, Zheng X, Secrist JP, Clark EA, Wilson DM, Fawell SE, Hird AW. Discovery of Mcl-1-specific inhibitor AZD5991 and preclinical activity in multiple myeloma and acute myeloid leukemia. Nat Commun. 2018 Dec 17;9(1):5341. doi: 10.1038/s41467-018-07551-w. PubMed PMID: 30559424; PubMed Central PMCID: PMC6297231.
AMG 176	WEI, AndrewH, et al. Targeting MCL-1 in hematologic malignancies: Rationale and progress. Blood Reviews, 2020, 100672.
RUXOLITINIB	Verstovsek S, Passamonti F, Rambaldi A, Barosi G, Rosen PJ, Rumi E, Gattoni E, Pieri L, Guglielmelli P, Elena C, He S, Contel N, Mookerjee B, Sandor V, Cazzola M, Kantarjian HM, Barbui T, Vannucchi AM. A phase 2 study of ruxolitinib, an oral JAK1 and JAK2 Inhibitor, in patients with advanced polycythemia vera who are refractory or intolerant to hydroxyurea. Cancer. 2014 Feb 15;120(4):513-20. PubMed PMID: 24258498; PubMed Central PMCID: PMC4231215. Furumoto Y, Gadina M. The arrival of JAK inhibitors: advancing the treatment of immune and hematologic disorders. BioDrugs. 2013 Oct;27(5):431-8. doi: 10.1007/s40259-013-0040-7. Review. PubMed PMID: 23743669; PubMed Central PMCID: PMC3778139. Rumi E, Milosevic JD, Casetti I, Dambruoso I, Pietra D, Boveri E, Boni M, Bernasconi P, Passamonti F, Kralovics R, Cazzola M. Efficacy of ruxolitinib in chronic eosinophilic leukemia associated with a PCM1-JAK2 fusion gene. J Clin Oncol. 2013 Jun 10;31(17):e269-71. doi: 10.1200/JCO.2012.46.4370. Epub 2013 Apr 29. PubMed PMID: 23630205. An HJ, Choi EK, Kim JS, Hong SW, Moon JH, Shin JS, Ha SH, Kim KP, Hong YS, Lee JL, Choi EK, Lee JS, Jin DH, Kim TW. INCB018424 induces apoptotic cell death through the suppression of pJAK1 in human colon cancer cells. Neoplasma. 2013 Sep 20. doi: 10.4149/neo_2014_009. [Epub ahead of print] PubMed PMID: 24050550. Loh ML, Tasian SK, Rabin KR, Brown P, Magoon D, Reid JM, Chen X, Ahern CH, Weigel BJ, Blaney SM. A phase 1 dosing study of ruxolitinib in children with relapsed or refractory solid tumors, leukemias, or myeloproliferative neoplasms: A Children's Oncology Group phase 1 consortium study (ADVL1011). Pediatr Blood Cancer. 2015 Oct;62 (10):1717-24. doi: 10.1002/pbc.25575. Epub 2015 May 13. PubMed PMID: 25976292; PubMed Central PMCID: PMC4546537.
MK-2461	Katz JD, Jewell JP, Guerin DJ, Lim J, Dinsmore CJ, Deshmukh SV, Pan BS, Marshall CG, Lu W, Altman MD, Dahlberg WK, Davis L, Falcone D, Gabarda AE, Hang G, Hatch H, Holmes R, Kunii K, Lumb KJ, Lutterbach B, Mathvink R, Nazef N, Patel SB, Qu X, Reilly JF, Rickert KW, Rosenstein C, Soisson SM, Spencer KB, Szewczak AA, Walker D, Wang W, Young J, Zeng Q. Discovery of a 5H-benzo[4,5]cyclohepta[1,2-b]pyridin-5-one (MK-2461) inhibitor of c-Met kinase for the treatment of cancer. J Med Chem. 2011 Jun 23;54(12):4092-108. doi: 10.1021/jm200112k. Epub 2011 May 24. PubMed PMID: 21608528. Inoue K, Ohtsuka H, Tachikawa M, Motoi F, Shijo M, Douchi D, Kawasaki S, Kawaguchi K, Masuda K, Fukase K, Naitoh T, Katayose Y, Egawa S, Unno M, Terasaki T. MK2461, a Multitargeted Kinase Inhibitor, Suppresses the Progression of Pancreatic Cancer by Disrupting the Interaction Between Pancreatic Cancer Cells and Stellate Cells. Pancreas. 2017 Apr;46(4):557-566. doi: 10.1097/MPA.0000000000000778. PubMed PMID: 28196027.
IDELALISIB	Thorpe LM, Yuzugullu H, Zhao JJ. PI3K in cancer: divergent roles of isoforms, modes of activation and therapeutic targeting. Nat Rev Cancer. 2015 Jan;15(1):7-24. doi: 10.1038/nrc3860. Review. PubMed PMID: 25533673; PubMed Central PMCID: PMC4384662. Bleckmann A, Dierks S, Schildhaus HU, Hellige N, Bacher U, Trümper L, Wulf G. Treatment response to idelalisib in a patient with immunodeficiency-associated Burkitt lymphoma harboring a PIK3CA H1047R mutation. Ann Hematol. 2021 Jan;100(1):277-279. doi: 10.1007/s00277-020-03974-y. Epub 2020 Feb 20. PubMed PMID: 32193631; PubMed Central PMCID: PMC7782442. Tasian SK, Casas JA, Posocco D, Gandre-Babbe S, Gagne AL, Liang G, Loh ML, Weiss MJ, French DL, Chou ST. Mutation-specific signaling profiles and kinase inhibitor sensitivities of juvenile myelomonocytic leukemia revealed by induced pluripotent stem cells. Leukemia. 2018 Jun 8. doi: 10.1038/s41375-018-0169-y. [Epub ahead of print] PubMed PMID: 29884903. Jones JA, Robak T, Brown JR, Awan FT, Badoux X, Coutre S, Loscertales J, Taylor K, Vandenberghe E, Wach M, Wagner-Johnston N, Ysebaert L, Dreiling L, Dubowy R, Xing G, Flinn IW, Owen C. Efficacy and safety of idelalisib in combination with ofatumumab for previously treated chronic lymphocytic leukaemia: an open-label, randomised phase 3 trial. Lancet Haematol. 2017 Mar;4(3):e114-e126. doi: 10.1016/S2352-3026(17)30019-4. PubMed PMID: 28257752. Miller BW, Przepiorka D, de Claro RA, Lee K, Nie L, Simpson N, Gudi R, Saber H, Shord S, Bullock J, Marathe D, Mehrotra N, Hsieh LS, Ghosh D, Brown J, Kane RC, Justice R, Kaminskas E, Farrell AT, Pazdur R. FDA approval: idelalisib monotherapy for the treatment of patients with follicular lymphoma and small lymphocytic lymphoma. Clin Cancer Res. 2015 Apr 1;21(7):1525-9. doi: 10.1158/1078-0432.CCR-14-2522. Epub 2015 Feb 2. PubMed PMID: 25645861.
ZOTIRACICLIB	

Einsiedlerstrasse 23, 8834 Schindellegi, SWITZERLAND
E-mail: info@realtimeoncology.com **Web:** www.realtimeoncology.com

HATÓANYAG NEVE	REFERENCIA
	Goh KC, Novotny-Diermayr V, Hart S, Ong LC, Loh YK, Cheong A, Tan YC, Hu C, Jayaraman R, William AD, Sun ET, Dymock BW, Ong KH, Ethirajulu K, Burrows F, Wood JM. TG02, a novel oral multi-kinase inhibitor of CDKs, JAK2 and FLT3 with potent anti-leukemic properties. Leukemia. 2012 Feb;26(2):236-43. doi: 10.1038/leu.2011.218. Epub 2011 Aug 23. PubMed PMID: 21860433.
PIMASERTIB	Ryan MB, Der CJ, Wang-Gillam A, Cox AD. Targeting RAS-mutant cancers: is ERK the key? Trends Cancer. 2015 Nov 1;1(3):183-198. PubMed PMID: 26858988; PubMed Central PMCID: PMC4743050. Martinelli E, Troiani T, D'Aiuto E, Morgillo F, Vitagliano D, Capasso A, Costantino S, Ciuffreda LP, Merolla F, Vecchione L, De Vriendt V, Tejpar S, Nappi A, Sforza V, Martini G, Berrino L, De Palma R, Ciardiello F. Antitumor activity of pimasertib, a selective MEK 1/2 inhibitor, in combination with PI3K/mTOR inhibitors or with multi-targeted kinase inhibitors in pimasertib-resistant human lung and colorectal cancer cells. Int J Cancer. 2013 Nov;133(9):2089-101. doi: 10.1002/ijc.28236. Epub 2013 May 29. PubMed PMID: 23629727. Akinleye A, Furqan M, Mukhi N, Ravella P, Liu D. MEK and the inhibitors: from bench to bedside. J Hematol Oncol. 2013 Apr 12;6:27. doi: 10.1186/1756-8722-6-27. Review. PubMed PMID: 23587417; PubMed Central PMCID: PMC3626705. A. W. Tolcher, S. M. Mikulski, W. A. Messersmith, E. L. Kwak, D. Gibbon, J. Boylan, Z. X. Xu, M. DeMario and J. J. Whele. A phase I study of RO4929097, a novel gamma secretase inhibitor, in patients with advanced solid tumors. J Clin Oncol (Meeting Abstracts) May 2010 vol. 28 no. 15_suppl 2502.
BAY1895344	Lücking U, Wortmann L, Wengner AM, Lefranc J, Lienau P, Briem H, Siemeister G, Bömer U, Denner K, Schäfer M, Koppitz M, Eis K, Bartels F, Bader B, Bone W, Moosmayer D, Holton SJ, Eberspächer U, Grudzinska-Goebel J, Schatz C, Deeg G, Mumberg D, von Nussbaum F. Damage Incorporated: Discovery of the Potent, Highly Selective, Orally Available ATR Inhibitor BAY 1895344 with Favorable Pharmacokinetic Properties and Promising Efficacy in Monotherapy and in Combination Treatments in Preclinical Tumor Models. J Med Chem. 2020 Jul 09;63(13):7293-7325. doi: 10.1021/acs.jmedchem.0c00369. Epub 2020 Jul 28. PubMed PMID: 32502336.
PAZOPANIB	Sonpavde G, Hutson TE. Pazopanib: a novel multitargeted tyrosine kinase inhibitor. Curr Oncol Rep. 2007 Mar;9(2):115-9. Review. PubMed PMID: 17288876. Ganjoo KN, Villalobos VM, Kamaya A, Fisher GA, Butrynski JE, Morgan JA, Wagner AJ, D'Adamo D, McMillan A, Demetri GD, George S. A multicenter phase II study of pazopanib in patients with advanced gastrointestinal stromal tumors (GIST) following failure of at least imatinib and sunitinib. Ann Oncol. 2014 Jan;25(1):236-40. doi: 10.1093/annonc/mdt484. PubMed PMID: 24356634. Gupta S, Spiess PE. The prospects of pazopanib in advanced renal cell carcinoma. Ther Adv Urol. 2013 Oct;5(5):223-32. doi: 10.1177/1756287213495099. PubMed PMID: 24082917; PubMed Central PMCID: PMC3763778. Hashimoto A, Takada K, Takimoto R, Horiguchi H, Sato T, Iyama S, Murase K, Ono K, Tatekoshi A, Hayashi T, Miyanishi K, Sato Y, Kobune M, Hirayama Y, Kitamura H, Nakanishi K, Masumori N, Hasegawa T, Kato J. [Effective treatment of metastatic rhabdomyosarcoma with pazopanib]. Gan To Kagaku Ryoho. 2014 Aug;41(8):1041-4. Japanese. PubMed PMID: 25132042. Tamura A, Yamamoto N, Nino N, Ichikawa T, Nakatani N, Nakamura S, Saito A, Kozaki A, Kishimoto K, Ishida T, Yoshida M, Akasaka Y, Hasegawa D, Kosaka Y. Pazopanib maintenance therapy after tandem high-dose chemotherapy for disseminated Ewing sarcoma. Int Cancer Conf J. 2019 Jul;8(3):95-100. doi: 10.1007/s13691-019-00362-w. Epub 2019 Sep 14. PubMed PMID: 31218182; PubMed Central PMCID: PMC6545189.
LENVATINIB	Matsui J, Yamamoto Y, Funahashi Y, Tsuruoka A, Watanabe T, Wakabayashi T, Uenaka T, Asada M. E7080, a novel inhibitor that targets multiple kinases, has potent antitumor activities against stem cell factor producing human small cell lung cancer H146, based on angiogenesis inhibition. Int J Cancer. 2008 Feb 1;122(3):664-71. PubMed PMID: 17943726. Mulligan LM. RET revisited: expanding the oncogenic portfolio. Nat Rev Cancer. 2014 Mar;14(3):173-86. doi: 10.1038/nrc3680. Review. PubMed PMID: 24561444. Glen H, Mason S, Patel H, Macleod K, Brunton VG. E7080, a multi-targeted tyrosine kinase inhibitor suppresses tumor cell migration and invasion. BMC Cancer. 2011 Jul 22;11:309. doi: 10.1186/1471-2407-11-309. PubMed PMID: 21781317; PubMed Central PMCID: PMC3154179. Tohyama O, Matsui J, Kodama K, Hata-Sugi N, Kimura T, Okamoto K, Minoshima Y, Iwata M, Funahashi Y. Antitumor activity of lenvatinib (e7080): an angiogenesis inhibitor that targets multiple receptor tyrosine kinases in preclinical human thyroid cancer models. J Thyroid Res. 2014;2014:638747. doi: 10.1155/2014/638747. Epub 2014 Feb 10. PubMed PMID: 25295214; PubMed Central PMCID: PMC4177084. Schlumberger M, Tahara M, Wirth LJ, Robinson B, Brose MS, Elisei R, Habra MA, Newbold K, Shah MH, Hoff AO, Gianoukakis AG, Kiyota N, Taylor MH, Kim SB, Krzyzanowska MK, Dutcus CE, de las Heras B, Zhu J, Sherman SI. Lenvatinib versus placebo in radioiodine-refractory thyroid cancer. N Engl J Med. 2015 Feb 12;372(7):621-30. doi: 10.1056/NEJMoa1406470. PubMed PMID: 25671254.
MOMELOTINIB	Abubaker K, Luwor RB, Zhu H, McNally O, Quinn MA, Burns CJ, Thompson EW, Findlay JK, Ahmed N. Inhibition of the JAK2/STAT3 pathway in ovarian cancer results in the loss of cancer stem cell-like characteristics and a reduced tumor burden. BMC Cancer. 2014 May 6;14:317. doi: 10.1186/1471-2407-14-317. PubMed PMID: 24886434; PubMed Central PMCID: PMC4025194. Pardanani A, Laborde RR, Lasho TL, Finke C, Begna K, Al-Kali A, Hogan WJ, Litzow MR, Leontovich A, Kowalski M, Tefferi A. Safety and efficacy of CYT387, a JAK1 and JAK2 inhibitor, in myelofibrosis. Leukemia. 2013 Jun;27(6):1322-7. doi: 10.1038/leu.2013.71. Epub 2013 Mar 5. PubMed PMID: 23459451; PubMed Central PMCID: PMC3677140.

Einsiedlerstrasse 23, 8834 Schindellegi, SWITZERLAND
E-mail: info@realtimeoncology.com **Web:** www.realtimeoncology.com

HATÓANYAG NEVE	REFERENCIA
	Tasian SK, Casas JA, Posocco D, Gandre-Babbe S, Gagne AL, Liang G, Loh ML, Weiss MJ, French DL, Chou ST. Mutation-specific signaling profiles and kinase inhibitor sensitivities of juvenile myelomonocytic leukemia revealed by induced pluripotent stem cells. Leukemia. 2018 Jun 8. doi: 10.1038/s41375-018-0169-y. [Epub ahead of print] PubMed PMID: 29884903.
S49076	Clémenson C, Chargari C, Liu W, Mondini M, Ferté C, Burbridge MF, Cattan V, Jacquet-Bescond A, Deutsch E. The MET/AXL/FGFR Inhibitor S49076 Impairs Aurora B Activity and Improves the Antitumor Efficacy of Radiotherapy. Mol Cancer Ther. 2017 Oct;16(10):2107-2119. doi: 10.1158/1535-7163.MCT-17-0112. Epub 2017 Jun 15. PubMed PMID: 28619752. Burbridge MF, Bossard CJ, Saunier C, Fejes I, Bruno A, Léonce S, Ferry G, Da Violante G, Bouzom F, Cattan V, Jacquet-Bescond A, Comoglio PM, Lockhart BP, Boutin JA, Cordi A, Ortuno JC, Pierré A, Hickman JA, Cruzalegui FH, Depil S. S49076 is a novel kinase inhibitor of MET, AXL, and FGFR with strong preclinical activity alone and in association with bevacizumab. Mol Cancer Ther. 2013 Sep;12(9):1749-62. doi: 10.1158/1535-7163.MCT-13-0075. Epub 2013 Jun 26. PubMed PMID: 23804704.
	Burbridge MF, Bossard CJ, Saunier C, Fejes I, Bruno A, Léonce S, Ferry G, Da Violante G, Bouzom F, Cattan V, Jacquet-Bescond A, Comoglio PM, Lockhart BP, Boutin JA, Cordi A, Ortuno JC, Pierré A, Hickman JA, Cruzalegui FH, Depil S. S49076 is a novel kinase inhibitor of MET, AXL, and FGFR with strong preclinical activity alone and in association with bevacizumab. Mol Cancer Ther. 2013 Sep;12(9):1749-62. doi: 10.1158/1535-7163.MCT-13-0075. Epub 2013 Jun 26. PubMed PMID: 23804704.
BARICITINIB	Shi JG, Chen X, Lee F, Emm T, Scherle PA, Lo Y, Punwani N, Williams WV, Yeleswaram S. The Pharmacokinetics, Pharmacodynamics and Safety of Baricitinib, an Oral JAK 1/2 Inhibitor, in Healthy Volunteers. J Clin Pharmacol. 2014 Jun 26. doi: 10.1002/jcph.354. [Epub ahead of print] PubMed PMID: 24965573.
	Fridman JS, Scherle PA, Collins R, Burn TC, Li Y, Li J, Covington MB, Thomas B, Collier P, Favata MF, Wen X, Shi J, McGee R, Haley PJ, Shepard S, Rodgers JD, Yeleswaram S, Hollis G, Newton RC, Metcalf B, Friedman SM, Vaddi K. Selective inhibition of JAK1 and JAK2 is efficacious in rodent models of arthritis: preclinical characterization of INCB028050. J Immunol. 2010 May 1;184(9):5298-307. doi: 10.4049/jimmunol.0902819. Epub 2010 Apr 2. PubMed PMID: 20363976.
MASITINIB	Christiane R. Maroun1, Helene Ste-Croix1, Normand Beaulieu1, Claire Bonfils1, Marielle Fournel1, Isabelle Dupont1, Christian Lemoyne1, James Wand1, and Jeffrey M. Besterman1. Potent preclinical anti-tumor activity of MGCD265, an oral Met/VEGFR multitargeted kinase inhibitor in clinical development, in combination with taxanes. Proceedings of the 102nd Annual Meeting of the American Association for Cancer Research; 2011 Apr 2-6; Orlando, FL. Philadelphia (PA): AACR; Cancer Res 2011;71(8 Suppl):Abstract nr 3610. doi:10.1158/1538-7445.AM2011-3610.
	Dubreuil P, Letard S, Ciufolini M, Gros L, Humbert M, Castéran N, Borge L, Hajem B, Lermet A, Sippl W, Voisset E, Arock M, Auclair C, Leventhal PS, Mansfield CD, Moussy A, Hermine O. Masitinib (AB1010), a potent and selective tyrosine kinase inhibitor targeting KIT. PLoS One. 2009 Sep 30;4(9):e7258. doi: 10.1371/journal.pone.0007258. PubMed PMID: 19789626; PubMed Central PMCID: PMC2746281.
AT9283	Harry BL, Eckhardt SG, Jimeno A. JAK2 inhibition for the treatment of hematologic and solid malignancies. Expert Opin Investig Drugs. 2012 May;21(5):637-55. doi: 10.1517/13543784.2012.677432. Review. PubMed PMID: 22493978.
	Dawson MA, Curry JE, Barber K, Beer PA, Graham B, Lyons JF, Richardson CJ, Scott MA, Smyth T, Squires MS, Thompson NT, Green AR, Wallis NG. AT9283, a potent inhibitor of the Aurora kinases and Jak2, has therapeutic potential in myeloproliferative disorders. Br J Haematol. 2010 Jul;150(1):46-57. doi: 10.1111/j.1365-2141.2010.08175.x. Epub 2010 May 7. PubMed PMID: 20507304.
	Kimura S. AT-9283, a small-molecule multi-targeted kinase inhibitor for the potential treatment of cancer. Curr Opin Investig Drugs. 2010 Dec;11(12):1442-9. Review. PubMed PMID: 21154126.
SORAFENIB	Kim S, Yazici YD, Calzada G, Wang ZY, Younes MN, Jasser SA, El-Naggar AK, Myers JN. Sorafenib inhibits the angiogenesis and growth of orthotopic anaplastic thyroid carcinoma xenografts in nude mice. Mol Cancer Ther. 2007 Jun;6(6):1785-92. PubMed PMID: 17575107.
	Bellesoeur A, Carton E, Mir O, Groussin L, Blanchet B, Billemont B, Clerc J, Goldwasser F. Critical role of sorafenib exposure over time for its antitumor activity in thyroid cancer. Invest New Drugs. 2014 Jun;32(3):569-72. doi: 10.1007/s10637-013-0052-7. Epub 2014 Jan 8. PubMed PMID: 24399106.
	Jain L, Woo S, Gardner ER, Dahut WL, Kohn EC, Kummar S, Mould DR, Giaccone G, Yarchoan R, Venitz J, Figg WD. Population pharmacokinetic analysis of sorafenib in patients with solid tumours. Br J Clin Pharmacol. 2011 Aug;72 (2):294-305. doi: 10.1111/j.1365-2125.2011.03963.x. PubMed PMID: 21392074; PubMed Central PMCID: PMC3162659.
	Mulligan LM. RET revisited: expanding the oncogenic portfolio. Nat Rev Cancer. 2014 Mar;14(3):173-86. doi: 10.1038 /nrc3680. Review. PubMed PMID: 24561444.
	Wilhelm SM, Carter C, Tang L, Wilkie D, McNabola A, Rong H, Chen C, Zhang X, Vincent P, McHugh M, Cao Y, Shujath J, Gawlak S, Eveleigh D, Rowley B, Liu L, Adnane L, Lynch M, Auclair D, Taylor I, Gedrich R, Voznesensky A, Riedl B, Post LE, Bollag G, Trail PA. BAY 43-9006 exhibits broad spectrum oral antitumor activity and targets the RAF/MEK/ERK pathway and receptor tyrosine kinases involved in tumor progression and angiogenesis. Cancer Res. 2004 Oct 1;64(19):7099-109. PubMed PMID: 15466206.
BOSUTINIB	Creedon H, Brunton VG. Src kinase inhibitors: promising cancer therapeutics? Crit Rev Oncog. 2012;17(2):145-59. Review. PubMed PMID: 22471705.

Einsiedlerstrasse 23, 8834 Schindellegi, SWITZERLAND
E-mail: info@realtimeoncology.com **Web:** www.realtimeoncology.com

HATÓANYAG NEVE	REFERENCIA
	Rabbani SA, Valentino ML, Arakelian A, Ali S, Boschelli F. SKI-606 (Bosutinib) blocks prostate cancer invasion, growth, and metastasis in vitro and in vivo through regulation of genes involved in cancer growth and skeletal metastasis. Mol Cancer Ther. 2010 May;9(5):1147-57. doi: 10.1158/1535-7163.MCT-09-0962. Epub 2010 Apr 27. PubMed PMID: 20423991.
	Keller G, Schafhausen P, Brummendorf TH. Bosutinib: a dual SRC/ABL kinase inhibitor for the treatment of chronic myeloid leukemia. Expert Rev Hematol. 2009 Oct;2(5):489-97. doi: 10.1586/ehm.09.42. Review. PubMed PMID: 21083014.
	Stansfield L, Hughes TE, Walsh-Chocolaad TL. Bosutinib: a second-generation tyrosine kinase inhibitor for chronic myelogenous leukemia. Ann Pharmacother. 2013 Dec;47(12):1703-11. doi: 10.1177/1060028013503124. Review. PubMed PMID: 24396109.
	Gleixner KV, Mayerhofer M, Cerny-Reiterer S, Hörmann G, Rix U, Bennett KL, Hadzijusufovic E, Meyer RA, Pickl WF, Gotlib J, Horny HP, Reiter A, Mitterbauer-Hohendanner G, Superti-Furga G, Valent P. KIT-D816V-independent oncogenic signaling in neoplastic cells in systemic mastocytosis: role of Lyn and Btk activation and disruption by dasatinib and bosutinib. Blood. 2011 Aug 18;118(7):1885-98. doi: 10.1182/blood-2010-06-289959. Epub 2011 Feb 16. PubMed PMID: 21680801.
CABOZANTINIB	Yakes FM, Chen J, Tan J, Yamaguchi K, Shi Y, Yu P, Qian F, Chu F, Bentzien F, Cancilla B, Orf J, You A, Laird AD, Engst S, Lee L, Lesch J, Chou YC, Joly AH. Cabozantinib (XL184), a novel MET and VEGFR2 inhibitor, simultaneously suppresses metastasis, angiogenesis, and tumor growth. Mol Cancer Ther. 2011 Dec;10(12):2298-308. doi: 10.1158 /1535-7163.MCT-11-0264. Epub 2011 Sep 16. PubMed PMID: 21926191.
	Mulligan LM. RET revisited: expanding the oncogenic portfolio. Nat Rev Cancer. 2014 Mar;14(3):173-86. doi: 10.1038 /nrc3680. Review. PubMed PMID: 24561444.
	Italiano A, Penel N, Toulmonde M, et al. : Cabozantinib in patients with advanced osteosarcomas and Ewing sarcomas: a French Sarcoma Group (FSG)/US National Cancer Institute phase II collaborative study. Connective Tissue Oncology Society Annual Meeting Rome, Italy2018.
	Boxtel et al. A phase II study on the efficacy and toxicity of cabozantinib in recurrent/metastatic salivary gland cancer patients. Journal of Clinical Oncology. 38. 6529-6529. DOI: 10.1200/JCO.2020.38.15_suppl.6529
	Jennifer A. Chan, Jason Edward Faris, Janet E. Murphy, Lawrence Scott Blaszkowsky, Eunice Lee Kwak, Nadine Jackson McCleary, Charles S. Fuchs, Jeffrey A. Meyerhardt, Kimmie Ng, Andrew X. Zhu, Thomas Adam Abrams, Brian M. Wolpin, Sui Zhang, Amanda Reardon, Bridget Fitzpatrick, Matthew H. Kulke, and David P. Ryan; Phase II trial of cabozantinib in patients with carcinoid and pancreatic neuroendocrine tumors (pNET). Journal of Clinical Oncology 2017 35:4_suppl, 228-228
Flumatinib	Zhao J, Quan H, Xu Y, Kong X, Jin L, Lou L. Flumatinib, a selective inhibitor of BCR-ABL/PDGFR/KIT, effectively overcomes drug resistance of certain KIT mutants. Cancer Sci. 2014 Jan;105(1):117-25. doi: 10.1111/cas.12320. Epub 2014 Jan 4. PubMed PMID: 24205792; PubMed Central PMCID: PMC4317885.
AZD0424	Nowak D, Boehrer S, Hochmuth S, Trepohl B, Hofmann W, Hoelzer D, Hofmann WK, Mitrou PS, Ruthardt M, Chow KU. Src kinase inhibitors induce apoptosis and mediate cell cycle arrest in lymphoma cells. Anticancer Drugs. 2007 Oct;18(9):981-95. PubMed PMID: 17704648.
	Nowak D, Boehrer S, Hochmuth S, Trepohl B, Hofmann W, Hoelzer D, Hofmann WK, Mitrou PS, Ruthardt M, Chow KU. Src kinase inhibitors induce apoptosis and mediate cell cycle arrest in lymphoma cells. Anticancer Drugs. 2007 Oct;18(9):981-95. PubMed PMID: 17704648.
	Fischer PM. Approved and Experimental Small-Molecule Oncology Kinase Inhibitor Drugs: A Mid-2016 Overview. Med Res Rev. 2017 Mar;37(2):314-367. doi: 10.1002/med.21409. Epub 2016 Oct 24. Review. PubMed PMID: 27775829.
DUVELISIB	Thorpe LM, Yuzugullu H, Zhao JJ. PI3K in cancer: divergent roles of isoforms, modes of activation and therapeutic targeting. Nat Rev Cancer. 2015 Jan;15(1):7-24. doi: 10.1038/nrc3860. Review. PubMed PMID: 25533673; PubMed Central PMCID: PMC4384662.
	Flinn IW, Hillmen P, Montillo M, Nagy Z, Illés Á, Etienne G, Delgado J, Kuss BJ, Tam CS, Gasztonyi Z, Offner F, Lunin S, Bosch F, Davids MS, Lamanna N, Jaeger U, Ghia P, Cymbalista F, Portell CA, Skarbnik AP, Cashen AF, Weaver DT, Kelly VM, Turnbull B, Stilgenbauer S. The phase 3 DUO trial: duvelisib vs ofatumumab in relapsed and refractory CLL/SLL. Blood. 2018 12 06;132(23):2446-2455. doi: 10.1182/blood-2018-05-850461. Epub 2018 Aug 04. PubMed PMID: 30287523; PubMed Central PMCID: PMC6284216.
BI 836858	Vasu S, He S, Cheney C, Gopalakrishnan B, Mani R, Lozanski G, Mo X, Groh V, Whitman SP, Konopitzky R, Kössl C, Bucci D, Lucas DM, Yu J, Caligiuri MA, Blum W, Adam PJ, Borges E, Rueter B, Heider KH, Marcucci G, Muthusamy N. Decitabine enhances anti-CD33 monoclonal antibody BI 836858-mediated natural killer ADCC against AML blasts. Blood. 2016 06 09;127(23):2879-89. doi: 10.1182/blood-2015-11-680546. Epub 2016 Nov 24. PubMed PMID: 27013443; PubMed Central PMCID: PMC4900955.
	Burd A, Levine RL, Ruppert AS, Mims AS, Borate U, Stein EM, Patel P, Baer MR, Stock W, Deininger M, Blum W, Schiller G, Olin R, Litzow M, Foran J, Lin TL, Ball B, Boyiadzis M, Traer E, Odenike O, Arellano M, Walker A, Duong VH, Kovacsovics T, Collins R, Shoben AB, Heerema NA, Foster MC, Vergilio JA, Brennan T, Vietz C, Severson E, Miller M, Rosenberg L, Marcus S, Yocum A, Chen T, Stefanos M, Druker B, Byrd JC. Precision medicine treatment in acute myeloid leukemia using prospective genomic profiling: feasibility and preliminary efficacy of the Beat AML Master Trial. Nat Med. 2020 Oct 26;:. doi: 10.1038/s41591-020-1089-8. Epub 2020 Nov 26. PubMed PMID: 33106665.

Einsiedlerstrasse 23, 8834 Schindellegi, SWITZERLAND
E-mail: info@realtimeoncology.com **Web:** www.realtimeoncology.com

HATÓANYAG NEVE	REFERENCIA
DINACICLIB	Parry D, Guzi T, Shanahan F, Davis N, Prabhavalkar D, Wiswell D, Seghezzi W, Paruch K, Dwyer MP, Doll R, Nomeir A, Windsor W, Fischmann T, Wang Y, Oft M, Chen T, Kirschmeier P, Lees EM. Dinaciclib (SCH 727965), a novel and potent cyclin-dependent kinase inhibitor. Mol Cancer Ther. 2010 Aug;9(8):2344-53. doi: 10.1158/1535-7163.MCT-10-0324. Epub 2010 Jul 27. PubMed PMID: 20663931. Chen Z, Wang Z, Pang JC, Yu Y, Bieerkehazhi S, Lu J, Hu T, Zhao Y, Xu X, Zhang H, Yi JS, Liu S, Yang J. Multiple CDK inhibitor dinaciclib suppresses neuroblastoma growth via inhibiting CDK2 and CDK9 activity. Sci Rep. 2016 Jul 5;6:29090. doi: 10.1038/srep29090. PubMed PMID: 27378523; PubMed Central PMCID: PMC4932496.
AT 7519	Mariaule G, Belmont P. Cyclin-dependent kinase inhibitors as marketed anticancer drugs: where are we now? A short survey. Molecules. 2014 Sep 11;19(9):14366-82. doi: 10.3390/molecules190914366. Review. PubMed PMID: 25215591.
FAMITINIB	Zhou A, Zhang W, Chang C, Chen X, Zhong D, Qin Q, Lou D, Jiang H, Wang J. Phase I study of the safety, pharmacokinetics and antitumor activity of famitinib. Cancer Chemother Pharmacol. 2013 Nov;72(5):1043-53. doi: 10.1007/s00280-013-2282-y. Epub 2013 Sep 17. PubMed PMID: 24043137.
AZD5438	Byth KF, Thomas A, Hughes G, Forder C, McGregor A, Geh C, Oakes S, Green C, Walker M, Newcombe N, Green S, Growcott J, Barker A, Wilkinson RW. AZD5438, a potent oral inhibitor of cyclin-dependent kinases 1, 2, and 9, leads to pharmacodynamic changes and potent antitumor effects in human tumor xenografts. Mol Cancer Ther. 2009 Jul; 8(7):1856-66. doi: 10.1158/1535-7163.MCT-08-0836. Epub 2009 Jun 9. PubMed PMID: 19509270.
BERZOSERTIB	Yap TA, O'Carrigan B, Penney MS, Lim JS, Brown JS, de Miguel Luken MJ, Tunariu N, Perez-Lopez R, Rodrigues DN, Riisnaes R, Figueiredo I, Carreira S, Hare B, McDermott K, Khalique S, Williamson CT, Natrajan R, Pettitt SJ, Lord CJ, Banerji U, Pollard J, Lopez J, de Bono JS. Phase I Trial of First-in-Class ATR Inhibitor M6620 (VX-970) as Monotherapy or in Combination With Carboplatin in Patients With Advanced Solid Tumors. J Clin Oncol. 2020 Jun 22;:JCO1902404. doi: 10.1200/JCO.19.02404. Epub 2020 Jul 22. PubMed PMID: 32568634. Hall AB, Newsome D, Wang Y, Boucher DM, Eustace B, Gu Y, Hare B, Johnson MA, Milton S, Murphy CE, Takemoto D, Tolman C, Wood M, Charlton P, Charrier JD, Furey B, Golec J, Reaper PM, Pollard JR. Potentiation of tumor responses to DNA damaging therapy by the selective ATR inhibitor VX-970. Oncotarget. 2014 Jul 30;5(14):5674-85. doi: 10.18632/oncotarget.2158. PubMed PMID: 25010037; PubMed Central PMCID: PMC4170644. Konstantinopoulos PA, Cheng SC, Wahner Hendrickson AE, Penson RT, Schumer ST, Doyle LA, Lee EK, Kohn EC, Duska LR, Crispens MA, Olawaiye AB, Winer IS, Barroilhet LM, Fu S, McHale MT, Schilder RJ, Färkkilä A, Chowdhury D, Curtis J, Quinn RS, Bowes B, D'Andrea AD, Shapiro GI, Matulonis UA. Berzosertib plus gemcitabine versus gemcitabine alone in platinum-resistant high-grade serous ovarian cancer: a multicentre, open-label, randomised, phase 2 trial. Lancet Oncol. 2020 07;21(7):957-968. doi: 10.1016/S1470-2045(20)30180-7. Epub 2020 Jul 15. PubMed PMID: 32553118.
CT 1578	Madan B, Goh KC, Hart S, William AD, Jayaraman R, Ethirajulu K, Dymock BW, Wood JM. SB1578, a novel inhibitor of JAK2, FLT3, and c-Fms for the treatment of rheumatoid arthritis. J Immunol. 2012 Oct 15;189(8):4123-34. doi: 10.4049/jimmunol.1200675. Epub 2012 Sep 7. PubMed PMID: 22962687.
AEG 41174	Lipka DB, Hoffmann LS, Heidel F, Markova B, Blum MC, Breitenbuecher F, Kasper S, Kindler T, Levine RL, Huber C, Fischer T. LS104, a non-ATP-competitive small-molecule inhibitor of JAK2, is potently inducing apoptosis in JAK2V617F-positive cells. Mol Cancer Ther. 2008 May;7(5):1176-84. doi: 10.1158/1535-7163.MCT-07-2215. PubMed PMID: 18483305.
XL019	Verstovsek, Srdan, Pardanani, Animesh D., Shah, Neil P., Sokol, Lubomir, Wadleigh, Martha, Gilliland, D. Gary, List, Alan F., Tefferi, Ayalew, Kantarjian, Hagop M., Bui, Lynne A., Clary, Douglas O. A Phase I Study of XL019, a Selective JAK2 Inhibitor, in Patients with Primary Myelofibrosis and Post-Polycythemia Vera/Essential Thrombocythemia Myelofibrosis. ASH Annual Meeting Abstracts 2007 110: 553
PACRITINIB	Hart S, Goh KC, Novotny-Diermayr V, Tan YC, Madan B, Amalini C, Ong LC, Kheng B, Cheong A, Zhou J, Chng WJ, Wood JM. Pacritinib (SB1518), a JAK2/FLT3 inhibitor for the treatment of acute myeloid leukemia. Blood Cancer J. 2011 Nov;1(11):e44. doi: 10.1038/bcj.2011.43. Epub 2011 Nov 11. PubMed PMID: 22829080; PubMed Central PMCID: PMC3256753.
VENETOCLAX	SEYMOUR, John F., et al. The single-agent Bcl-2 inhibitor ABT-199 (GDC-0199) in patients with relapsed/refractory (R/R) non-Hodgkin lymphoma (NHL): responses observed in all mantle cell lymphoma (MCL) patients. 2013. Andrew H. Wei, Pau Montesinos, Vladimir Ivanov, Courtney Denton Dinardo, Jan Novak, Kamel Laribi, Inho Kim, Don A. Stevens, Walter M. Fiedler, Maria Pagoni, Olga Samoilova, Jianxiang Wang, Achilles Anagnostopoulos, Julie Bergeron, Jing-Zhou Hou, Takahiro Yamauchi, Qi Jiang, Wellington Mendes, John W. Hayslip, and Panayiotis Panayiotidis. A phase III study of venetoclax plus low-dose cytarabine in previously untreated older patients with acute myeloid leukemia (VIALE-C): A six-month update. Journal of Clinical Oncology 2020 38:15_suppl, 7511-7511. doi: 10.1200/JCO.2020.38.15_suppl.7511 Othman Al-Sawaf, Can Zhang, Maneesh Tandon, Arijit Sinha, Anna Maria Fink, Sandra Robrecht, Eugen Tausch, William L. Schary, Matthias Ritgen, Clemens Martin Wendtner, Karl A Kreuzer, Barbara Eichhorst, Stephan Stilgenbauer, Michael J. Hallek, Kirsten Fischer. Fixed-duration venetoclax-obinutuzumab for previously untreated patients with chronic lymphocytic leukemia: Follow-up of efficacy and safety results from the multicenter, open-label, randomized, phase III CLL14 trial. Journal of Clinical Oncology 38, no. 15_suppl (May 20, 2020) 8027-8027. doi: 10.1200/JCO.2020.38.15_suppl.8027 Eyre TA, Kirkwood AA, Gohill S, Follows G, Walewska R, Walter H, Cross M, Forconi F, Shah N, Chasty R, Hart A, Broom A, Marr H, Patten PEM, Dann A, Arumainathan A, Munir T, Shankara P, Bloor A, Johnston R, Orchard K, Schuh AH, Fox CP, . Efficacy of venetoclax monotherapy in patients with relapsed chronic lymphocytic leukaemia in the post-BCR inhibitor setting: a UK wide analysis. Br J Haematol. 2019 05;185(4):656-669. doi: 10.1111/bjh.15802. Epub 2019 Oct 15. PubMed PMID: 30768675.

Einsiedlerstrasse 23, 8834 Schindellegi, SWITZERLAND
E-mail: info@realtimeoncology.com **Web:** www.realtimeoncology.com

HATÓANYAG NEVE	REFERENCIA
	Eyre TA, Walter HS, Iyengar S, Follows G, Cross M, Fox CP, Hodson A, Coats J, Narat S, Morley N, Dyer MJS, Collins GP. Efficacy of venetoclax monotherapy in patients with relapsed, refractory mantle cell lymphoma after Bruton tyrosine kinase inhibitor therapy. Haematologica. 2019 Feb;104(2):e68-e71. doi: 10.3324/haematol.2018.198812. Epub 2018 Sep 6. PubMed PMID: 30190341; PubMed Central PMCID: PMC6355471.
GSK126	Bitler BG, Aird KM, Garipov A, Li H, Amatangelo M, Kossenkov AV, Schultz DC, Liu Q, Shih IeM, Conejo-Garcia JR, Speicher DW, Zhang R. Synthetic lethality by targeting EZH2 methyltransferase activity in ARID1A-mutated cancers. Nat Med. 2015 Mar;21(3):231-8. doi: 10.1038/nm.3799. Epub 2015 Feb 16. PubMed PMID: 25686104; PubMed Central PMCID: PMC4352133.
BEVACIZUMAB	Todorovic V, Cicmil Saric N, Lakicevic J, Sorat M. Evaluation of safety of bevacizumab as second-line treatment of patients with metastatic colorectal cancer. J BUON. 2017 Sep-Oct;22(5):1131-1136. PubMed PMID: 29135093. Srivastava H, Dewan A, Sharma SK, Negi P, Dewan AK, Pasricha S, Mehrotra K. Adjuvant Radiation Therapy and Temozolomide in Gliosarcoma: Is It Enough? Case Series of Seven Patients. Asian J Neurosurg. 2018 Apr-Jun;13(2): 297-301. doi: 10.4103/ajns.AJNS_151_16. PubMed PMID: 29682024; PubMed Central PMCID: PMC5898095. Coleman RL, Brady MF, Herzog TJ, Sabbatini P, Armstrong DK, Walker JL, et al. A phase III randomized controlled clinical trial of carboplatin and paclitaxel alone or in combination with bevacizumab followed by bevacizumab and secondary cytoreductive surgery in platinum-sensitive, recurrent ovarian, peritoneal primary and fallopian tube cancer (Gynecologic Oncology Group 0213). Gynecologic Oncology. 2015 Apr 1;137:3–4. Echarri MJ, Lopez-Martin A, Hitt R. Targeted Therapy in Locally Advanced and Recurrent/Metastatic Head and Neck Squamous Cell Carcinoma (LA-R/M HNSCC). Cancers (Basel). 2016 Feb 26;8(3). pii: E27. doi: 10.3390 /cancers8030027. Review. PubMed PMID: 26927178; PubMed Central PMCID: PMC4810111. L. Moreno, V. Moroz, C. Owens, D. Valteau-Couanet, M. Gambart, V. Castel, N. van Eijkelenburg, A. Castellano, K. Nysom, N. Gerber, G. Laureys, R. Ladenstein, E. Thebaud, D. Murphy, B. Morland, S. Vaidya, M. Elliott, A.D. Pearson, K. Wheatley. LBA64 - Bevacizumab for children with relapsed & refractory high-risk neuroblastoma (RR-HRNB): Results of the BEACON-neuroblastoma randomized phase II trial - A European ITCC-SIOPEN trial. Annals of Oncology. 2019;30:(Supplement 5):v901. doi: 10.1093/annonc/mdz394.061.
CCT3833	Saturno G, Lopes F, Girotti MR, Niculescu-Duvaz I, Niculescu-Duvaz D, Zambon A, et al. Abstract LB-212: Therapeutic efficacy of the paradox-breaking panRAF and SRC drug CCT3833/BAL3833 in KRAS-driven cancer models. Cancer Res. 2016 Jul 15;76(14 Supplement):LB-212-LB-212.
SECLIDEMSTAT	Soldi R, Ghosh Halder T, Weston A, Thode T, Drenner K, Lewis R, Kaadige MR, Srivastava S, Daniel Ampanattu S, Rodriguez Del Villar R, Lang J, Vankayalapati H, Weissman B, Trent JM, Hendricks WPD, Sharma S. The novel reversible LSD1 inhibitor SP-2577 promotes anti-tumor immunity in SWItch/Sucrose-NonFermentable (SWI/SNF) complex mutated ovarian cancer. PLoS One. 2020;15(7):e0235705. doi: 10.1371/journal.pone.0235705. Epub 2020 Oct 10. PubMed PMID: 32649682; PubMed Central PMCID: PMC7351179.
NILOTINIB	Reinwald M, Schleyer E, Kiewe P, Blau IW, Burmeister T, Pursche S, Neumann M, Notter M, Thiel E, Hofmann WK, Kolb HJ, Burdach S, Bender HU. Efficacy and pharmacologic data of second-generation tyrosine kinase inhibitor nilotinib in BCR-ABL-positive leukemia patients with central nervous system relapse after allogeneic stem cell transplantation. Biomed Res Int. 2014;2014:637059. doi: 10.1155/2014/637059. Epub 2014 Jun 15. PubMed PMID: 25025064; PubMed Central PMCID: PMC4082894. Redaelli S, Piazza R, Rostagno R, Magistroni V, Perini P, Marega M, Gambacorti-Passerini C, Boschelli F. Activity of bosutinib, dasatinib, and nilotinib against 18 imatinib-resistant BCR/ABL mutants. J Clin Oncol. 2009 Jan 20;27(3): 469-71. doi: 10.1200/JCO.2008.19.8853. Epub 2008 Dec 15. PubMed PMID: 19075254. Wei J, Freytag M, Schober Y, Nockher WA, Mautner VF, Friedrich RE, Manley PW, Kluwe L, Kurtz A. Nilotinib is more potent than imatinib for treating plexiform neurofibroma in vitro and in vivo. PLoS One. 2014 Oct 23;9(10):e107760. doi: 10.1371/journal.pone.0107760. eCollection 2014. PubMed PMID: 25340526; PubMed Central PMCID: PMC4207688. An X, Tiwari AK, Sun Y, Ding PR, Ashby CR Jr, Chen ZS. BCR-ABL tyrosine kinase inhibitors in the treatment of Philadelphia chromosome positive chronic myeloid leukemia: a review. Leuk Res. 2010 Oct;34(10):1255-68. doi: 10.1016/j.leukres.2010.04.016. Review. PubMed PMID: 20537386. Swords R, Mahalingam D, Padmanabhan S, Carew J, Giles F. Nilotinib: optimal therapy for patients with chronic myeloid leukemia and resistance or intolerance to imatinib. Drug Des Devel Ther. 2009 Sep 21;3:89-101. PubMed PMID: 19920925; PubMed Central PMCID: PMC2769239.
TAZEMETOSTAT	Giulino-Roth L. EZH2: a potential new target in T-cell lymphoma? Leuk Lymphoma. 2015 Jul;56(7):1924-5. doi: 10.3109/10428194.2014.987770. Epub 2015 Feb 14. PubMed PMID: 25407652. Morschhauser F, Tilly H, Chaidos A, McKay P, Phillips T, Assouline S, Batlevi CL, Campbell P, Ribrag V, Damaj GL, Dickinson M, Jurczak W, Kazmierczak M, Opat S, Radford J, Schmitt A, Yang J, Whalen J, Agarwal S, Adib D, Salles G. Tazemetostat for patients with relapsed or refractory follicular lymphoma: an open-label, single-arm, multicentre, phase 2 trial. Lancet Oncol. 2020 Oct 06;:. doi: 10.1016/S1470-2045(20)30441-1. Epub 2020 Oct 06. PubMed PMID: 33035457. Chan-Penebre E, Armstrong K, Drew A, Grassian AR, Feldman I, Knutson SK, Kuplast-Barr K, Roche M, Campbell J, Ho P, Copeland RA, Chesworth R, Smith JJ, Keilhack H, Ribich SA. Selective Killing of SMARCA2- and SMARCA4-deficient Small Cell Carcinoma of the Ovary, Hypercalcemic Type Cells by Inhibition of EZH2: In Vitro and In Vivo Preclinical Models. Mol Cancer Ther. 2017 05;16(5):850-860. doi: 10.1158/1535-7163.MCT-16-0678. Epub 2017 Oct 14. PubMed PMID: 28292935.
CERDULATINIB	Ma J, Xing W, Coffey G, Dresser K, Lu K, Guo A, Raca G, Pandey A, Conley P, Yu H, Wang YL. Cerdulatinib, a novel dual SYK/JAK kinase inhibitor, has broad anti-tumor activity in both ABC and GCB types of diffuse large B cell

Einsiedlerstrasse 23, 8834 Schindellegi, SWITZERLAND
E-mail: info@realtimeoncology.com **Web:** www.realtimeoncology.com

HATÓANYAG NEVE	REFERENCIA
	lymphoma. Oncotarget. 2015 Dec 22;6(41):43881-96. doi: 10.18632/oncotarget.6316. PubMed PMID: 26575169; PubMed Central PMCID: PMC4791274. Guo A, Lu P, Coffey G, Conley P, Pandey A, Wang YL. Dual SYK/JAK inhibition overcomes ibrutinib resistance in chronic lymphocytic leukemia: Cerdulatinib, but not ibrutinib, induces apoptosis of tumor cells protected by the microenvironment. Oncotarget. 2017 Feb 21;8(8):12953-12967. doi: 10.18632/oncotarget.14588. PubMed PMID: 28088788; PubMed Central PMCID: PMC5355069.
AZM 475271	Gill AL, Verdonk M, Boyle RG, Taylor R. A comparison of physicochemical property profiles of marketed oral drugs and orally bioavailable anti-cancer protein kinase inhibitors in clinical development. Curr Top Med Chem. 2007;7 (14):1408-22. Review. PubMed PMID: 17692029.
KW 2449	Pratz KW, Cortes J, Roboz GJ, Rao N, Arowojolu O, Stine A, Shiotsu Y, Shudo A, Akinaga S, Small D, Karp JE, Levis M. A pharmacodynamic study of the FLT3 inhibitor KW-2449 yields insight into the basis for clinical response. Blood. 2009 Apr 23;113(17):3938-46. doi: 10.1182/blood-2008-09-177030. Epub 2008 Nov 24. PubMed PMID: 19029442; PubMed Central PMCID: PMC2673122.
XL228	King ER, Wong KK. Insulin-like growth factor: current concepts and new developments in cancer therapy. Recent Pat Anticancer Drug Discov. 2012 Jan;7(1):14-30. Review. PubMed PMID: 21875414; PubMed Central PMCID: PMC3724215.
BAFETINIB	Yokota A, Kimura S, Masuda S, Ashihara E, Kuroda J, Sato K, Kamitsuji Y, Kawata E, Deguchi Y, Urasaki Y, Terui Y, Ruthardt M, Ueda T, Hatake K, Inui K, Maekawa T. INNO-406, a novel BCR-ABL/Lyn dual tyrosine kinase inhibitor, suppresses the growth of Ph+ leukemia cells in the central nervous system, and cyclosporine A augments its in vivo activity. Blood. 2007 Jan 1;109(1):306-14. Epub 2006 Sep 5. PubMed PMID: 16954504.
REBASTINIB	O'Hare T, Eide CA, Agarwal A, Adrian LT, Zabriskie MS, Mackenzie RJ, Latocha DH, Johnson KJ, You H, Luo J, Riddle SM, Marks BD, Vogel KW, Koop DR, Apgar J, Tyner JW, Deininger MW, Druker BJ. Threshold levels of ABL tyrosine kinase inhibitors retained in chronic myeloid leukemia cells determine their commitment to apoptosis. Cancer Res. 2013 Jun 1;73(11):3356-70. doi: 10.1158/0008-5472.CAN-12-3904. Epub 2013 Apr 10. PubMed PMID: 23576564; PubMed Central PMCID: PMC3674150.
Filgotinib	Shien K, Papadimitrakopoulou VA, Ruder D, Behrens C, Shen L, Kalhor N, Song J, Lee JJ, Wang J, Tang X, Herbst RS, Toyooka S, Girard L, Minna JD, Kurie JM, Wistuba II, Izzo JG. JAK1/STAT3 activation through a proinflammatory cytokine pathway leads to resistance to molecularly targeted therapy in non-small cell lung cancer. Mol Cancer Ther. 2017 Jul 20. pii: molcanther.0148.2016. doi: 10.1158/1535-7163.MCT-17-0148. [Epub ahead of print] PubMed PMID: 28729401.
PF-04965842	Degryse S, Cools J. JAK kinase inhibitors for the treatment of acute lymphoblastic leukemia. J Hematol Oncol. 2015 Jul 26;8:91. doi: 10.1186/s13045-015-0192-7. PubMed PMID: 26208852; PubMed Central PMCID: PMC4545857.
Itacitinib	Bose P, Abou Zahr A, Verstovsek S. Investigational Janus kinase inhibitors in development for myelofibrosis. Expert Opin Investig Drugs. 2017 Jun;26(6):723-734. doi: 10.1080/13543784.2017.1323871. Epub 2017 May 8. Review. PubMed PMID: 28441920.
INCB047986	Buchert M, Burns CJ, Ernst M. Targeting JAK kinase in solid tumors: emerging opportunities and challenges. Oncogene. 2016 Feb 25;35(8):939-51. doi: 10.1038/onc.2015.150. Epub 2015 May 18. Review. PubMed PMID: 25982279.
SURUFATINIB	Jinghong Zhou, Jun Ni, Min Cheng, Na Yang, Junqing Liang, Liang Ge, Wei Zhang, Jianxing Tang, qiaoling Sun, Fu Li, Jia Hu, Dongxia Shi, Hongbo Chen, Jingwen Long, Junen Sun, Fang Yin, Xuelei Ge, Hong Jia, Feng Zhou, Yongxin ren, Weiguo Qing and Weiguo Su. Abstract 4187: Preclinical evaluation of sulfatinib, a novel angio-immuno kinase inhibitor targeting VEGFR, FGFR1 and CSF1R kinases. Cancer Res. July 1 2017 (77) (13 Supplement) 4187; DOI: 10.1158/1538-7445.AM2017-4187 Xu J, Shen L, Zhou Z, Li J, Bai C, Chi Y, Li Z, Xu N, Li E, Liu T, Bai Y, Yuan Y, Li X, Wang X, Chen J, Ying J, Yu X, Qin S, Yuan X, Zhang T, Deng Y, Xiu D, Cheng Y, Tao M, Jia R, Wang W, Li J, Fan S, Peng M, Su W. Surufatinib in advanced extrapancreatic neuroendocrine tumours (SANET-ep): a randomised, double-blind, placebo-controlled, phase 3 study. Lancet Oncol. 2020 Sep 18;:. doi: 10.1016/S1470-2045(20)30496-4. Epub 2020 Oct 18. PubMed PMID: 32966811.
CRENOLANIB	Heinrich MC, Griffith D, McKinley A, Patterson J, Presnell A, Ramachandran A, Debiec-Rychter M. Crenolanib inhibits the drug-resistant PDGFRA D842V mutation associated with imatinib-resistant gastrointestinal stromal tumors. Clin Cancer Res. 2012 Aug 15;18(16):4375-84. doi: 10.1158/1078-0432.CCR-12-0625. Epub 2012 Jun 27. PubMed PMID: 22745105. Weisberg E, Meng C, Case AE, Tiv HL, Gokhale PC, Toure AA, Buhrlage S, Liu X, Wang J, Gray N, Stone R, Adamia S, Winer E, Sattler M, Griffin JD. The combination of FLT3 and SYK kinase inhibitors is toxic to leukaemia cells with CBL mutations. J Cell Mol Med. 2020 02;24(3):2145-2156. doi: 10.1111/jcmm.14820. Epub 2020 Feb 14. PubMed PMID: 31943762; PubMed Central PMCID: PMC7011134.
Barasertib	Goto H, Yoshino Y, Ito M, Nagai J, Kumamoto T, Inukai T, Sakurai Y, Miyagawa N, Keino D, Yokosuka T, Iwasaki F, Hamanoue S, Shiomi M, Goto S. Aurora B kinase as a therapeutic target in acute lymphoblastic leukemia. Cancer Chemother Pharmacol. 2020 Apr;85(4):773-783. doi: 10.1007/s00280-020-04045-9. Epub 2020 Jun 06. PubMed PMID: 32144432. Kantarjian HM, Martinelli G, Jabbour EJ, Quintás-Cardama A, Ando K, Bay JO, Wei A, Gröpper S, Papayannidis C, Owen K, Pike L, Schmitt N, Stockman PK, Giagounidis A, . Stage I of a phase 2 study assessing the efficacy, safety, and tolerability of barasertib (AZD1152) versus low-dose cytosine arabinoside in elderly patients with acute myeloid leukemia. Cancer. 2013 Jul 15;119(14):2611-9. doi: 10.1002/cncr.28113. Epub 2013 Jun 19. PubMed PMID: 23605952; PubMed Central PMCID: PMC4132839.
ZANDELISIB	Andrew David Zelenetz, Deepa Jagadeesh, Nishitha M. Reddy, Anastasios Stathis, Huda S. Salman, Adam Steven Asch, Vaishalee Padgaonkar Kenkre, Haresh S. Jhangiani, Alexia Iasonos, Jacob D. Soumerai, Judith Llorin, John M.

Einsiedlerstrasse 23, 8834 Schindellegi, SWITZERLAND
E-mail: info@realtimeoncology.com **Web:** www.realtimeoncology.com

HATÓANYAG NEVE	REFERENCIA
	Pagel. Results of the PI3K inhibitor ME-401 alone or with rituximab in relapsed/refractory (R/R) follicular lymphoma (FL). Journal of Clinical Oncology 37, no. 15_suppl (May 20, 2019) 7512-7512. doi: 10.1200/JCO.2019.37.15_suppl.7512
SHC 014748M	Fan L, Wang C, Zhao L, Wang Z, Zhang X, Liu X, Cao L, Xu W, Li J. SHC014748M, a novel selective inhi-bitor of PI3K, demonstrates promising preclinical antitumor activity in B cell lymphomas and chronic lymphocytic leukemia. Neoplasia. 2020 12;22(12):714-724. doi: 10.1016/j.neo.2020.10.004. Epub 2020 Jan 23. PubMed PMID: 33142237; PubMed Central PMCID: PMC7586065.
ALISERTIB	Venkataraman S, Alimova I, Tello T, Harris PS, Knipstein JA, Donson AM, Foreman NK, Liu AK, Vibhakar R. Targeting Aurora Kinase A enhances radiation sensitivity of atypical teratoid rhabdoid tumor cells. J Neurooncol. 2012 May;107(3):517-26. doi: 10.1007/s11060-011-0795-y. Epub 2012 Jan 15. PubMed PMID: 22246202; PubMed Central PMCID: PMC4681522.
LY3295668	Du J, Yan L, Torres R, Gong X, Bian H, Marugán C, Boehnke K, Baquero C, Hui YH, Chapman SC, Yang Y, Zeng Y, Bogner SM, Foreman RT, Capen A, Donoho GP, Van Horn RD, Barnard DS, Dempsey JA, Beckmann RP, Marshall MS, Chio LC, Qian Y, Webster YW, Aggarwal A, Chu S, Bhattachar S, Stancato LF, Dowless MS, Iversen PW, Manro JR, Walgren JL, Halstead BW, Dieter MZ, Martinez R, Bhagwat SV, Kreklau EL, Lallena MJ, Ye XS, Patel BKR, Reinhard C, Plowman GD, Barda DA, Henry JR, Buchanan SG, Campbell RM. Aurora A-Selective Inhibitor LY3295668 Leads to Dominant Mitotic Arrest, Apoptosis in Cancer Cells, and Shows Potent Preclinical Antitumor Efficacy. Mol Cancer Ther. 2019 12;18(12):2207-2219. doi: 10.1158/1535-7163.MCT-18-0529. Epub 2019 Jun 17. PubMed PMID: 31530649.
IPI-549	De Henau O, Rausch M, Winkler D, Campesato LF, Liu C, Cymerman DH, Budhu S, Ghosh A, Pink M, Tchaicha J, Douglas M, Tibbitts T, Sharma S, Proctor J, Kosmider N, White K, Stern H, Soglia J, Adams J, Palombella VJ, McGovern K, Kutok JL, Wolchok JD, Merghoub T. Overcoming resistance to checkpoint blockade therapy by targeting PI3K in myeloid cells. Nature. 2016 11 17;539(7629):443-447. doi: 10.1038/nature20554. Epub 2016 Nov 09. PubMed PMID: 27828943; PubMed Central PMCID: PMC5634331.
PUQUITINIB	Xie C, He Y, Zhen M, Wang Y, Xu Y, Lou L. Puquitinib, a novel orally available PI3K inhibitor, exhibits potent antitumor efficacy against acute myeloid leukemia. Cancer Sci. 2017 Jul;108(7):1476-1484. doi: 10.1111/cas.13263. Epub 2017 May 23. PubMed PMID: 28418085; PubMed Central PMCID: PMC5497803.
AMG 319	Castillo JJ, Iyengar M, Kuritzky B, Bishop KD. Isotype-specific inhibition of the phosphatidylinositol-3-kinase pathway in hematologic malignancies. Onco Targets Ther. 2014 Feb 21;7:333-42. doi: 10.2147/OTT.S34641. eCollection 2014. Review. PubMed PMID: 24591840; PubMed Central PMCID: PMC3937185. Thorpe LM, Yuzugullu H, Zhao JJ. PI3K in cancer: divergent roles of isoforms, modes of activation and therapeutic targeting. Nat Rev Cancer. 2015 Jan;15(1):7-24. doi: 10.1038/nrc3860. Review. PubMed PMID: 25533673; PubMed Central PMCID: PMC4384662.
JQ1	Chen C, Liu Y, Rappaport AR, Kitzing T, Schultz N, Zhao Z, Shroff AS, Dickins RA, Vakoc CR, Bradner JE, Stock W, LeBeau MM, Shannon KM, Kogan S, Zuber J, Lowe SW. MLL3 is a haploinsufficient 7q tumor suppressor in acute myeloid leukemia. Cancer Cell. 2014 May 12;25(5):652-65. doi: 10.1016/j.ccr.2014.03.016. PubMed PMID: 24794707; PubMed Central PMCID: PMC4206212.
ANLOTINIB	Xie C, Wan X, Quan H, Zheng M, Fu L, Li Y, Lou L. Preclinical characterization of anlotinib, a highly potent and selective vascular endothelial growth factor receptor-2 inhibitor. Cancer Sci. 2018 Apr;109(4):1207-1219. doi: 10.1111/cas.13536. Epub 2018 Jul 25. PubMed PMID: 29446853; PubMed Central PMCID: PMC5891194. The efficacy and safety of anlotinib in refractory colorectal cancer: A double-blinded, placebo controlled, randomized phase III ALTER0703 trial. doi: 10.1200/JCO.2021.39.3_suppl.65 Journal of Clinical Oncology 39, no. 3_suppl (January 20, 2021) 65-65. Y. Chi, M. Gao, Y. Zhang, F. Shi, Y. Cheng, Z. Guo, M. Ge, J. Qin, J. Zhang, Z. Li, X. Zhou, R. Huang, X. Chen, H. Liu, R. Cheng, Z. Xu, X. Zheng, D. Li, P. Tang. 265O - Anlotinib in locally advanced or metastatic radioiodine-refractory differentiated thyroid carcinoma: A randomized, double-blind, multicenter phase II trial. Annals of Oncology (2020) 31 (suppl_6): S1347-S1354. 10.1016/annonc/annonc360
OLARATUMAB	Chiorean EG, Sweeney C, Youssoufian H, Qin A, Dontabhaktuni A, Loizos N, Nippgen J, Amato R. A phase I study of olaratumab, an anti-platelet-derived growth factor receptor alpha (PDGFR) monoclonal antibody, in patients with advanced solid tumors. Cancer Chemother Pharmacol. 2014 Mar;73(3):595-604. doi: 10.1007/s00280-014-2389-9. Epub 2014 Jan 23. PubMed PMID: 24452395. William D. Tap, Robin L Jones, Bartosz Chmielowski, Anthony D. Elias, Douglas Adkins, Brian Andrew Van Tine, Mark Agulnik, Matthew M. Cooney, Michael B. Livingston, Gregory K. Pennock, Amy Qin, Ashwin Shahir, Robert L. Ilaria, Ilaria Conti, Jan Cosaert, Gary K. Schwartz. A randomized phase Ib/II study evaluating the safety and efficacy of olaratumab (IMC-3G3), a human anti-platelet-derived growth factor (PDGFR) monoclonal antibody, with or without doxorubicin (Dox), in advanced soft tissue sarcoma (STS). DOI: 10.1200/jco.2015.33.15_suppl.10501 Journal of Clinical Oncology 33, no. 15_suppl Andrick BJ, Gandhi A. Olaratumab: A Novel Platelet-Derived Growth Factor Receptor -Inhibitor for Advanced Soft Tissue Sarcoma. Ann Pharmacother. 2017 Aug 1:1060028017723935. doi: 10.1177/1060028017723935. [Epub ahead of print] PubMed PMID: 28778132. Tobias A, O'brien MP, Agulnik M. Olaratumab for advanced soft tissue sarcoma. Expert Rev Clin Pharmacol. 2017 Jul;10(7):699-705. doi: 10.1080/17512433.2017.1324295. Epub 2017 May 5. Review. PubMed PMID: 28447475.
VORINOSTAT	Steven G. DuBois, Meaghan Granger, Susan G. Groshen, Denice Tsao-Wei, Anasheh Shamirian, Scarlett Czarnecki, Fariba Goodarzian, Rachel Berkovich, Hiroyuki Shimada, Yael P. Mosse, Suzanne Shusterman, Susan Lerner Cohn, Kelly C. Goldsmith, Brian D. Weiss, Gregory A. Yanik, Clare Twist, Meredith Irwin, Julie R. Park, Araz Marachelian, Katherine K. Matthay; Dana-Farber/Boston Children's Cancer and Blood Disorders Center, Boston, MA; Cook Children's Medical Center, Fort Worth, TX; University of Southern California, Los Angeles, CA; Children's Hospital Los Angeles, Los Angeles, CA; Loma Linda University Children's Hospital, Riverside, CA; Children's Hospital Los

Einsiedlerstrasse 23, 8834 Schindellegi, SWITZERLAND
E-mail: info@realtimeoncology.com **Web:** www.realtimeoncology.com

HATÓANYAG NEVE	REFERENCIA
	Angeles, Keck School of Medicine, University of Southern California, Los Angeles, CA; Stanford University Medical Center, Stanford, CA; Children's Hospital of Philadelphia, Philadelphia, PA; Dana-Farber/Boston Childrens Cancer and Blood Disorders Center, Boston, MA; The University of Chicago Medicine, Chicago, IL; Emory University School of Medicine, Atlanta, GA; Cincinnati Children's Hospital Medical Center, Cincinnati, OH; Roswell Park Comprehensive Cancer Center, Buffalo, NY; The Hospital for Sick Children, Toronto, ON, Canada; Seattle Children's Hospital, Seattle, WA; University of California San Francisco, San Francisco, CA. Randomized phase II trial of MIBG versus MIBG/vincristine/irinotecan versus MIBG/vorinostat for relapsed/refractory neuroblastoma: A report from the New Approaches to Neuroblastoma Therapy Consortium. J Clin Oncol 38: 2020 (suppl; abstr 10500). doi: 10.1200 /JCO.2020.38.15_suppl.10500. Palmieri D, Lockman PR, Thomas FC, Hua E, Herring J, Hargrave E, Johnson M, Flores N, Qian Y, Vega-Valle E, Taskar KS, Rudraraju V, Mittapalli RK, Gaasch JA, Bohn KA, Thorsheim HR, Liewehr DJ, Davis S, Reilly JF, Walker R, Bronder JL, Feigenbaum L, Steinberg SM, Camphausen K, Meltzer PS, Richon VM, Smith QR, Steeg PS. Vorinostat inhibits brain metastatic colonization in a model of triple-negative breast cancer and induces DNA double-strand breaks. Clin Cancer Res. 2009 Oct 1;15(19):6148-57. doi: 10.1158/1078-0432.CCR-09-1039. Epub 2009 Sep 29. PubMed PMID: 19789319. Buglio D, Georgakis GV, Hanabuchi S, Arima K, Khaskhely NM, Liu YJ, Younes A. Vorinostat inhibits STAT6-mediated TH2 cytokine and TARC production and induces cell death in Hodgkin lymphoma cell lines. Blood. 2008 Aug 15;112(4):1424-33. doi: 10.1182/blood-2008-01-133769. Epub 2008 Oct 09. PubMed PMID: 18541724; PubMed Central PMCID: PMC2515130. Telford BJ, Chen A, Beetham H, Frick J, Brew TP, Gould CM, Single A, Godwin T, Simpson KJ, Guilford P. Synthetic Lethal Screens Identify Vulnerabilities in GPCR Signaling and Cytoskeletal Organization in E-Cadherin-Deficient Cells. Mol Cancer Ther. 2015 May;14(5):1213-23. doi: 10.1158/1535-7163.MCT-14-1092. Epub 2015 Mar 16. PubMed PMID: 25777964.
AXITINIB	B. Rini, O. Rixe, R. Bukowski, M. D. Michaelson, G. Wilding, G. Hudes, O. Bolte, H. Steinfeldt, S. D. Reich and R. Motzer. AG-013736, a multi-target tyrosine kinase receptor inhibitor, demonstrates anti-tumor activity in a Phase 2 study of cytokine-refractory, metastatic renal cell cancer (RCC). J Clin Oncol (Meeting Abstracts) June 2005 vol. 23 no. 16_suppl 4509. Donson, A., Werner, E., Amani, V., Griesinger, A., Witt, D., Nellan, A., Foreman, N. (2017). EPND-12. TYROSINE KINASE INHIBITORS AXITINIB, IMATINIB AND PAZOPANIB ARE SELECTIVELY POTENT IN EPENDYMOMA. Neuro-Oncology, 19(Suppl 4), iv17. http://doi.org/10. Cohen EE, Tortorici M, Kim S, Ingrosso A, Pithavala YK, Bycott P. A Phase II trial of axitinib in patients with various histologic subtypes of advanced thyroid cancer: long-term outcomes and pharmacokinetic/pharmacodynamic analyses. Cancer Chemother Pharmacol. 2014 Dec;74(6):1261-70. doi: 10.1007/s00280-014-2604-8. Epub 2014 Oct 15. PubMed PMID: 25315258; PubMed Central PMCID: PMC4236619.
TOFACITINIB	Meyer DM, Jesson MI, Li X, Elrick MM, Funckes-Shippy CL, Warner JD, Gross CJ, Dowty ME, Ramaiah SK, Hirsch JL, Saabye MJ, Barks JL, Kishore N, Morris DL. Anti-inflammatory activity and neutrophil reductions mediated by the JAK1/JAK3 inhibitor, CP-690,550, in rat adjuvant-induced arthritis. J Inflamm (Lond). 2010 Aug 11;7:41. doi: 10.1186 /1476-9255-7-41. PubMed PMID: 20701804; PubMed Central PMCID: PMC2928212. Bouchekioua A, Scourzic L, de Wever O, Zhang Y, Cervera P, Aline-Fardin A, Mercher T, Gaulard P, Nyga R, Jeziorowska D, Douay L, Vainchenker W, Louache F, Gespach C, Solary E, Coppo P. JAK3 deregulation by activating mutations confers invasive growth advantage in extranodal nasal-type natural killer cell lymphoma. Leukemia. 2014 Feb;28(2):338-48. doi: 10.1038/leu.2013.157. Epub 2013 May 21. PubMed PMID: 23689514.
LUCITANIB	Bello E, Colella G, Scarlato V, Oliva P, Berndt A, Valbusa G, Serra SC, D'Incalci M, Cavalletti E, Giavazzi R, Damia G, Camboni G. E-3810 is a potent dual inhibitor of VEGFR and FGFR that exerts antitumor activity in multiple preclinical models. Cancer Res. 2011 Feb 15;71(4):1396-405. doi: 10.1158/0008-5472.CAN-10-2700. Epub 2011 Jan 6. PubMed PMID: 21212416. Bello E, Colella G, Scarlato V, Oliva P, Berndt A, Valbusa G, Serra SC, D'Incalci M, Cavalletti E, Giavazzi R, Damia G, Camboni G. E-3810 is a potent dual inhibitor of VEGFR and FGFR that exerts antitumor activity in multiple preclinical models. Cancer Res. 2011 Feb 15;71(4):1396-405. doi: 10.1158/0008-5472.CAN-10-2700. Epub 2011 Jan 6. PubMed PMID: 21212416. Mayer IA, Arteaga CL, Nanda R, Miller KD, Jhaveri K, Brufsky AM, Rugo H, Yardley DA, Vahdat LT, Sadeghi S, Audeh MW, Rolfe L, Litten J, Knox A, Raponi M, Tankersley C, Isaacson J, Wride K, Morganstern DE, Vogel C, Connolly RM, Gradishar WJ, Patel R, Pusztai L, Abu-Khalaf M. A phase 2 open-label study of lucitanib in patients (pts) with FGF aberrant metastatic breast cancer (MBC) [abstract]. In: Proceedings of the 2016 San Antonio Breast Cancer Symposium; 2016 Dec 6-10; San Antonio, TX. Philadelphia (PA): AACR; Cancer Res 2017;77(4 Suppl):Abstract nr P6-11-03.
BRIVANIB	Huynh H, Ngo VC, Fargnoli J, Ayers M, Soo KC, Koong HN, Thng CH, Ong HS, Chung A, Chow P, Pollock P, Byron S, Tran E. Brivanib alaninate, a dual inhibitor of vascular endothelial growth factor receptor and fibroblast growth factor receptor tyrosine kinases, induces growth inhibition in mouse models of human hepatocellular carcinoma. Clin Cancer Res. 2008 Oct 1;14(19):6146-53. doi: 10.1158/1078-0432.CCR-08-0509. PubMed PMID: 18829493. Cai ZW, Zhang Y, Borzilleri RM, Qian L, Barbosa S, Wei D, Zheng X, Wu L, Fan J, Shi Z, Wautlet BS, Mortillo S, Jeyaseelan R Sr, Kukral DW, Kamath A, Marathe P, D'Arienzo C, Derbin G, Barrish JC, Robl JA, Hunt JT, Lombardo LJ, Fargnoli J, Bhide RS. Discovery of brivanib alaninate ((S)-((R)-1-(4-(4-fluoro-2-methyl-1H-indol-5-yloxy)-5-methylpyrrolo[2,1-f][1,2,4] triazin-6-yloxy)propan-2-yl)2-aminopropanoate), a novel prodrug of dual vascular endothelial growth factor receptor-2 and fibroblast growth factor receptor-1 kinase inhibitor (BMS-540215). J Med Chem. 2008 Mar 27;51(6):1976-80. doi: 10.1021/jm7013309. Epub 2008 Feb 21. PubMed PMID: 18288793.
PTC596	

Einsiedlerstrasse 23, 8834 Schindellegi, SWITZERLAND
E-mail: info@realtimeoncology.com **Web:** www.realtimeoncology.com

HATÓANYAG NEVE	REFERENCIA
	Flamier A, Abdouh M, Hamam R, Barabino A, Patel N, Gao A, Hanna R, Bernier G. Off-target effect of the BMI1 inhibitor PTC596 drives epithelial-mesenchymal transition in glioblastoma multiforme. NPJ Precis Oncol. 2020;4:1. doi: 10.1038/s41698-019-0106-1. Epub 2020 Oct 06. PubMed PMID: 31934644; PubMed Central PMCID: PMC6944693.
AZD4547	IBRAHIM, Tony, et al. Clinical development of FGFR3 inhibitors for the treatment of urothelial cancer. Bladder Cancer, 2019, 5.2: 87-102. Liu L, Ye TH, Han YP, Song H, Zhang YK, Xia Y, Wang NY, Xiong Y, Song XJ, Zhu YX, Li de L, Zeng J, Ran K, Peng CT, Wei YQ, Yu LT. Reductions in myeloid-derived suppressor cells and lung metastases using AZD4547 treatment of a metastatic murine breast tumor model. Cell Physiol Biochem. 2014;33(3):633-45. doi: 10.1159/000358640. Epub 2014 Mar 4. PubMed PMID: 24642893.
UNC1999	Alzrigat M, Párraga AA, Agarwal P, Zureigat H, Österborg A, Nahi H, Ma A, Jin J, Nilsson K, Öberg F, Kalushkova A, Jernberg-Wiklund H. EZH2 inhibition in multiple myeloma downregulates myeloma associated oncogenes and upregulates microRNAs with potential tumor suppressor functions. Oncotarget. 2017 Feb 07;8(6):10213-10224. doi: 10.18632/oncotarget.14378. PubMed PMID: 28052011; PubMed Central PMCID: PMC5354653.
XL-092	Hsu J et al. XL092, A multi-targeted inhibitor of MET, VEGFR2, AXL and MER with an optimized pharmacokinetic profile. European Journal of Cancer.32nd EORTC-NCI-AACR Symposium on Molecular Targets and Cancer Therapeutics. Volume 138, S16. doi: 10.1016/S0959-8049(20)31107-2.
KX01	Creedon H, Brunton VG. Src kinase inhibitors: promising cancer therapeutics? Crit Rev Oncog. 2012;17(2):145-59. Review. PubMed PMID: 22471705.
ROGARATINIB	IBRAHIM, Tony, et al. Clinical development of FGFR3 inhibitors for the treatment of urothelial cancer. Bladder Cancer, 2019, 5.2: 87-102.
SAVOLITINIB	Gavine PR, Ren Y, Han L, Lv J, Fan S, Zhang W, Xu W, Liu YJ, Zhang T, Fu H, Yu Y, Wang H, Xu S, Zhou F, Su X, Yin X, Xie L, Wang L, Qing W, Jiao L, Su W, Wang QM. Volitinib, a potent and highly selective c-Met inhibitor, effectively blocks c-Met signaling and growth in c-MET amplified gastric cancer patient-derived tumor xenograft models. Mol Oncol. 2014 Sep 10. pii: S1574-7891(14)00210-5. doi: 10.1016/j.molonc.2014.08.015. [Epub ahead of print] PubMed PMID: 25248999.
PEMIGATINIB	IBRAHIM, Tony, et al. Clinical development of FGFR3 inhibitors for the treatment of urothelial cancer. Bladder Cancer, 2019, 5.2: 87-102.
R 348	Deuse T, Velotta JB, Hoyt G, Govaert JA, Taylor V, Masuda E, Herlaar E, Park G, Carroll D, Pelletier MP, Robbins RC, Schrepfer S. Novel immunosuppression: R348, a JAK3- and Syk-inhibitor attenuates acute cardiac allograft rejection. Transplantation. 2008 Mar 27;85(6):885-92. doi: 10.1097/TP.0b013e318166acc4. PubMed PMID: 18360272.
WHIP 131	Bhavsar SK, Singh Y, Sharma P, Khairnar V, Hosseinzadeh Z, Zhang S, Palmada M, Sabolic I, Koepsell H, Lang KS, Lang PA, Lang F. Expression of JAK3 Sensitive Na+ Coupled Glucose Carrier SGLT1 in Activated Cytotoxic T Lymphocytes. Cell Physiol Biochem. 2016;39(3):1209-28. doi: 10.1159/000447827. Epub 2016 Sep 5. PubMed PMID: 27595398.
ENTINOSTAT	Telford BJ, Chen A, Beetham H, Frick J, Brew TP, Gould CM, Single A, Godwin T, Simpson KJ, Guilford P. Synthetic Lethal Screens Identify Vulnerabilities in GPCR Signaling and Cytoskeletal Organization in E-Cadherin-Deficient Cells. Mol Cancer Ther. 2015 May;14(5):1213-23. doi: 10.1158/1535-7163.MCT-14-1092. Epub 2015 Mar 16. PubMed PMID: 25777964.
SELICICLIB	Kawakami M, Mustachio LM, Rodriguez-Canales J, Mino B, Roszik J, Tong P, Wang J, Lee JJ, Myung JH, Heymach JV, Johnson FM, Hong S, Zheng L, Hu S, Villalobos PA, Behrens C, Wistuba I, Freemantle S, Liu X, Dmitrovsky E. Next-Generation CDK2/9 Inhibitors and Anaphase Catastrophe in Lung Cancer. J Natl Cancer Inst. 2017 Jun 1;109 (6). doi: 10.1093/jnci/djw297. PubMed PMID: 28376145.
FADRACICLIB	Kawakami M, Mustachio LM, Rodriguez-Canales J, Mino B, Roszik J, Tong P, Wang J, Lee JJ, Myung JH, Heymach JV, Johnson FM, Hong S, Zheng L, Hu S, Villalobos PA, Behrens C, Wistuba I, Freemantle S, Liu X, Dmitrovsky E. Next-Generation CDK2/9 Inhibitors and Anaphase Catastrophe in Lung Cancer. J Natl Cancer Inst. 2017 Jun 1;109 (6). doi: 10.1093/jnci/djw297. PubMed PMID: 28376145.
debio 1347	Nakanishi Y, Mizuno H, Sase H, Fujii T, Sakata K, Akiyama N, Aoki Y, Aoki M, Ishii N. ERK Signal Suppression and Sensitivity to CH5183284/Debio 1347, a Selective FGFR Inhibitor. Mol Cancer Ther. 2015 Dec;14(12):2831-9. doi: 10.1158/1535-7163.MCT-15-0497. Epub 2015 Oct 5. PubMed PMID: 26438159.
SNS-032	Mariaule G, Belmont P. Cyclin-dependent kinase inhibitors as marketed anticancer drugs: where are we now? A short survey. Molecules. 2014 Sep 11;19(9):14366-82. doi: 10.3390/molecules190914366. Review. PubMed PMID: 25215591.
SSR128129E	Ader I, Delmas C, Skuli N, Bonnet J, Schaeffer P, Bono F, Cohen-Jonathan-Moyal E, Toulas C. Preclinical evidence that SSR128129E--a novel small-molecule multi-fibroblast growth factor receptor blocker--radiosensitises human glioblastoma. Eur J Cancer. 2014 Sep;50(13):2351-9. doi: 10.1016/j.ejca.2014.05.012. Epub 2014 Jun 18. PubMed PMID: 24953334.
HGS1036	Harding TC, Long L, Palencia S, Zhang H, Sadra A, Hestir K, Patil N, Levin A, Hsu AW, Charych D, Brennan T, Zanghi J, Halenbeck R, Marshall SA, Qin M, Doberstein SK, Hollenbaugh D, Kavanaugh WM, Williams LT, Baker KP. Blockade of nonhormonal fibroblast growth factors by FP-1039 inhibits growth of multiple types of cancer. Sci Transl Med. 2013 Mar 27;5(178):178ra39. doi: 10.1126/scitranslmed.3005414. PubMed PMID: 23536011.
FORETINIB	Zillhardt M, Park SM, Romero IL, Sawada K, Montag A, Krausz T, Yamada SD, Peter ME, Lengyel E. Foretinib (GSK1363089), an orally available multikinase inhibitor of c-Met and VEGFR-2, blocks proliferation, induces anoikis, and impairs ovarian cancer metastasis. Clin Cancer Res. 2011 Jun 15;17(12):4042-51. doi: 10.1158/1078-0432.CCR-10-3387. Epub 2011 May 6. PubMed PMID: 21551255; PubMed Central PMCID: PMC3169439.
SARACATINIB	Nam HJ, Im SA, Oh DY, Elvin P, Kim HP, Yoon YK, Min A, Song SH, Han SW, Kim TY, Bang YJ. Antitumor activity of saracatinib (AZD0530), a c-Src/Abl kinase inhibitor, alone or in combination with chemotherapeutic agents in gastric cancer. Mol Cancer Ther. 2013 Jan;12(1):16-26. doi: 10.1158/1535-7163.MCT-12-0109. Epub 2012 Nov 9. PubMed PMID: 23144237.

Einsiedlerstrasse 23, 8834 Schindellegi, SWITZERLAND
E-mail: info@realtimeoncology.com **Web:** www.realtimeoncology.com

HATÓANYAG NEVE	REFERENCIA
	Creedon H, Brunton VG. Src kinase inhibitors: promising cancer therapeutics? Crit Rev Oncog. 2012;17(2):145-59. Review. PubMed PMID: 22471705.
CAPMATINIB	Liu X, Wang Q, Yang G, Marando C, Koblish HK, Hall LM, Fridman JS, Behshad E, Wynn R, Li Y, Boer J, Diamond S, He C, Xu M, Zhuo J, Yao W, Newton RC, Scherle PA. A novel kinase inhibitor, INCB28060, blocks c-MET-dependent signaling, neoplastic activities, and cross-talk with EGFR and HER-3. Clin Cancer Res. 2011 Nov 15;17(22): 7127-38. doi: 10.1158/1078-0432.CCR-11-1157. Epub 2011 Sep 14. PubMed PMID: 21918175.
ZM39923	Wang H, Wang Y, Jiang X, Wang Z, Zhong B, Fang Y. The molecular mechanism of curcumol on inducing cell growth arrest and apoptosis in Jurkat cells, a model of CD4 T cells. Int Immunopharmacol. 2014 Aug;21(2):375-82. doi: 10.1016/j.intimp.2014.05.021. Epub 2014 May 28. PubMed PMID: 24877754.
WHI-P154	Amin HM, Medeiros LJ, Ma Y, Feretzaki M, Das P, Leventaki V, Rassidakis GZ, O'Connor SL, McDonnell TJ, Lai R. Inhibition of JAK3 induces apoptosis and decreases anaplastic lymphoma kinase activity in anaplastic large cell lymphoma. Oncogene. 2003 Aug 21;22(35):5399-407. PubMed PMID: 12934099.
DECERNOTINIB	Kyttaris VC. Kinase inhibitors: a new class of antirheumatic drugs. Drug Des Devel Ther. 2012;6:245-50. doi: 10.2147 /DDDT.S25426. Epub 2012 Sep 21. Review. PubMed PMID: 23055694; PubMed Central PMCID: PMC3457674. Farmer LJ, Ledeboer MW, Hoock T, Arnost MJ, Bethiel RS, Bennani YL, Black JJ, Brummel CL, Chakilam A, Dorsch WA, Fan B, Cochran JE, Halas S, Harrington EM, Hogan JK, Howe D, Huang H, Jacobs DH, Laitinen LM, Liao S, Mahajan S, Marone V, Martinez-Botella G, McCarthy P, Messersmith D, Namchuk M, Oh L, Penney MS, Pierce AC, Raybuck SA, Rugg A, Salituro FG, Saxena K, Shannon D, Shlyakter D, Swenson L, Tian SK, Town C, Wang J, Wang T, Wannamaker MW, Winquist RJ, Zuccola HJ. Discovery of VX-509 (Decernotinib): A Potent and Selective Janus Kinase 3 Inhibitor for the Treatment of Autoimmune Diseases. J Med Chem. 2015 Sep 24;58(18):7195-216. doi: 10.1021/acs.jmedchem.5b00301. Epub 2015 Sep 10. PubMed PMID: 26230873.
ORANTINIB	Machida S, Saga Y, Takei Y, Mizuno I, Takayama T, Kohno T, Konno R, Ohwada M, Suzuki M. Inhibition of peritoneal dissemination of ovarian cancer by tyrosine kinase receptor inhibitor SU6668 (TSU-68). Int J Cancer. 2005 Mar 20; 114(2):224-9. PubMed PMID: 15551349.
DOVITINIB	Wan X, Corn PG, Yang J, Palanisamy N, Starbuck MW, Efstathiou E, Tapia EM, Zurita AJ, Aparicio A, Ravoori MK, Vazquez ES, Robinson DR, Wu YM, Cao X, Iyer MK, McKeehan W, Kundra V, Wang F, Troncoso P, Chinnaiyan AM, Logothetis CJ, Navone NM. Prostate cancer cell-stromal cell crosstalk via FGFR1 mediates antitumor activity of dovitinib in bone metastases. Sci Transl Med. 2014 Sep 3;6(252):252ra122. doi: 10.1126/scitranslmed.3009332. PubMed PMID: 25186177. André F, Bachelot T, Campone M, Dalenc F, Perez-Garcia JM, Hurvitz SA, Turner N, Rugo H, Smith JW, Deudon S, Shi M, Zhang Y, Kay A, Porta DG, Yovine A, Baselga J. Targeting FGFR with dovitinib (TKI258): preclinical and clinical data in breast cancer. Clin Cancer Res. 2013 Jul 1;19(13):3693-702. doi: 10.1158/1078-0432.CCR-13-0190. Epub 2013 May 8. PubMed PMID: 23658459.
SGX523	Buchanan SG, Hendle J, Lee PS, Smith CR, Bounaud PY, Jessen KA, Tang CM, Huser NH, Felce JD, Froning KJ, Peterman MC, Aubol BE, Gessert SF, Sauder JM, Schwinn KD, Russell M, Rooney IA, Adams J, Leon BC, Do TH, Blaney JM, Sprengeler PA, Thompson DA, Smyth L, Pelletier LA, Atwell S, Holme K, Wasserman SR, Emtage S, Burley SK, Reich SH. SGX523 is an exquisitely selective, ATP-competitive inhibitor of the MET receptor tyrosine kinase with antitumor activity in vivo. Mol Cancer Ther. 2009 Dec;8(12):3181-90. doi: 10.1158/1535-7163.MCT-09-0477. Epub . PubMed PMID: 19934279.
SAR125844	Laurent Schio1, Conception Nemecek1, Antonio Ugolini1, Sylvie Wentzler1, Sandrine Grapinet1, Jean Khider1, Eva Albert1, Nathalie Dischamps1, Frédéric Gay1, Véronique Sonnefraud1, Eric Bacqué1, Mireille Kenigsberg1, Hélène Goulaouic1, Anne Dagallier2, François Vallée2, Fabrice Bonche3, and Christoph Lengauer1. SAR125844: a potent and selective ATP-competitive inhibitor of MET kinase. Proceedings of the 103rd Annual Meeting of the American Association for Cancer Research; 2012 Mar 31-Apr 4; Chicago, IL. Philadelphia (PA): AACR; Cancer Res 2012;72(8 Suppl):Abstract nr 2911. doi:1538-7445.AM2012-2911.
ONARTUZUMAB	Merchant M, Ma X, Maun HR, Zheng Z, Peng J, Romero M, Huang A, Yang NY, Nishimura M, Greve J, Santell L, Zhang YW, Su Y, Kaufman DW, Billeci KL, Mai E, Moffat B, Lim A, Duenas ET, Phillips HS, Xiang H, Young JC, Vande Woude GF, Dennis MS, Reilly DE, Schwall RH, Starovasnik MA, Lazarus RA, Yansura DG. Monovalent antibody design and mechanism of action of onartuzumab, a MET antagonist with anti-tumor activity as a therapeutic agent. Proc Natl Acad Sci U S A. 2013 Aug 6;110(32):E2987-96. doi: 10.1073/pnas.1302725110. Epub 2013 Jul 23. PubMed PMID: 23882082; PubMed Central PMCID: PMC3740879.
PF-04217903	Zou HY, Li Q, Lee JH, Arango ME, Burgess K, Qiu M, Engstrom LD, Yamazaki S, Parker M, Timofeevski S, Cui JJ, McTigue M, Los G, Bender SL, Smeal T, Christensen JG. Sensitivity of selected human tumor models to PF-04217903, a novel selective c-Met kinase inhibitor. Mol Cancer Ther. 2012 Apr;11(4):1036-47. doi: 10.1158/1535-7163. MCT-11-0839. Epub 2012 Mar 2. PubMed PMID: 22389468.
PD173074	Taylor JG 6th, Cheuk AT, Tsang PS, Chung JY, Song YK, Desai K, Yu Y, Chen QR, Shah K, Youngblood V, Fang J, Kim SY, Yeung C, Helman LJ, Mendoza A, Ngo V, Staudt LM, Wei JS, Khanna C, Catchpoole D, Qualman SJ, Hewitt SM, Merlino G, Chanock SJ, Khan J. Identification of FGFR4-activating mutations in human rhabdomyosarcomas that promote metastasis in xenotransplanted models. J Clin Invest. 2009 Nov;119(11):3395-407. doi: 10.1172 /JCI39703. Epub 2009 Oct 5. PubMed PMID: 19809159; PubMed Central PMCID: PMC2769177.
LY287445	Zhao G, Li WY, Chen D, Henry JR, Li HY, Chen Z, Zia-Ebrahimi M, Bloem L, Zhai Y, Huss K, Peng SB, McCann DJ. A novel, selective inhibitor of fibroblast growth factor receptors that shows a potent broad spectrum of antitumor activity in several tumor xenograft models. Mol Cancer Ther. 2011 Nov;10(11):2200-10. doi: 10.1158/1535-7163.MCT-11-0306. Epub 2011 Sep 7. PubMed PMID: 21900693.
ERDAFITINIB	IBRAHIM, Tony, et al. Clinical development of FGFR3 inhibitors for the treatment of urothelial cancer. Bladder Cancer, 2019, 5.2: 87-102.
TEPOTINIB	Bladt F, Faden B, Friese-Hamim M, Knuehl C, Wilm C, Fittschen C, Grädler U, Meyring M, Dorsch D, Jaehrling F, Pehl U, Stieber F, Schadt O, Blaukat A. EMD 1214063 and EMD 1204831 constitute a new class of potent and highly selective c-Met inhibitors. Clin Cancer Res. 2013 Jun 1;19(11):2941-51. doi: 10.1158/1078-0432.CCR-12-3247. Epub 2013 Apr 3. PubMed PMID: 23553846.

Einsiedlerstrasse 23, 8834 Schindellegi, SWITZERLAND
E-mail: info@realtimeoncology.com **Web:** www.realtimeoncology.com

HATÓANYAG NEVE	REFERENCIA
EMD 1204831	Bladt F, Faden B, Friese-Hamim M, Knuehl C, Wilm C, Fittschen C, Grädler U, Meyring M, Dorsch D, Jaehrling F, Pehl U, Stieber F, Schadt O, Blaukat A. EMD 1214063 and EMD 1204831 constitute a new class of potent and highly selective c-Met inhibitors. Clin Cancer Res. 2013 Jun 1;19(11):2941-51. doi: 10.1158/1078-0432.CCR-12-3247. Epub 2013 Apr 3. PubMed PMID: 23553846.
GOLVATINIB	Wang W, Li Q, Takeuchi S, Yamada T, Koizumi H, Nakamura T, Matsumoto K, Mukaida N, Nishioka Y, Sone S, Nakagawa T, Uenaka T, Yano S. Met kinase inhibitor E7050 reverses three different mechanisms of hepatocyte growth factor-induced tyrosine kinase inhibitor resistance in EGFR mutant lung cancer. Clin Cancer Res. 2012 Mar 15;18(6):1663-71. doi: 10.1158/1078-0432.CCR-11-1171. Epub 2012 Feb 8. PubMed PMID: 22317763.
INFIGRATINIB	IBRAHIM, Tony, et al. Clinical development of FGFR3 inhibitors for the treatment of urothelial cancer. Bladder Cancer, 2019, 5.2: 87-102.
TIVANTINIB	Previdi S, Abbadessa G, Dalò F, France DS, Broggini M. Breast cancer-derived bone metastasis can be effectively reduced through specific c-MET inhibitor tivantinib (ARQ 197) and shRNA c-MET knockdown. Mol Cancer Ther. 2012 Jan;11(1):214-23. doi: 10.1158/1535-7163.MCT-11-0277. Epub 2011 Oct 25. PubMed PMID: 22027690.
AMG 337	Paul E. Hughes, Yajing Yang, Karen Rex, Yihong Zhang, Paula J. Kaplan-Lefko, Sean Caenepeel, Jodi Moriguchi, Martin Broome, Deborah Choquette, Robert Radinsky, Richard Kendall, Angela Coxon, and Isabelle Dussault. AMG 337, a novel, potent and selective MET kinase inhibitor, has robust growth inhibitory activity in MET-dependent cancer models. doi: 10.1158/1538-7445.AM2014-728 Cancer Res October 1, 2014 74; 728.
AMG 208	David S. Hong, Peter J. Rosen, A. Craig Lockhart, Siqing Fu, Filip Janku, Razelle Kurzrock, Rabia Khan, Benny Amore, Isaac Caudillo, Hongjie Deng, Yuying C. Hwang, Robert D. Loberg, Poornima Shubhakar, Stephen Zoog, Darrin M. Beaupre, Peter Lee; The University of Texas MD Anderson Cancer Center, Houston, TX; Tower Cancer Research Foundation, Beverly Hills, CA; Washington University School of Medicine, St. Louis, MO; Amgen Inc., Seattle, WA; Amgen Inc., Thousand Oaks, CA. First-in-human study of AMG 208, an oral MET inhibitor, in adult patients (pts) with advanced solid tumors. J Clin Oncol 31, 2013 (suppl 6; abstr 41)
RILOTUMUMAB	Burgess TL, Sun J, Meyer S, Tsuruda TS, Sun J, Elliott G, Chen Q, Haniu M, Barron WF, Juan T, Zhang K, Coxon A, Kendall RL. Biochemical characterization of AMG 102: a neutralizing, fully human monoclonal antibody to human and nonhuman primate hepatocyte growth factor. Mol Cancer Ther. 2010 Feb;9(2):400-9. doi: 10.1158/1535-7163.MCT-09-0824. Epub 2010 Feb 2. PubMed PMID: 20124448.
GSK 2816126	Giulino-Roth L. EZH2: a potential new target in T-cell lymphoma? Leuk Lymphoma. 2015 Jul;56(7):1924-5. doi: 10.3109/10428194.2014.987770. Epub 2015 Feb 14. PubMed PMID: 25407652.
CPI-1205	Zeng D, Liu M, Pan J. Blocking EZH2 methylation transferase activity by GSK126 decreases stem cell-like myeloma cells. Oncotarget. 2017 Jan 10;8(2):3396-3411. doi: 10.18632/oncotarget.13773. PubMed PMID: 27926488; PubMed Central PMCID: PMC5356890.
GSK343	Amatangelo MD, Garipov A, Li H, Conejo-Garcia JR, Speicher DW, Zhang R. Three-dimensional culture sensitizes epithelial ovarian cancer cells to EZH2 methyltransferase inhibition. Cell Cycle. 2013 Jul 1;12(13):2113-9. doi: 10.4161/cc.25163. Epub 2013 Jun 10. PubMed PMID: 23759589; PubMed Central PMCID: PMC3737313.
RAMUCIRUMAB	Rouanne M, Loriot Y, Lebret T, Soria JC. Novel therapeutic targets in advanced urothelial carcinoma. Crit Rev Oncol Hematol. 2016 Feb;98:106-15. doi: 10.1016/j.critrevonc.2015.10.021. Epub 2015 Nov 9. Review. PubMed PMID: 26589398. Javle M, Smyth EC, Chau I. Ramucirumab: successfully targeting angiogenesis in gastric cancer. Clin Cancer Res. 2014 Dec 1;20(23):5875-81. doi: 10.1158/1078-0432.CCR-14-1071. Epub 2014 Oct 3. Review. PubMed PMID: 25281695; PubMed Central PMCID: PMC4252869. Verdaguer H, Tabernero J, Macarulla T. Ramucirumab in metastatic colorectal cancer: evidence to date and place in therapy. Ther Adv Med Oncol. 2016 May;8(3):230-42. doi: 10.1177/1758834016635888. Epub 2016 Mar 11. Review. PubMed PMID: 27239240; PubMed Central PMCID: PMC4872251. Tabernero J, Yoshino T, Cohn AL, Obermannova R, Bodoky G, Garcia-Carbonero R, Ciuleanu TE, Portnoy DC, Van Cutsem E, Grothey A, Prausová J, Garcia-Alfonso P, Yamazaki K, Clingan PR, Lonardi S, Kim TW, Simms L, Chang SC, Nasroulah F; RAISE Study Investigators. Ramucirumab versus placebo in combination with second-line FOLFIRI in patients with metastatic colorectal carcinoma that progressed during or after first-line therapy with bevacizumab, oxaliplatin, and a fluoropyrimidine (RAISE): a randomised, double-blind, multicentre, phase 3 study. Lancet Oncol. 2015 May;16(5):499-508. doi: 10.1016/S1470-2045(15)70127-0. Epub 2015 Apr 12. Erratum in: Lancet Oncol. 2015 Jun;16(6):e262. PubMed PMID: 25877855. Garon EB, Ciuleanu TE, Arrieta O, Prabhash K, Syrigos KN, Goksel T, Park K, Gorbunova V, Kowalyszyn RD, Pikiel J, Czyzewicz G, Orlov SV, Lewanski CR, Thomas M, Bidoli P, Dakhil S, Gans S, Kim JH, Grigorescu A, Karaseva N, Reck M, Cappuzzo F, Alexandris E, Sashegyi A, Yurasov S, Pérol M. Ramucirumab plus docetaxel versus placebo plus docetaxel for second-line treatment of stage IV non-small-cell lung cancer after disease progression on platinum-based therapy (REVEL): a multicentre, double-blind, randomised phase 3 trial. Lancet. 2014 Aug 23;384(9944):665-73. doi: 10.1016/S0140-6736(14)60845-X. Epub 2014 Jun 2. PubMed PMID: 24933332.
VEMURAFENIB	Nelson DS, Quispel W, Badalian-Very G, van Halteren AG, van den Bos C, Bovée JV, Tian SY, Van Hummelen P, Ducar M, MacConaill LE, Egeler RM, Rollins BJ. Somatic activating ARAF mutations in Langerhans cell histiocytosis. Blood. 2014 May 15;123(20):3152-5. doi: 10.1182/blood-2013-06-511139. Epub 2014 Mar 20. PubMed PMID: 24652991.
TAS-102	Shitara K, Doi T, Dvorkin M, Mansoor W, Arkenau HT, Prokharau A, Alsina M, Ghidini M, Faustino C, Gorbunova V, Zhavrid E, Nishikawa K, Hosokawa A, Yalçın Ş, Fujitani K, Beretta GD, Cutsem EV, Winkler RE, Makris L, Ilson DH, Tabernero J. Trifluridine/tipiracil versus placebo in patients with heavily pretreated metastatic gastric cancer (TAGS): a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet Oncol. 2018 11;19(11):1437-1448. doi: 10.1016/S1470-2045(18)30739-3. Epub 2018 Feb 21. PubMed PMID: 30355453. Yoshino T, Mizunuma N, Yamazaki K, Nishina T, Komatsu Y, Baba H, Tsuji A, Yamaguchi K, Muro K, Sugimoto N, Tsuji Y, Moriwaki T, Esaki T, Hamada C, Tanase T, Ohtsu A. TAS-102 monotherapy for pretreated metastatic

Einsiedlerstrasse 23, 8834 Schindellegi, SWITZERLAND
E-mail: info@realtimeoncology.com **Web:** www.realtimeoncology.com

HATÓANYAG NEVE	REFERENCIA
	colorectal cancer: a double-blind, randomised, placebo-controlled phase 2 trial. Lancet Oncol. 2012 Oct;13(10):993-1001. doi: 10.1016/S1470-2045(12)70345-5. PubMed PMID: 22951287. Mayer RJ, Van Cutsem E, Falcone A, Yoshino T, Garcia-Carbonero R, Mizunuma N, Yamazaki K, Shimada Y, Tabernero J, Komatsu Y, Sobrero A, Boucher E, Peeters M, Tran B, Lenz HJ, Zaniboni A, Hochster H, Cleary JM, Prenen H, Benedetti F, Mizuguchi H, Makris L, Ito M, Ohtsu A; RECOURSE Study Group.. Randomized trial of TAS-102 for refractory metastatic colorectal cancer. N Engl J Med. 2015 May 14;372(20):1909-19. doi: 10.1056/NEJMoa1414325. PubMed PMID: 25970050.
IADADEMSTAT	Przespolewski A, Wang ES. Inhibitors of LSD1 as a potential therapy for acute myeloid leukemia. Expert Opin Investig Drugs. 2016 Jul;25(7):771-80. doi: 10.1080/13543784.2016.1175432. Epub 2016 Apr 21. Review. PubMed PMID: 27077938. Maes T, Mascaró C, Tirapu I, Estiarte A, Ciceri F, Lunardi S, Guibourt N, Perdones A, Lufino MMP, Somervaille TCP, Wiseman DH, Duy C, Melnick A, Willekens C, Ortega A, Martinell M, Valls N, Kurz G, Fyfe M, Castro-Palomino JC, Buesa C. ORY-1001, a Potent and Selective Covalent KDM1A Inhibitor, for the Treatment of Acute Leukemia. Cancer Cell. 2018 03 12;33(3):495-511.e12. doi: 10.1016/j.ccell.2018.02.002. Epub 2018 Nov 01. PubMed PMID: 29502954.
INCB059872	Gianluca Civenni, Giada Zoppi, Ramiro Vazquez, Dhreeraj Shinde, Alyssa Paganoni, Aleksandra Kokanovic, Sang Hyun Lee, Bruce Ruggeri, Giuseppina M. Carbone, Carlo V. Catapano. INCB059872, a novel FAD-directed LSD1 Inhibitor, is active in prostate cancer models and impacts prostate cancer stem-like cells [abstract]. In: Proceedings of the American Association for Cancer Research Annual Meeting 2018; 2018 Apr 14-18; Chicago, IL. Philadelphia (PA): AACR; Cancer Res 2018;78(13 Suppl):Abstract nr 1379. doi: 10.1158/1538-7445.AM2018-1379
CELECOXIB	Yang J, Yue JB, Liu J, Sun XD, Hu XD, Sun JJ, Li YH, Yu JM. Effect of celecoxib on inhibiting tumor repopulation during radiotherapy in human FaDu squamous cell carcinoma. Contemp Oncol (Pozn). 2014;18(4):260-7. doi: 10.5114/wo.2014.43932. Epub 2014 Aug 3. PubMed PMID: 25258584; PubMed Central PMCID: PMC4171473. Bertagnolli MM, Eagle CJ, Zauber AG, Redston M, Solomon SD, Kim K, Tang J, Rosenstein RB, Wittes J, Corle D, Hess TM, Woloj GM, Boisserie F, Anderson WF, Viner JL, Bagheri D, Burn J, Chung DC, Dewar T, Foley TR, Hoffman N, Macrae F, Pruitt RE, Saltzman JR, Salzberg B, Sylwestrowicz T, Gordon GB, Hawk ET; APC Study Investigators.. Celecoxib for the prevention of sporadic colorectal adenomas. N Engl J Med. 2006 Aug 31;355(9):873-84. PubMed PMID: 16943400. Solomon SD, McMurray JJ, Pfeffer MA, Wittes J, Fowler R, Finn P, Anderson WF, Zauber A, Hawk E, Bertagnolli M; Adenoma Prevention with Celecoxib (APC) Study Investigators.. Cardiovascular risk associated with celecoxib in a clinical trial for colorectal adenoma prevention. N Engl J Med. 2005 Mar 17;352(11):1071-80. PubMed PMID: 15713944.
GSK2879552	Pishas KI, Lessnick SL. Recent advances in targeted therapy for Ewing sarcoma. F1000Res. 2016 Aug 25;5. pii: F1000 Faculty Rev-2077. doi: 10.12688/f1000research.8631.1. eCollection 2016. Review. PubMed PMID: 27635231; PubMed Central PMCID: PMC5007751.
TRANYLCYPROMINE	Pishas KI, Lessnick SL. Recent advances in targeted therapy for Ewing sarcoma. F1000Res. 2016 Aug 25;5. pii: F1000 Faculty Rev-2077. doi: 10.12688/f1000research.8631.1. eCollection 2016. Review. PubMed PMID: 27635231; PubMed Central PMCID: PMC5007751.
IBRUTINIB	Rauf F, Festa F, Park JG, Magee M, Eaton S, Rinaldi C, Betanzos CM, Gonzalez-Malerva L, LaBaer J. Ibrutinib inhibition of ERBB4 reduces cell growth in a WNT5A-dependent manner. Oncogene. 2018 04;37(17):2237-2250. doi: 10.1038/s41388-017-0079-x. Epub 2018 Oct 05. PubMed PMID: 29398709; PubMed Central PMCID: PMC5916919. Wu C, de Miranda NF, Chen L, Wasik AM, Mansouri L, Jurczak W, Galazka K, Dlugosz-Danecka M, Machaczka M, Zhang H, Peng R, Morin RD, Rosenquist R, Sander B, Pan-Hammarström Q. Genetic heterogeneity in primary and relapsed mantle cell lymphomas: Impact of recurrent CARD11 mutations. Oncotarget. 2016 Jun 21;7(25):38180-38190. doi: 10.18632/oncotarget.9500. PubMed PMID: 27224912; PubMed Central PMCID: PMC5122381. Burger JA, Barr PM, Robak T, Owen C, Ghia P, Tedeschi A, Bairey O, Hillmen P, Coutre SE, Devereux S, Grosicki S, McCarthy H, Simpson D, Offner F, Moreno C, Dai S, Lal I, Dean JP, Kipps TJ. Long-term efficacy and safety of first-line ibrutinib treatment for patients with CLL/SLL: 5 years of follow-up from the phase 3 RESONATE-2 study. Leukemia. 2020 03;34(3):787-798. doi: 10.1038/s41375-019-0602-x. Epub 2019 Jan 18. PubMed PMID: 31628428; PubMed Central PMCID: PMC7214263. Byrd JC, Hillmen P, O'Brien S, Barrientos JC, Reddy NM, Coutre S, Tam CS, Mulligan SP, Jaeger U, Barr PM, Furman RR, Kipps TJ, Thornton P, Moreno C, Montillo M, Pagel JM, Burger JA, Woyach JA, Dai S, Vezan R, James DF, Brown JR. Long-term follow-up of the RESONATE phase 3 trial of ibrutinib vs ofatumumab. Blood. 2019 05 09;133(19):2031-2042. doi: 10.1182/blood-2018-08-870238. Epub 2019 Oct 06. PubMed PMID: 30842083; PubMed Central PMCID: PMC6509542. Woyach JA, Ruppert AS, Heerema NA, Zhao W, Booth AM, Ding W, Bartlett NL, Brander DM, Barr PM, Rogers KA, Parikh SA, Coutre S, Hurria A, Brown JR, Lozanski G, Blachly JS, Ozer HG, Major-Elechi B, Fruth B, Nattam S, Larson RA, Erba H, Litzow M, Owen C, Kuzma C, Abramson JS, Little RF, Smith SE, Stone RM, Mandrekar SJ, Byrd JC. Ibrutinib Regimens versus Chemoimmunotherapy in Older Patients with Untreated CLL. N Engl J Med. 2018 12 27;379(26):2517-2528. doi: 10.1056/NEJMoa1812836. Epub 2018 Jan 01. PubMed PMID: 30501481; PubMed Central PMCID: PMC6325637.
PINOMETOSTAT	Rau RE, Rodriguez BA, Luo M, Jeong M, Rosen A, Rogers JH, Campbell CT, Daigle SR, Deng L, Song Y, Sweet S, Chevassut T, Andreeff M, Kornblau SM, Li W, Goodell MA. DOT1L as a therapeutic target for the treatment of DNMT3A-mutant acute myeloid leukemia. Blood. 2016 Aug 18;128(7):971-81. doi: 10.1182/blood-2015-11-684225. Epub 2016 Jun 22. PubMed PMID: 27335278; PubMed Central PMCID: PMC4990856.
GEMTUZUMAB OZOGAMICIN	Gamis AS, Alonzo TA, Meshinchi S, Sung L, Gerbing RB, Raimondi SC, Hirsch BA, Kahwash SB, Heerema-McKenney A, Winter L, Glick K, Davies SM, Byron P, Smith FO, Aplenc R. Gemtuzumab ozogamicin in children and adolescents

Einsiedlerstrasse 23, 8834 Schindellegi, SWITZERLAND
E-mail: info@realtimeoncology.com **Web:** www.realtimeoncology.com

HATÓANYAG NEVE	REFERENCIA
	with de novo acute myeloid leukemia improves event-free survival by reducing relapse risk: results from the randomized phase III Childrens Oncology Group trial AAML0531. J Clin Oncol. 2014 Sep 20;32(27):3021-32. doi: 10.1200/JCO.2014.55.3628. PubMed PMID: 25092781; PubMed Central PMCID: PMC4162498.
LXH254	Sharma P, Hu-Lieskovan S, Wargo JA, Ribas A. Primary, Adaptive, and Acquired Resistance to Cancer Immunotherapy. Cell. 2017 Feb 9;168(4):707-723. doi: 10.1016/j.cell.2017.01.017. Review. PubMed PMID: 28187290; PubMed Central PMCID: PMC5391692.
LY-3009120	Müller E, Bauer S, Stühmer T, Mottok A, Scholz CJ, Steinbrunn T, Brünnert D, Brandl A, Schraud H, Kreßmann S, Beilhack A, Rosenwald A, Bargou RC, Chatterjee M. Pan-Raf co-operates with PI3K-dependent signalling and critically contributes to myeloma cell survival independently of mutated RAS. Leukemia. 2017 Apr;31(4):922-933. doi: 10.1038/leu.2016.264. Epub 2016 Sep 30. PubMed PMID: 27686868.
TAK 580	Müller E, Bauer S, Stühmer T, Mottok A, Scholz CJ, Steinbrunn T, Brünnert D, Brandl A, Schraud H, Kreßmann S, Beilhack A, Rosenwald A, Bargou RC, Chatterjee M. Pan-Raf co-operates with PI3K-dependent signalling and critically contributes to myeloma cell survival independently of mutated RAS. Leukemia. 2017 Apr;31(4):922-933. doi: 10.1038/leu.2016.264. Epub 2016 Sep 30. PubMed PMID: 27686868.
ARQ 736	Rusconi P, Caiola E, Broggini M. RAS/RAF/MEK inhibitors in oncology. Curr Med Chem. 2012;19(8):1164-76. Review. PubMed PMID: 22257058. Caronia LM, Phay JE, Shah MH. Role of BRAF in thyroid oncogenesis. Clin Cancer Res. 2011 Dec 15;17(24):7511-7. doi: 10.1158/1078-0432.CCR-11-1155. Epub 2011 Sep 7. Review. PubMed PMID: 21900390.
ENZALUTAMIDE	Sternberg CN, de Bono JS, Chi KN, Fizazi K, Mulders P, Cerbone L, Hirmand M, Forer D, Scher HI. Improved outcomes in elderly patients with metastatic castration-resistant prostate cancer treated with the androgen receptor inhibitor enzalutamide: results from the phase III AFFIRM trial. Ann Oncol. 2014 Feb;25(2):429-34. doi: 10.1093 /annonc/mdt571. PubMed PMID: 24478320. Hussain M, Fizazi K, Saad F, Rathenborg P, Shore N, Ferreira U, Ivashchenko P, Demirhan E, Modelska K, Phung , Krivoshik A, Sternberg CN. Enzalutamide in Men with Nonmetastatic, Castration-Resistant Prostate Cancer. N Engl J Med. 2018 Jun 28;378(26):2465-2474. doi: 10.1056/NEJMoa1800536. PubMed PMID: 29949494. Davis ID, Martin AJ, Stockler MR, Begbie S, Chi KN, Chowdhury S, Coskinas X, Frydenberg M, Hague WE, Horvath LG, Joshua AM, Lawrence NJ, Marx G, McCaffrey J, McDermott R, McJannett M, North SA, Parnis F, Parulekar W, Pook DW, Reaume MN, Sandhu SK, Tan A, Tan TH, Thomson A, Tu E, Vera-Badillo F, Williams SG, Yip S, Zhang AY, Zielinski RR, Sweeney CJ, . Enzalutamide with Standard First-Line Therapy in Metastatic Prostate Cancer. N Engl J Med. 2019 07 11;381(2):121-131. doi: 10.1056/NEJMoa1903835. Epub 2019 Oct 02. PubMed PMID: 31157964. Beer TM, Armstrong AJ, Rathkopf DE, Loriot Y, Sternberg CN, Higano CS, Iversen P, Bhattacharya S, Carles J, Chowdhury S, Davis ID, de Bono JS, Evans CP, Fizazi K, Joshua AM, Kim CS, Kimura G, Mainwaring P, Mansbach H, Miller K, Noonberg SB, Perabo F, Phung D, Saad F, Scher HI, Taplin ME, Venner PM, Tombal B; PREVAIL Investigators.. Enzalutamide in metastatic prostate cancer before chemotherapy. N Engl J Med. 2014 Jul 31;371(5): 424-33. doi: 10.1056/NEJMoa1405095. PubMed PMID: 24881730; PubMed Central PMCID: PMC4418931.
APALUTAMIDE	Rathkopf DE et al., Final results from ACIS, a randomized, placebo (PBO)-controlled double-blind phase 3 study of apalutamide (APA) and abiraterone acetate plus prednisone (AAP) versus AAP in patients (pts) with chemo-naive metastatic castration-resistant prostate cancer (mCRPC). J Clin Oncol. 2021;39(suppl 6):abstr 9. doi: 10.1200/JCO. 2021.39.6_suppl.9. Smith MR, Antonarakis ES, Ryan CJ, Berry WR, Shore ND, Liu G, Alumkal JJ, Higano CS, Chow Maneval E, Bandekar R, de Boer CJ, Yu MK, Rathkopf DE. Phase 2 Study of the Safety and Antitumor Activity of Apalutamide (ARN-509), a Potent Androgen Receptor Antagonist, in the High-risk Nonmetastatic Castration-resistant Prostate Cancer Cohort. Eur Urol. 2016 Dec;70(6):963-970. doi: 10.1016/j.eururo.2016.04.023. PubMed PMID: 27160947. Chi KN, Agarwal N, Bjartell A, Chung BH, Pereira de Santana Gomes AJ, Given R, Juárez Soto Á, Merseburger AS, Özgüroğlu M, Uemura H, Ye D, Deprince K, Naini V, Li J, Cheng S, Yu MK, Zhang K, Larsen JS, McCarthy S, Chowdhury S, . Apalutamide for Metastatic, Castration-Sensitive Prostate Cancer. N Engl J Med. 2019 07 04;381(1): 13-24. doi: 10.1056/NEJMoa1903307. Epub 2019 Oct 31. PubMed PMID: 31150574. Smith MR, Saad F, Chowdhury S, Oudard S, Hadaschik BA, Graff JN, Olmos D, Mainwaring PN, Lee JY, Uemura H, Lopez-Gitlitz A, Trudel GC, Espina BM, Shu Y, Park YC, Rackoff WR, Yu MK, Small EJ; SPARTAN Investigators. Apalutamide Treatment and Metastasis-free Survival in Prostate Cancer. N Engl J Med. 2018 Apr 12;378(15):1408-1418. doi: 10.1056/NEJMoa1715546. Epub 2018 Feb 8. PubMed PMID: 29420164.
TOZASERTIB LACTATE	http://www.ncbi.nlm.nih.gov/pubmed/28102363
MITOMYCIN C	Kim Y, Spitz GS, Veturi U, Lach FP, Auerbach AD, Smogorzewska A. Regulation of multiple DNA repair pathways by the Fanconi anemia protein SLX4. Blood. 2013 Jan 03;121(1):54-63. doi: 10.1182/blood-2012-07-441212. Epub 2012 Nov 23. PubMed PMID: 23093618; PubMed Central PMCID: PMC3538331. Narayan G, Arias-Pulido H, Nandula SV, Basso K, Sugirtharaj DD, Vargas H, Mansukhani M, Villella J, Meyer L, Schneider A, Gissmann L, Dürst M, Pothuri B, Murty VV. Promoter hypermethylation of FANCF: disruption of Fanconi Anemia-BRCA pathway in cervical cancer. Cancer Res. 2004 May 1;64(9):2994-7. PubMed PMID: 15126331.
OTX015	Coudé MM, Braun T, Berrou J, Dupont M, Bertrand S, Masse A, Raffoux E, Itzykson R, Delord M, Riveiro ME, Herait P, Baruchel A, Dombret H, Gardin C. BET inhibitor OTX015 targets BRD2 and BRD4 and decreases c-MYC in acute leukemia cells. Oncotarget. 2015 Jul 10;6(19):17698-712. doi: 10.18632/oncotarget.4131. PubMed PMID: 25989842; PubMed Central PMCID: PMC4627339.
RO6870810	SHAPIRO, Geoffrey I., et al. Abstract A49: Clinically efficacy of the BET bromodomain inhibitor TEN-010 in an open-label substudy with patients with documented NUT-midline carcinoma (NMC). 2015.
NEO2734	

Einsiedlerstrasse 23, 8834 Schindellegi, SWITZERLAND
E-mail: info@realtimeoncology.com **Web:** www.realtimeoncology.com

HATÓANYAG NEVE	REFERENCIA
	Spriano F, Gaudio E, Cascione L, Tarantelli C, Melle F, Motta G, Priebe V, Rinaldi A, Golino G, Mensah AA, Aresu L, Zucca E, Pileri S, Witcher M, Brown B, Wahlestedt C, Giles F, Stathis A, Bertoni F. Antitumor activity of the dual BET and CBP/EP300 inhibitor NEO2734. Blood Adv. 2020 Sep 08;4(17):4124-4135. doi: 10.1182/bloodadvances.2020001879. PubMed PMID: 32882003; PubMed Central PMCID: PMC7479962.
	Ryan KR, Giles F, Morgan GJ. Targeting both BET and CBP/EP300 proteins with the novel dual inhibitors NEO2734 and NEO1132 leads to anti-tumor activity in Multiple Myeloma. Eur J Haematol. 2020 Sep 30;:. doi: 10.1111/ejh.13525. Epub 2020 Oct 30. PubMed PMID: 32997383.
CC-90010	Moreno V, Sepulveda JM, Vieito M, Hernández-Guerrero T, Doger B, Saavedra O, Ferrero O, Sarmiento R, Arias M, De Alvaro J, Di Martino J, Zuraek M, Sanchez-Pérez T, Aronchik I, Filvaroff EH, Lamba M, Hanna B, Nikolova Z, Braña I. Phase I study of CC-90010, a reversible, oral BET inhibitor in patients with advanced solid tumors and relapsed/refractory non-Hodgkin's lymphoma. Ann Oncol. 2020 Mar 30;:. doi: 10.1016/j.annonc.2020.03.294. Epub 2020 Jun 30. PubMed PMID: 32240793.
PELABRESIB	Albrecht BK, Gehling VS, Hewitt MC, Vaswani RG, Côté A, Leblanc Y, Nasveschuk CG, Bellon S, Bergeron L, Campbell R, Cantone N, Cooper MR, Cummings RT, Jayaram H, Joshi S, Mertz JA, Neiss A, Normant E, O'Meara M, Pardo E, Poy F, Sandy P, Supko J, Sims RJ 3rd, Harmange JC, Taylor AM, Audia JE. Identification of a Benzoisoxazoloazepine Inhibitor (CPI-0610) of the Bromodomain and Extra-Terminal (BET) Family as a Candidate for Human Clinical Trials. J Med Chem. 2016 Feb 25;59(4):1330-9. doi: 10.1021/acs.jmedchem.5b01882. Epub 2016 Feb 4. PubMed PMID: 26815195.
AZD5153	Rhyasen GW, Hattersley MM, Yao Y, Dulak A, Wang W, Petteruti P, Dale IL, Boiko S, Cheung T, Zhang J, Wen S, Castriotta L, Lawson D, Collins M, Bao L, Ahdesmaki MJ, Walker G, O'Connor G, Yeh TC, Rabow AA, Dry JR, Reimer C, Lyne P, Mills GB, Fawell SE, Waring MJ, Zinda M, Clark E, Chen H. AZD5153: A Novel Bivalent BET Bromodomain Inhibitor Highly Active against Hematologic Malignancies. Mol Cancer Ther. 2016 Nov;15(11):2563-2574. Epub 2016 Aug 29. PubMed PMID: 27573426.
MOLIBRESIB	DAWSON, Mark, et al. A phase I study of GSK525762, a selective bromodomain (BRD) and extra terminal protein (BET) inhibitor: results from part 1 of phase I/II open label single agent study in patients with acute myeloid leukemia (AML). 2017.
BMS-986158	Ocaña A, Nieto-Jiménez C, Pandiella A. BET inhibitors as novel therapeutic agents in breast cancer. Oncotarget. 2017 Aug 1;8(41):71285-71291. doi: 10.18632/oncotarget.19744. eCollection 2017 Sep 19. Review. PubMed PMID: 29050361; PubMed Central PMCID: PMC5642636.
Fruquintinib	Li J, Qin S, Xu RH, Shen L, Xu J, Bai Y, Yang L, Deng Y, Chen ZD, Zhong H, Pan H, Guo W, Shu Y, Yuan Y, Zhou J, Xu N, Liu T, Ma D, Wu C, Cheng Y, Chen D, Li W, Sun S, Yu Z, Cao P, Chen H, Wang J, Wang S, Wang H, Fan S, Hua Y, Su W. Effect of Fruquintinib vs Placebo on Overall Survival in Patients With Previously Treated Metastatic Colorectal Cancer: The FRESCO Randomized Clinical Trial. JAMA. 2018 06 26;319(24):2486-2496. doi: 10.1001/jama.2018.7855. PubMed PMID: 29946728; PubMed Central PMCID: PMC6583690.
DAROLUTAMIDE	Aragon-Ching JB. Darolutamide: a novel androgen-signaling agent in nonmetastatic castration-resistant prostate cancer. Asian J Androl. 2020 Jan-Feb;22(1):76-78. doi: 10.4103/aja.aja_52_19. PubMed PMID: 31249268; PubMed Central PMCID: PMC6958984.
	Fizazi K, Shore N, Tammela TL, Ulys A, Vjaters E, Polyakov S, Jievaltas M, Luz M, Alekseev B, Kuss I, Kappeler C, Snapir A, Sarapohja T, Smith MR; ARAMIS Investigators. Darolutamide in Nonmetastatic, Castration-Resistant Prostate Cancer. N Engl J Med. 2019 Mar 28;380(13):1235-1246. doi: 10.1056/NEJMoa1815671. Epub 2019 Feb 14. PubMed PMID: 30763142.
ENFORTUMAB VEDOTIN-EJFV	Rosenberg JE, O'Donnell PH, Balar AV, McGregor BA, Heath EI, Yu EY, Galsky MD, Hahn NM, Gartner EM, Pinelli JM, Liang SY, Melhem-Bertrandt A, Petrylak DP. Pivotal Trial of Enfortumab Vedotin in Urothelial Carcinoma After Platinum and Anti-Programmed Death 1/Programmed Death Ligand 1 Therapy. J Clin Oncol. 2019 Oct 10;37(29):2592-2600. doi: 10.1200/JCO.19.01140. Epub 2019 Jul 29. PubMed PMID: 31356140; PubMed Central PMCID: PMC6784850.
	Powles T, Rosenberg JE, Sonpavde GP, Loriot Y, Durán I, Lee JL, Matsubara N, Vulsteke C, Castellano D, Wu C, Campbell M, Matsangou M, Petrylak DP. Enfortumab Vedotin in Previously Treated Advanced Urothelial Carcinoma. N Engl J Med. 2021 Feb 12;:. doi: 10.1056/NEJMoa2035807. Epub 2021 Feb 12. PubMed PMID: 33577729.
BLINATUMOMAB	Viardot A, Hess G, Bargou RC, Morley NJ, Gritti G, Goebeler ME, Iskander K, Cohan D, Zhang A, Franklin J, Coyle L. Durability of complete response after blinatumomab therapy for relapsed/refractory diffuse large B-cell lymphoma. Leuk Lymphoma. 2020 Jul 07;:1-4. doi: 10.1080/10428194.2020.1783442. Epub 2020 Aug 07. PubMed PMID: 32633177.
	Brown PA, Ji L, Xu X, Devidas M, Hogan LE, Borowitz MJ, Raetz EA, Zugmaier G, Sharon E, Bernhardt MB, Terezakis SA, Gore L, Whitlock JA, Pulsipher MA, Hunger SP, Loh ML. Effect of Postreinduction Therapy Consolidation With Blinatumomab vs Chemotherapy on Disease-Free Survival in Children, Adolescents, and Young Adults With First Relapse of B-Cell Acute Lymphoblastic Leukemia: A Randomized Clinical Trial. JAMA. 2021 03 02;325(9):833-842. doi: 10.1001/jama.2021.0669. PubMed PMID: 33651090.
	Locatelli F, Zugmaier G, Rizzari C, Morris JD, Gruhn B, Klingebiel T, Parasole R, Linderkamp C, Flotho C, Petit A, Micalizzi C, Mergen N, Mohammad A, Kormany WN, Eckert C, Möricke A, Sartor M, Hrusak O, Peters C, Saha V, Vinti L, von Stackelberg A. Effect of Blinatumomab vs Chemotherapy on Event-Free Survival Among Children With High-risk First-Relapse B-Cell Acute Lymphoblastic Leukemia: A Randomized Clinical Trial. JAMA. 2021 03 02;325(9):843-854. doi: 10.1001/jama.2021.0987. PubMed PMID: 33651091.
SACITUZUMAB GOVITECAN	A. Bardia, S.M. Tolaney, D. Loirat, K. Punie, M. Oliveira, H.S. Rugo, A. Brufsky, K. Kalinsky, J. Cortés, J. O'Shaughnessy, V.C. Dieras, L.A. Carey, L. Gianni, M. Piccart, S. Loibl, D. Goldenberg, Q. Honh, M.S. Olivo, L.M. Itri, S.A. Hurvitz. ASCENT: A randomized phase III study of sacituzumab govitecan (SG) vs treatment of physicians choice (TPC) in patients (pts) with previously treated metastatic triple-negative breast cancer (mTNBC). Annals of Oncology (2020) 31 (suppl_4): S1142-S1215. doi: 10.1016/j.annonc.2020.08.2245.

Einsiedlerstrasse 23, 8834 Schindellegi, SWITZERLAND
E-mail: info@realtimeoncology.com **Web:** www.realtimeoncology.com

HATÓANYAG NEVE	REFERENCIA
	S.T. Tagawa, A. Balar, D.P. Petrylak, P. Grivas, N. Agarwal, C.N. Sternberg, Q. Hong, A. Gladden, C. Kanwal, P. Siemon-Hryczyk, T. Goswami, L.M. Itri Y. Loriot. Initial results from THROPHY-U-01: a phase II open-label study of sacituzumab govitecan in patients with metastatic urothelial caner (MUC) after failure of platinum-based regimens or immunotherapy. Annals of Oncology (2019) 30 (suppl_5): v851-v934. 10.1093/annonc/mdz394 Kalinsky K, Diamond JR, Vahdat LT, Tolaney SM, Juric D, O'Shaughnessy J, Moroose RL, Mayer IA, Abramson VG, Goldenberg DM, Sharkey RM, Maliakal P, Hong Q, Goswami T, Wegener WA, Bardia A. Sacituzumab Govitecan in Previously Treated Hormone Receptor-Positive/HER2-Negative Metastatic Breast Cancer: Final Results from a Phase 1/2, Single-Arm, Basket Trial. Ann Oncol. 2020 Sep 15;:. doi: 10.1016/j.annonc.2020.09.004. Epub 2020 Sep 15. PubMed PMID: 32946924. Bardia A, Mayer IA, Vahdat LT, Tolaney SM, Isakoff SJ, Diamond JR, O'Shaughnessy J, Moroose RL, Santin AD, Abramson VG, Shah NC, Rugo HS, Goldenberg DM, Sweidan AM, Iannone R, Washkowitz S, Sharkey RM, Wegener WA, Kalinsky K. Sacituzumab Govitecan-hziy in Refractory Metastatic Triple-Negative Breast Cancer. N Engl J Med. 2019 02 21;380(8):741-751. doi: 10.1056/NEJMoa1814213. PubMed PMID: 30786188.
CABAZITAXEL	Oudard S. TROPIC: Phase III trial of cabazitaxel for the treatment of metastatic castration-resistant prostate cancer. Future Oncol. 2011 Apr;7(4):497-506. doi: 10.2217/fon.11.23. PubMed PMID: 21463139. Bahl A, Oudard S, Tombal B, Ozgüroglu M, Hansen S, Kocak I, Gravis G, Devin J, Shen L, de Bono JS, Sartor AO; TROPIC Investigators.. Impact of cabazitaxel on 2-year survival and palliation of tumour-related pain in men with metastatic castration-resistant prostate cancer treated in the TROPIC trial. Ann Oncol. 2013 Sep;24(9):2402-8. doi: 10.1093/annonc/mdt194. PubMed PMID: 23723295; PubMed Central PMCID: PMC3755329. de Wit R, de Bono J, Sternberg CN, Fizazi K, Tombal B, Wülfing C, Kramer G, Eymard JC, Bamias A, Carles J, Iacovelli R, Melichar B, Sverrisdóttir Á, Theodore C, Feyerabend S, Helissey C, Ozatilgan A, Geffriaud-Ricouard C, Castellano D, . Cabazitaxel versus Abiraterone or Enzalutamide in Metastatic Prostate Cancer. N Engl J Med. 2019 12 26;381(26):2506-2518. doi: 10.1056/NEJMoa1911206. Epub 2019 Oct 30. PubMed PMID: 31566937.
PREXASERTIB	Heidler CL, Roth EK, Thiemann M, Blattmann C, Perez RL, Huber PE, Kovac M, Amthor B, Neu-Yilik G, Kulozik AE. Prexasertib (LY2606368) reduces clonogenic survival by inducing apoptosis in primary patient-derived osteosarcoma cells and synergizes with cisplatin and talazoparib. Int J Cancer. 2019 Nov 28;:. doi: 10.1002/ijc.32814. Epub 2019 Jun 28. PubMed PMID: 31782150. Ritu Chaudhary, Robbert Slebos, Feifei Song, Keegan McCleary-Sharpe, Jude Masannat, Aik Choon Tan, Xuefeng Wang, Nelusha Amaladas, Wenjuan Wu, Gerald Hall, Christine H. Chung. Effects of prexasertib, a CHK1 inhibitor, in the immune microenvironment of head and neck squamous cell carcinoma (HNSCC). J Clin Oncol. 2020;38:(suppl; abstr e18541). doi: 10.1200/JCO.2020.38.15_suppl.e18541. Parmar K, Kochupurakkal BS, Lazaro JB, Wang ZC, Palakurthi S, Kirschmeier PT, Yang C, Sambel LA, Färkkilä A, Reznichenko E, Reavis HD, Dunn CE, Zou L, Do KT, Konstantinopoulos PA, Matulonis UA, Liu JF, D'Andrea AD, Shapiro GI. The CHK1 Inhibitor Prexasertib Exhibits Monotherapy Activity in High-Grade Serous Ovarian Cancer Models and Sensitizes to PARP Inhibition. Clin Cancer Res. 2019 10 15;25(20):6127-6140. doi: 10.1158/1078-0432.CCR-19-0448. Epub 2019 Jul 13. PubMed PMID: 31409614; PubMed Central PMCID: PMC6801076. Gatti-Mays ME, Karzai FH, Soltani SN, Zimmer A, Green JE, Lee MJ, Trepel JB, Yuno A, Lipkowitz S, Nair J, McCoy A, Lee JM. A Phase II Single Arm Pilot Study of the CHK1 Inhibitor Prexasertib (LY2606368) in BRCA Wild-Type, Advanced Triple-Negative Breast Cancer. Oncologist. 2020 Jun 08;:. doi: 10.1634/theoncologist.2020-0491. Epub 2020 Jul 08. PubMed PMID: 32510664. Lee JM, Nair J, Zimmer A, Lipkowitz S, Annunziata CM, Merino MJ, Swisher EM, Harrell MI, Trepel JB, Lee MJ, Bagheri MH, Botesteanu DA, Steinberg SM, Minasian L, Ekwede I, Kohn EC. Prexasertib, a cell cycle checkpoint kinase 1 and 2 inhibitor, in BRCA wild-type recurrent high-grade serous ovarian cancer: a first-in-class proof-of-concept phase 2 study. Lancet Oncol. 2018 02;19(2):207-215. doi: 10.1016/S1470-2045(18)30009-3. Epub 2018 Jul 18. PubMed PMID: 29361470.
ZIV-AFLIBERCEPT	Ruff P, Van Cutsem E, Lakomy R, Prausova J, van Hazel GA, Moiseyenko VM, Soussan-Lazard K, Dochy E, Magherini E, Macarulla T, Papamichael D. Observed benefit and safety of aflibercept in elderly patients with metastatic colorectal cancer: An age-based analysis from the randomized placebo-controlled phase III VELOUR trial. J Geriatr Oncol. 2018 Jan;9(1):32-39. doi: 10.1016/j.jgo.2017.07.010. Epub 2017 Aug 12. PubMed PMID: 28807738. Van Cutsem E, Tabernero J, Lakomy R, Prenen H, Prausová J, Macarulla T, Ruff P, van Hazel GA, Moiseyenko V, Ferry D, McKendrick J, Polikoff J, Tellier A, Castan R, Allegra C. Addition of aflibercept to fluorouracil, leucovorin, and irinotecan improves survival in a phase III randomized trial in patients with metastatic colorectal cancer previously treated with an oxaliplatin-based regimen. J Clin Oncol. 2012 Oct 1;30(28):3499-506. Epub 2012 Sep 4. PubMed PMID: 22949147. Coleman RL, Duska LR, Ramirez PT, Heymach JV, Kamat AA, Modesitt SC, Schmeler KM, Iyer RB, Garcia ME, Miller DL, Jackson EF, Ng CS, Kundra V, Jaffe R, Sood AK. Phase 1-2 study of docetaxel plus aflibercept in patients with recurrent ovarian, primary peritoneal, or fallopian tube cancer. Lancet Oncol. 2011 Nov;12(12):1109-17. doi: 10.1016/S1470-2045(11)70244-3. Epub 2011 Oct 10. PubMed PMID: 21992853; PubMed Central PMCID: PMC3444811.
OBINUTUZUMAB	Awasthi A, Ayello J, Van de Ven C, Elmacken M, Sabulski A, Barth MJ, Czuczman MS, Islam H, Klein C, Cairo MS. Obinutuzumab (GA101) compared to rituximab significantly enhances cell death and antibody-dependent cytotoxicity and improves overall survival against CD20(+) rituximab-sensitive/-resistant Burkitt lymphoma (BL) and precursor B-acute lymphoblastic leukaemia (pre-B-ALL): potential targeted therapy in patients with poor risk CD20(+) BL and pre-B-ALL. Br J Haematol. 2015 Dec;171(5):763-75. doi: 10.1111/bjh.13764. Epub 2015 Oct 16. PubMed PMID: 26471982.

Einsiedlerstrasse 23, 8834 Schindellegi, SWITZERLAND
E-mail: info@realtimeoncology.com **Web:** www.realtimeoncology.com

HATÓANYAG NEVE	REFERENCIA
	Nadine Kutsch, Christian Pallasch, Thomas Decker, Holger Hebart, Kai Uwe Chow, Ullrich Graeven, Jens Kisro, Alexander Kroeber, Eugen Tausch, Clemens-Martin Wendtner, Michael J. Eckart, Stephan Stilgenbauer, Xi Huang, Juliane M. Jürgensmeier, Pankaj Bhargava, Michael Hallek, Barbara F. Eichhorst; A Prospective, Open-Label, Multicenter, Phase 2 Trial to Evaluate the Safety and Efficacy of the Combination of Tirabrutinib (ONO/GS-4059) and Idelalisib with and without Obinutuzumab in Patients with Relapsed/Refractory Chronic Lymphocytic Leukemia (CLL). Blood 2019; 134 (Supplement_1): 3047. doi: https://doi.org/10.1182/blood-2019-131025 Marcus R, Davies A, Ando K, Klapper W, Opat S, Owen C, Phillips E, Sangha R, Schlag R, Seymour JF, Townsend W, Trněný M, Wenger M, Fingerle-Rowson G, Rufibach K, Moore T, Herold M, Hiddemann W. Obinutuzumab for the First-Line Treatment of Follicular Lymphoma. N Engl J Med. 2017 Oct 5;377(14):1331-1344. doi: 10.1056/NEJMoa1614598. PubMed PMID: 28976863.
BORTEZOMIB	Durie BGM, Hoering A, Sexton R, Abidi MH, Epstein J, Rajkumar SV, Dispenzieri A, Kahanic SP, Thakuri MC, Reu FJ, Reynolds CM, Orlowski RZ, Barlogie B. Longer term follow-up of the randomized phase III trial SWOG S0777: bortezomib, lenalidomide and dexamethasone vs. lenalidomide and dexamethasone in patients (Pts) with previously untreated multiple myeloma without an intent for immediate autologous stem cell transplant (ASCT). Blood Cancer J. 2020 May 11;10(5):53. doi: 10.1038/s41408-020-0311-8. Epub 2020 Aug 11. PubMed PMID: 32393732; PubMed Central PMCID: PMC7214419. Putzer D, Gabriel M, Kroiss A, Madleitner R, Eisterer W, Kendler D, Uprimny C, Bale RJ, Gastl G, Virgolini IJ. First experience with proteasome inhibitor treatment of radioiodine nonavid thyroid cancer using bortezomib. Clin Nucl Med. 2012 Jun;37(6):539-44. doi: 10.1097/RLU.0b013e31824c5f24. PubMed PMID: 22614183. Robak T, Huang H, Jin J, Zhu J, Liu T, Samoilova O, Pylypenko H, Verhoef G, Siritanaratkul N, Osmanov E, Alexeeva J, Pereira J, Drach J, Mayer J, Hong X, Okamoto R, Pei L, Rooney B, van de Velde H, Cavalli F; LYM-3002 Investigators. Bortezomib-based therapy for newly diagnosed mantle-cell lymphoma. N Engl J Med. 2015 Mar 5;372 (10):944-53. doi: 10.1056/NEJMoa1412096. PubMed PMID: 25738670.
RITUXIMAB	Véronique V, Anne A, Marta M, G A Amos GAA, Donald A DA, Keith K, Rafael F RF, Sarah S, Anne A, Catherine M CM, József J, Monika M, Bernarda B, Alan K AK, Rodney R RR, Andrew A, Peter C PC, Gilles G, Catherine C, Thomas G TG, . Rituximab for High-Risk, Mature B-Cell Non-Hodgkin's Lymphoma in Children. N Engl J Med. 2020 06 04; 382(23):2207-2219. doi: 10.1056/NEJMoa1915315. PubMed PMID: 32492302
DINUTUXIMAB	Ploessl C, Pan A, Maples KT, Lowe DK. Dinutuximab: An Anti-GD2 Monoclonal Antibody for High-Risk Neuroblastoma. Ann Pharmacother. 2016 May;50(5):416-22. doi: 10.1177/1060028016632013. Epub 2016 Feb 25. Review. PubMed PMID: 26917818. Yu AL, Gilman AL, Ozkaynak MF, London WB, Kreissman SG, Chen HX, Smith M, Anderson B, Villablanca JG, Matthay KK, Shimada H, Grupp SA, Seeger R, Reynolds CP, Buxton A, Reisfeld RA, Gillies SD, Cohn SL, Maris JM, Sondel PM; Children's Oncology Group. Anti-GD2 antibody with GM-CSF, interleukin-2, and isotretinoin for neuroblastoma. N Engl J Med. 2010 Sep 30;363(14):1324-34. doi: 10.1056/NEJMoa0911123. PubMed PMID: 20879881; PubMed Central PMCID: PMC3086629.
ABIRATERONE	Ryan CJ, Smith MR, de Bono JS, Molina A, Logothetis CJ, de Souza P, Fizazi K, Mainwaring P, Piulats JM, Ng S, Carles J, Mulders PF, Basch E, Small EJ, Saad F, Schrijvers D, Van Poppel H, Mukherjee SD, Suttmann H, Gerritsen WR, Flaig TW, George DJ, Yu EY, Efstathiou E, Pantuck A, Winquist E, Higano CS, Taplin ME, Park Y, Kheoh T, Griffin T, Scher HI, Rathkopf DE; COU-AA-302 Investigators.. Abiraterone in metastatic prostate cancer without previous chemotherapy. N Engl J Med. 2013 Jan 10;368(2):138-48. doi: 10.1056/NEJMoa1209096. Erratum in: N Engl J Med. 2013 Feb 7;368(6):584. PubMed PMID: 23228172; PubMed Central PMCID: PMC3683570.
NAB-PACLITAXEL	Von Hoff DD, Ervin T, Arena FP, Chiorean EG, Infante J, Moore M, Seay T, Tjulandin SA, Ma WW, Saleh MN, Harris M, Reni M, Dowden S, Laheru D, Bahary N, Ramanathan RK, Tabernero J, Hidalgo M, Goldstein D, Van Cutsem E, Wei X, Iglesias J, Renschler MF. Increased survival in pancreatic cancer with nab-paclitaxel plus gemcitabine. N Engl J Med. 2013 Oct 31;369(18):1691-703. doi: 10.1056/NEJMoa1304369. Epub 2013 Oct 16. PubMed PMID: 24131140; PubMed Central PMCID: PMC4631139.
FOLFIRINOX	Conroy T, Desseigne F, Ychou M, Bouché O, Guimbaud R, Bécouarn Y, Adenis A, Raoul JL, Gourgou-Bourgade S, de la Fouchardière C, Bennouna J, Bachet JB, Khemissa-Akouz F, Péré-Vergé D, Delbaldo C, Assenat E, Chauffert B, Michel P, Montoto-Grillot C, Ducreux M; Groupe Tumeurs Digestives of Unicancer; PRODIGE Intergroup. FOLFIRINOX versus gemcitabine for metastatic pancreatic cancer. N Engl J Med. 2011 May 12;364(19):1817-25. doi: 10.1056/NEJMoa1011923. PubMed PMID: 21561347.
SELINEXOR	Grosicki S, Simonova M, Spicka I, Pour L, Kriachok I, Gavriatopoulou M, Pylypenko H, Auner HW, Leleu X, Doronin V, Usenko G, Bahlis NJ, Hajek R, Benjamin R, Dolai TK, Sinha DK, Venner CP, Garg M, Gironella M, Jurczyszyn A, Robak P, Galli M, Wallington-Beddoe C, Radinoff A, Salogub G, Stevens DA, Basu S, Liberati AM, Quach H, Goranova-Marinova VS, Bila J, Katodritou E, Oliynyk H, Korenkova S, Kumar J, Jagannath S, Moreau P, Levy M, White D, Gatt ME, Facon T, Mateos MV, Cavo M, Reece D, Anderson LD, Saint-Martin JR, Jeha J, Joshi AA, Chai Y, Li L, Peddagali V, Arazy M, Shah J, Shacham S, Kauffman MG, Dimopoulos MA, Richardson PG, Delimpasi S. Once-per-week selinexor, bortezomib, and dexamethasone versus twice-per-week bortezomib and dexamethasone in patients with multiple myeloma (BOSTON): a randomised, open-label, phase 3 trial. Lancet. 2020 Nov 14;396 (10262):1563-1573. doi: 10.1016/S0140-6736(20)32292-3. PubMed PMID: 33189178.
CEDIRANIB	Ledermann JA, Embleton AC, Raja F, Perren TJ, Jayson GC, Rustin GJS, Kaye SB, Hirte H, Eisenhauer E, Vaughan M, Friedlander M, González-Martín A, Stark D, Clark E, Farrelly L, Swart AM, Cook A, Kaplan RS, Parmar MKB; ICON6 collaborators. Cediranib in patients with relapsed platinum-sensitive ovarian cancer (ICON6): a randomised, double-blind, placebo-controlled phase 3 trial. Lancet. 2016 Mar 12;387(10023):1066-1074. doi: 10.1016/S0140-6736(15) 01167-8. Erratum in: Lancet. 2016 Apr 23;387(10029):1722. PubMed PMID: 27025186.
RIPRETINIB	Janku F, Abdul Razak AR, Chi P, Heinrich MC, von Mehren M, Jones RL, Ganjoo K, Trent J, Gelderblom H, Somaiah N, Hu S, Rosen O, Su Y, Ruiz-Soto R, Gordon M, George S. Switch Control Inhibition of KIT and PDGFRA in Patients With Advanced Gastrointestinal Stromal Tumor: A Phase I Study of Ripretinib. J Clin Oncol. 2020 Oct 01;38(28): 3294-3303. doi: 10.1200/JCO.20.00522. Epub 2020 Feb 17. PubMed PMID: 32804590; PubMed Central PMCID: PMC7526717.

Einsiedlerstrasse 23, 8834 Schindellegi, SWITZERLAND
E-mail: info@realtimeoncology.com **Web:** www.realtimeoncology.com

HATÓANYAG NEVE	REFERENCIA
	Blay JY, Serrano C, Heinrich MC, Zalcberg J, Bauer S, Gelderblom H, Schöffski P, Jones RL, Attia S, D'Amato G, Chi P, Reichardt P, Meade J, Shi K, Ruiz-Soto R, George S, von Mehren M. Ripretinib in patients with advanced gastrointestinal stromal tumours (INVICTUS): a double-blind, randomised, placebo-controlled, phase 3 trial. Lancet Oncol. 2020 Jun 05;:. doi: 10.1016/S1470-2045(20)30168-6. Epub 2020 Jun 05. PubMed PMID: 32511981.
ETOPOSIDE	Ren Y, Chen Z, Chen L, Woods NT, Reuther GW, Cheng JQ, Wang HG, Wu J. Shp2E76K mutant confers cytokine-independent survival of TF-1 myeloid cells by up-regulating Bcl-XL. J Biol Chem. 2007 Dec 14;282(50):36463-73. Epub 2007 Oct 17. PubMed PMID: 17942397; PubMed Central PMCID: PMC3000740. Chamberlain MC. Salvage chemotherapy for recurrent spinal cord ependymona. Cancer. 2002 Sep 1;95(5):997-1002. PubMed PMID: 12209682. Moreno T et al., ARID2 deficiency promotes tumor progression and is associated with higher sensitivity to PARP inhibition in lung cancer. bioRxiv 2020.01.10.898726; doi: https://doi.org/10.1101/2020.01.10.898726
DENOSUMAB	Fizazi K, Carducci M, Smith M, Damião R, Brown J, Karsh L, Milecki P, Shore N, Rader M, Wang H, Jiang Q, Tadros S, Dansey R, Goessl C. Denosumab versus zoledronic acid for treatment of bone metastases in men with castration-resistant prostate cancer: a randomised, double-blind study. Lancet. 2011 Mar 5;377(9768):813-22. doi: 10.1016/S0140-6736(10)62344-6. Epub 2011 Feb 25. PubMed PMID: 21353695; PubMed Central PMCID: PMC3090685.
MIDOSTAURIN	Yoshikawa N, Nakamura K, Yamaguchi Y, Kagota S, Shinozuka K, Kunitomo M. Effect of PKC412, a selective inhibitor of protein kinase C, on lung metastasis in mice injected with B16 melanoma cells. Life Sci. 2003 Feb 7;72(12):1377-87. PubMed PMID: 12527035. Reindl C, Quentmeier H, Petropoulos K, Greif PA, Benthaus T, Argiropoulos B et al., CBL exon 8/9 mutants activate the FLT3 pathway and cluster in core binding factor/11q deletion acute myeloid leukemia/myelodysplastic syndrome subtypes. Clin Cancer Res. 2009 Apr 1;15(7):2238-47. PubMed PMID: 19276253
LY294002	Reindl C, Quentmeier H, Petropoulos K, Greif PA, Benthaus T, Argiropoulos B et al., CBL exon 8/9 mutants activate the FLT3 pathway and cluster in core binding factor/11q deletion acute myeloid leukemia/myelodysplastic syndrome subtypes. Clin Cancer Res. 2009 Apr 1;15(7):2238-47. PubMed PMID: 19276253
MELPHALAN	Joshi PM, Sutor SL, Huntoon CJ, Karnitz LM. Ovarian cancer-associated mutations disable catalytic activity of CDK12, a kinase that promotes homologous recombination repair and resistance to cisplatin and poly(ADP-ribose) polymerase inhibitors. J Biol Chem. 2014 Mar 28;289(13):9247-53. doi: 10.1074/jbc.M114.551143. Epub 2014 Feb 19. PubMed PMID: 24554720; PubMed Central PMCID: PMC3979363.
TREBANANIB	Marth C, Vergote I, Scambia G, Oberaigner W, Clamp A, Berger R, Kurzeder C, Colombo N, Vuylsteke P, Lorusso D, Hall M, Renard V, Pignata S, Kristeleit R, Altintas S, Rustin G, Wenham RM, Mirza MR, Fong PC, Oza A, Monk BJ, Ma H, Vogl FD, Bach BA. ENGOT-ov-6/TRINOVA-2: Randomised, double-blind, phase 3 study of pegylated liposomal doxorubicin plus trebananib or placebo in women with recurrent partially platinum-sensitive or resistant ovarian cancer. Eur J Cancer. 2017 Jan;70:111-121. doi: 10.1016/j.ejca.2016.09.004. Epub 2016 Dec 1. PubMed PMID: 27914241. Monk BJ, Poveda A, Vergote I, Raspagliesi F, Fujiwara K, Bae DS, Oaknin A, Ray-Coquard I, Provencher DM, Karlan BY, Lhommé C, Richardson G, Rincón DG, Coleman RL, Herzog TJ, Marth C, Brize A, Fabbro M, Redondo A, Bamias A, Tassoudji M, Navale L, Warner DJ, Oza AM. Anti-angiopoietin therapy with trebananib for recurrent ovarian cancer (TRINOVA-1): a randomised, multicentre, double-blind, placebo-controlled phase 3 trial. Lancet Oncol. 2014 Jul;15(8):799-808. doi: 10.1016/S1470-2045(14)70244-X. Epub 2014 Jun 17. PubMed PMID: 24950985.
MK-8776	Dai Y, Chen S, Kmieciak M, Zhou L, Lin H, Pei XY, Grant S. The novel Chk1 inhibitor MK-8776 sensitizes human leukemia cells to HDAC inhibitors by targeting the intra-S checkpoint and DNA replication and repair. Mol Cancer Ther. 2013 Jun;12(6):878-89. doi: 10.1158/1535-7163.MCT-12-0902. PubMed PMID: 23536721; PubMed Central PMCID: PMC3681875.
SCH 900776	Guertin AD, Martin MM, Roberts B, Hurd M, Qu X, Miselis NR, Liu Y, Li J, Feldman I, Benita Y, Bloecher A, Toniatti C, Shumway SD. Unique functions of CHK1 and WEE1 underlie synergistic anti-tumor activity upon pharmacologic inhibition. Cancer Cell Int. 2012 Nov 13;12(1):45. doi: 10.1186/1475-2867-12-45. PubMed PMID: 23148684; PubMed Central PMCID: PMC3517755.
PF-477736	Bryant C, Rawlinson R, Massey AJ. Chk1 inhibition as a novel therapeutic strategy for treating triple-negative breast and ovarian cancers. BMC Cancer. 2014 Aug 7;14:570. doi: 10.1186/1471-2407-14-570. PubMed PMID: 25104095; PubMed Central PMCID: PMC4137066.
RABUSERTIB	Wang FZ, Fei HR, Cui YJ, Sun YK, Li ZM, Wang XY, Yang XY, Zhang JG, Sun BL. The checkpoint 1 kinase inhibitor LY2603618 induces cell cycle arrest, DNA damage response and autophagy in cancer cells. Apoptosis. 2014 Sep;19(9):1389-98. doi: 10.1007/s10495-014-1010-3. PubMed PMID: 24928205.
BELANTAMAB MAFODOTIN	Lonial S, Lee HC, Badros A, Trudel S, Nooka AK, Chari A, Abdallah AO, Callander N, Lendvai N, Sborov D, Suvannasankha A, Weisel K, Karlin L, Libby E, Arnulf B, Facon T, Hulin C, Kortüm KM, Rodríguez-Otero P, Usmani SZ, Hari P, Baz R, Quach H, Moreau P, Voorhees PM, Gupta I, Hoos A, Zhi E, Baron J, Piontek T, Lewis E, Jewell RC, Dettman EJ, Popat R, Esposti SD, Opalinska J, Richardson P, Cohen AD. Belantamab mafodotin for relapsed or refractory multiple myeloma (DREAMM-2): a two-arm, randomised, open-label, phase 2 study. Lancet Oncol. 2020 Feb;21(2):207-221. doi: 10.1016/S1470-2045(19)30788-0. Epub 2019 Dec 16. PubMed PMID: 31859245.
ORTERONEL	Saad F, Fizazi K, Jinga V, Efstathiou E, Fong PC, Hart LL, Jones R, McDermott R, Wirth M, Suzuki K, MacLean DB, Wang L, Akaza H, Nelson J, Scher HI, Dreicer R, Webb IJ, de Wit R; ELM-PC 4 investigators.. Orteronel plus prednisone in patients with chemotherapy-naive metastatic castration-resistant prostate cancer (ELM-PC 4): a double-blind, multicentre, phase 3, randomised, placebo-controlled trial. Lancet Oncol. 2015 Mar;16(3):338-48. doi: 10.1016/S1470-2045(15)70027-6. PubMed PMID: 25701170.
TALIMOGENE LAHERPAREPVEC	Chesney J, Puzanov I, Collichio F, Singh P, Milhem MM, Glaspy J, Hamid O, Ross M, Friedlander P, Garbe C, Logan TF, Hauschild A, Lebbé C, Chen L, Kim JJ, Gansert J, Andtbacka RHI, Kaufman HL. Randomized, Open-Label Phase II Study Evaluating the Efficacy and Safety of Talimogene Laherparepvec in Combination With Ipilimumab Versus

Einsiedlerstrasse 23, 8834 Schindellegi, SWITZERLAND
E-mail: info@realtimeoncology.com **Web:** www.realtimeoncology.com

HATÓANYAG NEVE	REFERENCIA
	Ipilimumab Alone in Patients With Advanced, Unresectable Melanoma. J Clin Oncol. 2018 06 10;36(17):1658-1667. doi: 10.1200/JCO.2017.73.7379. Epub 2017 Aug 05. PubMed PMID: 28981385; PubMed Central PMCID: PMC6075852.
BELINOSTAT	O'Connor OA, Horwitz S, Masszi T, Van Hoof A, Brown P, Doorduijn J, Hess G, Jurczak W, Knoblauch P, Chawla S, Bhat G, Choi MR, Walewski J, Savage K, Foss F, Allen LF, Shustov A. Belinostat in Patients With Relapsed or Refractory Peripheral T-Cell Lymphoma: Results of the Pivotal Phase II BELIEF (CLN-19) Study. J Clin Oncol. 2015 Aug 10;33(23):2492-9. doi: 10.1200/JCO.2014.59.2782. Epub 2015 Oct 22. PubMed PMID: 26101246; PubMed Central PMCID: PMC5087312.
LENALIDOMIDE	Nowakowski GS, Hong F, Scott DW, Macon WR, King RL, Habermann TM, Wagner-Johnston N, Casulo C, Wade JL, Nagargoje GG, Reynolds CM, Cohen JB, Khan N, Amengual JE, Richards KL, Little RF, Leonard JP, Friedberg JW, Kostakoglu L, Kahl BS, Witzig TE. Addition of Lenalidomide to R-CHOP Improves Outcomes in Newly Diagnosed Diffuse Large B-Cell Lymphoma in a Randomized Phase II US Intergroup Study ECOG-ACRIN E1412. J Clin Oncol. 2021 Feb 08;:JCO2001375. doi: 10.1200/JCO.20.01375. Epub 2021 Feb 08. PubMed PMID: 33555941.
GLASDEGIB	Michael Heuser, Tadeusz Robak, Pau Montesinos, Brian Leber, Walter M. Fiedler, Daniel Aaron Pollyea, Andrew Brown, Ashleigh O'Connell, Wendy Ma, Geoffrey Chan, Jorge E. Cortes. Glasdegib (GLAS) plus low-dose cytarabine (LDAC) in AML or MDS: BRIGHT AML 1003 final report and four-year overall survival (OS) follow-up. Journal of Clinical Oncology 2020 38:15_suppl, 7509-7509. doi: 10.1200/JCO.2020.38.15_suppl.7509 Cortes JE, Heidel FH, Hellmann A, Fiedler W, Smith BD, Robak T, Montesinos P, Pollyea DA, DesJardins P, Ottmann O, Ma WW, Shaik MN, Laird AD, Zeremski M, O'Connell A, Chan G, Heuser M. Randomized comparison of low dose cytarabine with or without glasdegib in patients with newly diagnosed acute myeloid leukemia or high-risk myelodysplastic syndrome. Leukemia. 2019 02;33(2):379-389. doi: 10.1038/s41375-018-0312-9. Epub 2018 Aug 16. PubMed PMID: 30555165; PubMed Central PMCID: PMC6365492.
NS-398	Joki T, Heese O, Nikas DC, Bello L, Zhang J, Kraeft SK, Seyfried NT, Abe T, Chen LB, Carroll RS, Black PM. Expression of cyclooxygenase 2 (COX-2) in human glioma and in vitro inhibition by a specific COX-2 inhibitor, NS-398. Cancer Res. 2000 Sep 1;60(17):4926-31. PubMed PMID: 10987308.
TILMACOXIB	Yashiro M, Nakazawa K, Tendo M, Kosaka K, Shinto O, Hirakawa K. Selective cyclooxygenase-2 inhibitor downregulates the paracrine epithelial-mesenchymal interactions of growth in scirrhous gastric carcinoma. Int J Cancer. 2007 Feb 1;120(3):686-93. PubMed PMID: 17096355.
IXAZOMIB	Meletios A. Dimopoulos, Ivan Spicka, Hang Quach, Albert Oriol, Roman Hajek, Mamta Garg, Meral Beksac, Sara Bringhen, Eirini Katodritou, Wee Joo Chng, Xavier Leleu, Shinsuke Iida, Maria-Victoria Mateos, Gareth Morgan, Alexander Vorog, Richard Labotka, Bingxia Wang, Antonio Palumbo, Sagar Lonial;. Ixazomib vs placebo maintenance for newly diagnosed multiple myeloma (NDMM) patients not undergoing autologous stem cell transplant (ASCT): The phase III TOURMALINE-MM4 trial. J Clin Oncol 38: 2020 (suppl; abstr 8527). doi: 10.1200 /JCO.2020.38.15_suppl.8527. Kumar SK, Berdeja JG, Niesvizky R, Lonial S, Laubach JP, Hamadani M, Stewart AK, Hari P, Roy V, Vescio R, Kaufman JL, Berg D, Liao E, Rajkumar SV, Richardson PG. Ixazomib, lenalidomide, and dexamethasone in patients with newly diagnosed multiple myeloma: long-term follow-up including ixazomib maintenance. Leukemia. 2019 Jul; 33(7):1736-1746. doi: 10.1038/s41375-019-0384-1. Epub 2019 Jan 29. PubMed PMID: 30696949; PubMed Central PMCID: PMC6755968.
DARATUMUMAB	Dimopoulos MA et al., Apollo: phase 3 randomized study of subcutaneous daratumumab plus pomalidomide and dexamethasone (D-Pd) versus pomalidomide and dexamethasone (Pd) alone in patients (pts) with relapsed /refractory multiple myeloma (RRMM). 62nd (ASH) Annual Meeting and Exposition. 2020. Session: 653. Abstract: 412. Paper: 135874. Voorhees PM, Kaufman JL, Laubach J, Sborov DW, Reeves B, Rodriguez C, Chari A, Silbermann R, Costa LJ, Anderson LD, Nathwani N, Shah N, Efebera YA, Holstein SA, Costello C, Jakubowiak A, Wildes TM, Orlowski RZ, Shain KH, Cowan AJ, Murphy S, Lutska Y, Pei H, Ukropec J, Vermeulen J, de Boer C, Hoehn D, Lin TS, Richardson PG. Daratumumab, lenalidomide, bortezomib, and dexamethasone for transplant-eligible newly diagnosed multiple myeloma: the GRIFFIN trial. Blood. 2020 08 20;136(8):936-945. doi: 10.1182/blood.2020005288. PubMed PMID: 32325490; PubMed Central PMCID: PMC7441167.
ACALABRUTINIB	Byrd JC, Wierda WG, Schuh A, Devereux S, Chaves JM, Brown JR, Hillmen P, Martin P, Awan FT, Stephens DM, Ghia P, Barrientos J, Pagel JM, Woyach JA, Burke K, Covey T, Gulrajani M, Hamdy A, Izumi R, Frigault MM, Patel P, Rothbaum W, Wang MH, O'Brien S, Furman RR. Acalabrutinib monotherapy in patients with relapsed/refractory chronic lymphocytic leukemia: updated phase 2 results. Blood. 2020 04 09;135(15):1204-1213. doi: 10.1182/blood. 2018884940. PubMed PMID: 31876911; PubMed Central PMCID: PMC7146022.
BRENTUXIMAB VEDOTIN	Straus DJ, Długosz-Danecka M, Alekseev S, Illés Á, Picardi M, Lech-Maranda E, Feldman T, Smolewski P, Savage KJ, Bartlett NL, Walewski J, Ramchandren R, Zinzani PL, Hutchings M, Connors JM, Radford J, Munoz J, Kim WS, Advani R, Ansell SM, Younes A, Miao H, Liu R, Fenton K, Forero-Torres A, Gallamini A. Brentuximab vedotin with chemotherapy for stage III/IV classical Hodgkin lymphoma: 3-year update of the ECHELON-1 study. Blood. 2020 03 05;135(10):735-742. doi: 10.1182/blood.2019003127. PubMed PMID: 31945149.
NICLOSAMIDE	Osada T, Chen M, Yang XY, Spasojevic I, Vandeusen JB, Hsu D, Clary BM, Clay TM, Chen W, Morse MA, Lyerly HK. Antihelminth compound niclosamide downregulates Wnt signaling and elicits antitumor responses in tumors with activating APC mutations. Cancer Res. 2011 Jun 15;71(12):4172-82. doi: 10.1158/0008-5472.CAN-10-3978. Epub 2011 Apr 29. PubMed PMID: 21531761; PubMed Central PMCID: PMC3117125.
NILUTAMIDE	Dijkman GA, Janknegt RA, De Reijke TM, Debruyne FM. Long-term efficacy and safety of nilutamide plus castration in advanced prostate cancer, and the significance of early prostate specific antigen normalization. International Anandron Study Group. J Urol. 1997 Jul;158(1):160-3. PubMed PMID: 9186345.
silmitasertib	Nitta, R. T., Bolin, S., Luo, E., Solow-Codero, D. E., Samghabadi, P., Purzner, T., ... & Li, G. (2019). Casein kinase 2 inhibition sensitizes medulloblastoma to temozolomide. Oncogene, 1-13.

Einsiedlerstrasse 23, 8834 Schindellegi, SWITZERLAND
E-mail: info@realtimeoncology.com **Web:** www.realtimeoncology.com

HATÓANYAG NEVE	REFERENCIA
	Purzner T, Purzner J, Buckstaff T, Cozza G, Gholamin S, Rusert JM, Hartl TA, Sanders J, Conley N, Ge X, Langan M, Ramaswamy V, Ellis L, Litzenburger U, Bolin S, Theruvath J, Nitta R, Qi L, Li XN, Li G, Taylor MD, Wechsler-Reya RJ, Pinna LA, Cho YJ, Fuller MT, Elias JE, Scott MP. Developmental phosphoproteomics identifies the kinase CK2 as a driver of Hedgehog signaling and a therapeutic target in medulloblastoma. Sci Signal. 2018 Sep 11;11(547). pii: eaau5147. doi: 10.1126/scisignal.aau5147. PubMed PMID: 30206138; PubMed Central PMCID: PMC6475502.
AICAR	Bost F, Decoux-Poullot AG, Tanti JF, Clavel S. Energy disruptors: rising stars in anticancer therapy? Oncogenesis. 2016 Jan 18;5:e188. doi: 10.1038/oncsis.2015.46. Review. PubMed PMID: 26779810; PubMed Central PMCID: PMC4728676.
ELTANEXOR	Eltanexor (KPT-8602), a Second-Generation Selective Inhibitor of Nuclear Export (SINE) Compound, in Patients with Higher-Risk Myelodysplastic Syndrome. Sangmin Lee, MD, Bhavana Bhatnagar, DO, Sanjay R Mohan, MD MSCI, William T. Senapedis, Jr., Erkan Baloglu, PhD, Hongwei Wang, MD, Jatin J. Shah, MD, Sharon Shacham, PhD MBA, Michael G. Kauffman, MD PhD. Blood (2019) 134 (Supplement_1): 2997. doi: 10.1182/blood-2019-124136
DINUTUXIMAB BETA	LADENSTEIN, Ruth Lydia, et al. Immunotherapy with anti-GD2 antibody ch14. 18/CHO±IL2 within the HR-NBL1 /SIOPEN trial to improve outcome of high-risk neuroblastoma patients compared to historical controls. 2018.
TISOTUMAB VEDOTIN	R.L. Coleman, D. Lorusso, C. Gennigens, A. González-Martín, L. Randall, D. Cibula, B. Lund, L. Woelber, S. Pignata, F. Forget, A. Redondo, R. Rangwala, S.D. Vindeløv, M. Chen, J.R. Harris, L. Nicacio, M.S..L. Teng, M. Smith, B.J. Monk, I. B. Vergote. LBA32 - Tisotumab vedotin in previously treated recurrent or metastatic cervical cancer: Results from the phase II innovaTV 204/GOG-3023/ENGOT-cx6 study. Annals of Oncology (2020) 31 (suppl_4): S1142-S1215. 10.1016/annonc/annonc325
PERIFOSINE	Kushner BH, Cheung NV, Modak S, Becher OJ, Basu EM, Roberts SS, Kramer K, Dunkel IJ. A phase I/Ib trial targeting the Pi3k/Akt pathway using perifosine: Long-term progression-free survival of patients with resistant neuroblastoma. Int J Cancer. 2017 Jan 15;140(2):480-484. doi: 10.1002/ijc.30440. Epub 2016 Jun 30. PubMed PMID: 27649927; PubMed Central PMCID: PMC5118186.
UMBRALISIB	Maharaj K, Powers JJ, Achille A, Mediavilla-Varela M, Gamal W, Burger KL, Fonseca R, Jiang K, Miskin HP, Maryanski D, Monastyrskyi A, Duckett DR, Roush WR, Cleveland JL, Sahakian E, Pinilla-Ibarz J. The dual PI3K/CK1 inhibitor umbralisib exhibits unique immunomodulatory effects on CLL T cells. Blood Adv. 2020 Jul 14;4(13):3072-3084. doi: 10.1182/bloodadvances.2020001800. PubMed PMID: 32634240; PubMed Central PMCID: PMC7362385.
rigosertib	Shyamala C SC, Steven M SM, Rosalie R, Erin P EP, Michael E ME, Patrick S PS, James F JF, Lewis R LR. A phase 1/2 study of rigosertib in patients with myelodysplastic syndromes (MDS) and MDS progressed to acute myeloid leukemia. Leuk Res. 2018 01;64:10-16. pii: S0145-2126(17)30584-2. Epub 2017 Jun 11. PubMed PMID: 29144985
NUTLIN-3A	Bill KL, Garnett J, Meaux I, Ma X, Creighton CJ, Bolshakov S, Barriere C, Debussche L, Lazar AJ, Prudner BC, Casadei L, Braggio D, Lopez G, Zewdu A, Bid H, Lev D, Pollock RE. SAR405838: A Novel and Potent Inhibitor of the MDM2:p53 Axis for the Treatment of Dedifferentiated Liposarcoma. Clin Cancer Res. 2016 Mar 1;22(5):1150-60. doi: 10.1158/1078-0432.CCR-15-1522. Epub 2015 Oct 16. PubMed PMID: 26475335; PubMed Central PMCID: PMC4775372.
FLUVASTATIN	Li Y, He X, Ding Y, Chen H, Sun L. Statin uses and mortality in colorectal cancer patients: An updated systematic review and meta-analysis. Cancer Med. 2019 Jun;8(6):3305-3313. doi: 10.1002/cam4.2151. Epub 2019 May 8. PubMed PMID: 31069997; PubMed Central PMCID: PMC6558478.
ATORVASTATIN	Li Y, He X, Ding Y, Chen H, Sun L. Statin uses and mortality in colorectal cancer patients: An updated systematic review and meta-analysis. Cancer Med. 2019 Jun;8(6):3305-3313. doi: 10.1002/cam4.2151. Epub 2019 May 8. PubMed PMID: 31069997; PubMed Central PMCID: PMC6558478.
OCTREOTIDE	Li Y, He X, Ding Y, Chen H, Sun L. Statin uses and mortality in colorectal cancer patients: An updated systematic review and meta-analysis. Cancer Med. 2019 Jun;8(6):3305-3313. doi: 10.1002/cam4.2151. Epub 2019 May 8. PubMed PMID: 31069997; PubMed Central PMCID: PMC6558478.
PENTOSTATIN	Li Y, He X, Ding Y, Chen H, Sun L. Statin uses and mortality in colorectal cancer patients: An updated systematic review and meta-analysis. Cancer Med. 2019 Jun;8(6):3305-3313. doi: 10.1002/cam4.2151. Epub 2019 May 8. PubMed PMID: 31069997; PubMed Central PMCID: PMC6558478.
RILUZOLE	Dolfi SC, Medina DJ, Kareddula A, Paratala B, Rose A, Dhami J, Chen S, Ganesan S, Mackay G, Vazquez A, Hirshfield KM. Riluzole exerts distinct antitumor effects from a metabotropic glutamate receptor 1-specific inhibitor on breast cancer cells. Oncotarget. 2017 Jul 4;8(27):44639-44653. doi: 10.18632/oncotarget.17961. PubMed PMID: 28591718; PubMed Central PMCID: PMC5546507.
XELIRI	Cui C, Shu C, Yang Y, Liu J, Shi S, Shao Z, Wang N, Yang T, Hu S. XELIRI compared with FOLFIRI as a second-line treatment in patients with metastatic colorectal cancer. Oncol Lett. 2014 Oct;8(4):1864-1872. Epub 2014 Jul 10. PubMed PMID: 25202427; PubMed Central PMCID: PMC4156196.
MEDI-573	Zhong H, Fazenbaker C, Breen S, Chen C, Huang J, Morehouse C, Yao Y, Hollingsworth RE. MEDI-573, alone or in combination with mammalian target of rapamycin inhibitors, targets the insulin-like growth factor pathway in sarcomas. Mol Cancer Ther. 2014 Nov;13(11):2662-73. doi: 10.1158/1535-7163.MCT-14-0144. Epub 2014 Sep 5. Erratum in: Mol Cancer Ther. 2015 Mar;14(3):844. PubMed PMID: 25193511.
NAXITAMAB	Jaume Mora, Godfrey Chi-Fung Chan, Daniel A. Morgenstern, Karsten Nysom, Melissa K Bear, Lene Worsaae Dalby, Steen Lisby, Brian H. Kushner; Pediatric Cancer Center Barcelona, Hospital Sant Joan de Déu, Barcelona, Spain; Queen Mary Hospital, University of Hong Kong, Pokfulam, China; Hospital for Sick Children, Toronto, ON, Canada; Rigshospitalet, Copenhagen, Denmark; Riley Hospital for Children, Indianapolis, IN; Y-mAbs Therapeutics A/S, Hoersholm, Denmark; Memorial Sloan Kettering Cancer Center, New York, NY. Naxitamab, a new generation anti-GD2 monoclonal antibody (mAb) for treatment of relapsed/refractory high-risk neuroblastoma (HR-NB). J Clin Oncol 38: 2020 (suppl; abstr 10543). doi: 10.1200/JCO.2020.38.15_suppl.10543.
HER2-BBz-CAR T cells	Nellan, Anandani, Christopher Rota, Robbie Majzner, Cynthia M. Lester-McCully, Andrea M. Griesinger, Jean M. Mulcahy Levy, Nicholas K. Foreman, Katherine E. Warren, and Daniel W. Lee. "Durable regression of Medulloblastoma after regional and intravenous delivery of anti-HER2 chimeric antigen receptor T cells." Journal for immunotherapy of cancer 6, no. 1 (2018): 30.
CILTACABTAGENE AUTOLEUCEL	

Einsiedlerstrasse 23, 8834 Schindellegi, SWITZERLAND
E-mail: info@realtimeoncology.com **Web:** www.realtimeoncology.com

HATÓANYAG NEVE	REFERENCIA
	Fan F (Xiaohu), Zhao W, Liu J, He A, Chen Y, Cao X, et al. Durable remissions with BCMA-specific chimeric antigen receptor (CAR)-modified T cells in patients with refractory/relapsed multiple myeloma. JCO. 2017 Jun 13;35 (18_suppl):LBA3001-LBA3001.
TRILACICLIB	O'Shaughnessy J et al., PD1-06. Trilaciclib improves overall survival when given with gemcitabine/carboplatin in patients with metastatic triple-negative breast cancer: Final analysis of a randomized phase 2 trial. 2020 San Antonio Breast Cancer Symposium. Abstract PD1-06.
TRABECTEDIN	Preusser M, Spiegl-Kreinecker S, Lötsch D, Wöhrer A, Schmook M, Dieckmann K, Saringer W, Marosi C, Berger W. Trabectedin has promising antineoplastic activity in high-grade meningioma. Cancer. 2012 Oct 15;118(20):5038-49. doi: 10.1002/cncr.27460. Epub 2012 Dec 05. PubMed PMID: 22392434.
Metarrestin	Kanis MJ, Qiang W, Pineda M, Maniar KP, Kim JJ. A small molecule inhibitor of the perinucleolar compartment, ML246, attenuates growth and spread of ovarian cancer. Gynecol Oncol Res Pract. 2018;5:7. doi: 10.1186/s40661-018-0064-2. Epub 2018 Jul 02. PubMed PMID: 30305911; PubMed Central PMCID: PMC6167785.
ZOLEDRONIC ACID	Conry RM, Rodriguez MG, Pressey JG. Zoledronic acid in metastatic osteosarcoma: encouraging progression free survival in four consecutive patients. Clin Sarcoma Res. 2016 Apr 28;6:6. doi: 10.1186/s13569-016-0046-2. eCollection 2016. PubMed PMID: 27127605; PubMed Central PMCID: PMC4848872.
CD30 CAR T-cells	Hong LK, Chen Y, Smith CC, Montgomery SA, Vincent BG, Dotti G, Savoldo B. CD30-Redirected Chimeric Antigen Receptor T Cells Target CD30+ and CD30- Embryonal Carcinoma via Antigen-Dependent and Fas/FasL Interactions. Cancer Immunol Res. 2018 10;6(10):1274-1287. doi: 10.1158/2326-6066.CIR-18-0065. Epub 2018 Aug 07. PubMed PMID: 30087115.
PROPRANOLOL	Pasquier E, André N, Street J, Chougule A, Rekhi B, Ghosh J, Philip DSJ, Meurer M, MacKenzie KL, Kavallaris M, Banavali SD. Effective Management of Advanced Angiosarcoma by the Synergistic Combination of Propranolol and Vinblastine-based Metronomic Chemotherapy: A Bench to Bedside Study. EBioMedicine. 2016 Apr;6:87-95. doi: 10.1016/j.ebiom.2016.02.026. Epub 2016 Feb 17. PubMed PMID: 27211551; PubMed Central PMCID: PMC4856748.
NEO1132	Ryan KR, Giles F, Morgan GJ. Targeting both BET and CBP/EP300 proteins with the novel dual inhibitors NEO2734 and NEO1132 leads to anti-tumor activity in Multiple Myeloma. Eur J Haematol. 2020 Sep 30;:. doi: 10.1111/ejh.13525. Epub 2020 Oct 30. PubMed PMID: 32997383.
MIBG	Riad R, Kotb M, Omar W, Zaher A, Khalafalla K, Fawzy M, El-Wakil M, Ebeid E. Role of 131-I MIBG Therapy in the Treatment of Advanced Neuroblastoma. J Egypt Natl Canc Inst. 2009 Mar;21(1):51-8. PubMed PMID: 20601971.
Gandotinib	Lanikova L, Babosova O, Swierczek S, Wang L, Wheeler DA, Divoky V, Korinek V, Prchal JT. Coexistence of gain-of-function JAK2 germ line mutations with JAK2V617F in polycythemia vera. Blood. 2016 Nov 3;128(18):2266-2270. Epub 2016 Sep 19. PubMed PMID: 27647865; PubMed Central PMCID: PMC5095759.
AZACITIDINE	Bejar R, Lord A, Stevenson K, Bar-Natan M, Pérez-Ladaga A, Zaneveld J, Wang H, Caughey B, Stojanov P, Getz G, Garcia-Manero G, Kantarjian H, Chen R, Stone RM, Neuberg D, Steensma DP, Ebert BL. TET2 mutations predict response to hypomethylating agents in myelodysplastic syndrome patients. Blood. 2014 Oct 23;124(17):2705-12. doi: 10.1182/blood-2014-06-582809. Epub 2014 Sep 15. PubMed PMID: 25224413; PubMed Central PMCID: PMC4208285.
DECITABINE	Bejar R, Lord A, Stevenson K, Bar-Natan M, Pérez-Ladaga A, Zaneveld J, Wang H, Caughey B, Stojanov P, Getz G, Garcia-Manero G, Kantarjian H, Chen R, Stone RM, Neuberg D, Steensma DP, Ebert BL. TET2 mutations predict response to hypomethylating agents in myelodysplastic syndrome patients. Blood. 2014 Oct 23;124(17):2705-12. doi: 10.1182/blood-2014-06-582809. Epub 2014 Sep 15. PubMed PMID: 25224413; PubMed Central PMCID: PMC4208285.
ASP3026	Fontana D, Ceccon M, Gambacorti-Passerini C, Mologni L. Activity of second-generation ALK inhibitors against crizotinib-resistant mutants in an NPM-ALK model compared to EML4-ALK. Cancer Med. 2015 Jul;4(7):953-65. doi: 10.1002/cam4.413. Epub 2015 Feb 26. PubMed PMID: 25727400; PubMed Central PMCID: PMC4529334. S. Kuromitsu, M. Mori, I. Shimada, Y. Kondoh, N. Shindoh, T. Soga, T. Furutani, S. Konagai, H. Sakagami, M. Nakata, Y. Ueno, H. Fushiki, R. Saito, M. Sasamata, H. Mano, M. Kudou. Abstract A227: Antitumor activities of ASP3026 against EML4-ALK-dependent tumor models. Mol. Cancer Ther., 10 (2011) Abstract 227 Mologni L, Ceccon M, Pirola A, Chiriano G, Piazza R, Scapozza L, Gambacorti-Passerini C. NPM/ALK mutants resistant to ASP3026 display variable sensitivity to alternative ALK inhibitors but succumb to the novel compound PF-06463922. Oncotarget. 2015 Mar 20;6(8):5720-34. PubMed PMID: 25749034; PubMed Central PMCID: PMC4467397.
CERITINIB	Fontana D, Ceccon M, Gambacorti-Passerini C, Mologni L. Activity of second-generation ALK inhibitors against crizotinib-resistant mutants in an NPM-ALK model compared to EML4-ALK. Cancer Med. 2015 Jul;4(7):953-65. doi: 10.1002/cam4.413. Epub 2015 Feb 26. PubMed PMID: 25727400; PubMed Central PMCID: PMC4529334. Ou SH, Greenbowe J, Khan ZU, Azada MC, Ross JS, Stevens PJ, Ali SM, Miller VA, Gitlitz B. I1171 missense mutation (particularly I1171N) is a common resistance mutation in ALK-positive NSCLC patients who have progressive disease while on alectinib and is sensitive to ceritinib. Lung Cancer. 2015 May;88(2):231-4. doi: 10.1016/j.lungcan.2015.02.005. Epub 2015 Feb 12. PubMed PMID: 25736571. Ceritinib gains FDA approval for lung cancer. Cancer Discov. 2014 Jul;4(7):753-4. doi: 10.1158/2159-8290.CD-NB2014-074. Epub 2014 May 22. PubMed PMID: 25002599. Friboulet L, Li N, Katayama R, Lee CC, Gainor JF, Crystal AS, Michellys PY, Awad MM, Yanagitani N, Kim S, Pferdekamper AC, Li J, Kasibhatla S, Sun F, Sun X, Hua S, McNamara P, Mahmood S, Lockerman EL, Fujita N, Nishio M, Harris JL, Shaw AT, Engelman JA. The ALK inhibitor ceritinib overcomes crizotinib resistance in non-small cell lung cancer. Cancer Discov. 2014 Jun;4(6):662-673. doi: 10.1158/2159-8290.CD-13-0846. Epub 2014 Mar 27. PubMed PMID: 24675041; PubMed Central PMCID: PMC4068971.

Einsiedlerstrasse 23, 8834 Schindellegi, SWITZERLAND
E-mail: info@realtimeoncology.com **Web:** www.realtimeoncology.com

HATÓANYAG NEVE	REFERENCIA
	Okada K, Araki M, Sakashita T, Ma B, Kanada R, Yanagitani N, Horiike A, Koike S, Oh-Hara T, Watanabe K, Tamai K, Maemondo M, Nishio M, Ishikawa T, Okuno Y, Fujita N, Katayama R. Prediction of ALK mutations mediating ALK-TKIs resistance and drug re-purposing to overcome the resistance. EBioMedicine. 2019 Mar;41:105-119. doi: 10.1016/j.ebiom.2019.01.019. Epub 2019 Jan 17. PubMed PMID: 30662002; PubMed Central PMCID: PMC6441848.
HM95573	Lee Y-M, Bae I, Mo NG, Lee JH, Kim S, Song JY, et al. Abstract 2607: Antitumor activity of the selective RAF inhibitor HM95573 in solid tumors and hematologic malignancies. Cancer Res. 2015 Aug 1;75(15 Supplement): 2607–2607.
XL281	LeCluyse EL, Appel LE, Sutton SC. Relationship between drug absorption enhancing activity and membrane perturbing effects of acylcarnitines. Pharm Res. 1991 Jan;8(1):84-7. PubMed PMID: 2014213.
ENCORAFENIB	Stuart D, Li N, Poon DJ, Aardalen K, Kaufman S, Merritt H, Salangsang F, Lorenzana E, Li A, Ghoddusi M. Preclinical profile of LGX818: A potent and selective RAF kinase inhibitor. Cancer Res. 2012;6(Apr 25 supplement):3790.
PANOBINOSTAT	Weissmann S, Cloos PA, Sidoli S, Jensen ON, Pollard S, Helin K. The Tumor Suppressor CIC Directly Regulates MAPK Pathway Genes via Histone Deacetylation. Cancer Res. 2018 Aug 1;78(15):4114-4125. doi: 10.1158/0008-5472.CAN-18-0342. Epub 2018 May 29. PubMed PMID: 29844126; PubMed Central PMCID: PMC6076439.
BI-847325	Phadke MS, Sini P, Smalley KS. The Novel ATP-Competitive MEK/Aurora Kinase Inhibitor BI-847325 Overcomes Acquired BRAF Inhibitor Resistance through Suppression of Mcl-1 and MEK Expression. Mol Cancer Ther. 2015 Jun;14(6):1354-64. doi: 10.1158/1535-7163.MCT-14-0832. Epub 2015 Apr 14. PubMed PMID: 25873592; PubMed Central PMCID: PMC4458462.
DABRAFENIB	Da Vià MC, Solimando AG, Garitano-Trojaola A, Barrio S, Munawar U, Strifler S, Haertle L, Rhodes N, Teufel E, Vogt C, Lapa C, Beilhack A, Rasche L, Einsele H, Kortüm KM. CIC Mutation as a Molecular Mechanism of Acquired Resistance to Combined BRAF-MEK Inhibition in Extramedullary Multiple Myeloma with Central Nervous System Involvement. Oncologist. 2020 Feb;25(2):112-118. doi: 10.1634/theoncologist.2019-0356. Epub 2019 Jun 18. PubMed PMID: 32043788; PubMed Central PMCID: PMC7011664.
CYTARABINE	Chen C, Liu Y, Rappaport AR, Kitzing T, Schultz N, Zhao Z, Shroff AS, Dickins RA, Vakoc CR, Bradner JE, Stock W, LeBeau MM, Shannon KM, Kogan S, Zuber J, Lowe SW. MLL3 is a haploinsufficient 7q tumor suppressor in acute myeloid leukemia. Cancer Cell. 2014 May 12;25(5):652-65. doi: 10.1016/j.ccr.2014.03.016. PubMed PMID: 24794707; PubMed Central PMCID: PMC4206212.
DASATINIB	Nam S, Kim D, Cheng JQ, Zhang S, Lee JH, Buettner R, Mirosevich J, Lee FY, Jove R. Action of the Src family kinase inhibitor, dasatinib (BMS-354825), on human prostate cancer cells. Cancer Res. 2005 Oct 15;65(20):9185-9. PubMed PMID: 16230377. Schwarz LJ, Fox EM, Balko JM, Garrett JT, Kuba MG, Estrada MV, González-Angulo AM, Mills GB, Red-Brewer M, Mayer IA, Abramson V, Rizzo M, Kelley MC, Meszoely IM, Arteaga CL. LYN-activating mutations mediate antiestrogen resistance in estrogen receptor-positive breast cancer. J Clin Invest. 2014 Dec;124(12):5490-502. doi: 10.1172/JCI72573. Epub 2014 Jun 17. PubMed PMID: 25401474; PubMed Central PMCID: PMC4348968. Redaelli S, Piazza R, Rostagno R, Magistroni V, Perini P, Marega M, Gambacorti-Passerini C, Boschelli F. Activity of bosutinib, dasatinib, and nilotinib against 18 imatinib-resistant BCR/ABL mutants. J Clin Oncol. 2009 Jan 20;27(3):469-71. doi: 10.1200/JCO.2008.19.8853. Epub 2008 Dec 15. PubMed PMID: 19075254. Roger Belizaire, Sebastian H.J. Koochaki, Namrata D. Udeshi, Alexis Vedder, Lei Sun, Tanya Svinkina, Christina Hartigan, Caroline Stanclift, Monica Schenone, Steven A. Carr, Eric Padron, Benjamin L. Ebert. CBL mutations promote activation of PI3K/AKT signaling via LYN kinase. doi: https://doi.org/10.1101/2020.04.13.038448 Creedon H, Brunton VG. Src kinase inhibitors: promising cancer therapeutics? Crit Rev Oncog. 2012;17(2):145-59. Review. PubMed PMID: 22471705.
CRYPTOTANSHINONE	Liu W, Yu B, Xu G, Xu WR, Loh ML, Tang LD, Qu CK. Identification of cryptotanshinone as an inhibitor of oncogenic protein tyrosine phosphatase SHP2 (PTPN11). J Med Chem. 2013 Sep 26;56(18):7212-21. doi: 10.1021/jm400474r. Epub 2013 Sep 4. PubMed PMID: 23957426; PubMed Central PMCID: PMC4159095.
TNO155	Mullard A. Phosphatases start shedding their stigma of undruggability. Nat Rev Drug Discov. 2018 Nov 28;17(12):847-849. doi: 10.1038/nrd.2018.201. PubMed PMID: 30482950.
JAB-3068	https://endpts.com/qiming-hillhouse-bet-on-jacobios-nascent-pipeline-of-first-in-class-drugs-in-55m-round/
RMC 4630	Halliday PR, Blakely CM, Bivona TG. Emerging Targeted Therapies for the Treatment of Non-small Cell Lung Cancer. Curr Oncol Rep. 2019 Feb 26;21(3):21. doi: 10.1007/s11912-019-0770-x. Review. PubMed PMID: 30806814.
SHP099	LaRochelle JR, Fodor M, Vemulapalli V, Mohseni M, Wang P, Stams T, LaMarche MJ, Chopra R, Acker MG, Blacklow SC. Structural reorganization of SHP2 by oncogenic mutations and implications for oncoprotein resistance to allosteric inhibition. Nat Commun. 2018 10 30;9(1):4508. doi: 10.1038/s41467-018-06823-9. Epub 2018 Jul 30. PubMed PMID: 30375388; PubMed Central PMCID: PMC6207684. Sun X, Ren Y, Gunawan S, Teng P, Chen Z, Lawrence HR, Cai J, Lawrence NJ, Wu J. Selective inhibition of leukemia-associated SHP2(E69K) mutant by the allosteric SHP2 inhibitor SHP099. Leukemia. 2018 Jan 30. doi: 10.1038/s41375-018-0020-5. [Epub ahead of print] PubMed PMID: 29568093.
MIRDAMETINIB	Sogabe S, Togashi Y, Kato H, Kogita A, Mizukami T, Sakamoto Y, Banno E, Terashima M, Hayashi H, De Velasco MA, Sakai K, Fujita Y, Tomida S, Yasuda T, Takeyama Y, Okuno K, Nishio K. MEK inhibitor for gastric cancer with MEK1 gene mutations. Mol Cancer Ther. 2014 Sep 24. pii: molcanther.0429.2014. [Epub ahead of print] PubMed PMID: 25253779. Glassmann A, Winter J, Kraus D, Veit N, Probstmeier R. Pharmacological suppression of the Ras/MAPK pathway in thyroid carcinoma cells can provoke opposite effects on cell migration and proliferation: The appearance of yin-yang effects and the need of combinatorial treatments. Int J Oncol. 2014 Sep 23. doi: 10.3892/ijo.2014.2668. [Epub ahead of print] PubMed PMID: 25269412.

Einsiedlerstrasse 23, 8834 Schindellegi, SWITZERLAND
E-mail: info@realtimeoncology.com **Web:** www.realtimeoncology.com

HATÓANYAG NEVE	REFERENCIA
	Ryan MB, Der CJ, Wang-Gillam A, Cox AD. Targeting RAS-mutant cancers: is ERK the key? Trends Cancer. 2015 Nov 1;1(3):183-198. PubMed PMID: 26858988; PubMed Central PMCID: PMC4743050. Kiessling MK, Curioni-Fontecedro A, Samaras P, Lang S, Scharl M, Aguzzi A, Oldrige DA, Maris JM, Rogler G. Targeting the mTOR Complex by Everolimus in NRAS Mutant Neuroblastoma. PLoS One. 2016 Jan 28;11(1): e0147682. doi: 10.1371/journal.pone.0147682. Erratum in: PLoS One. 2017 Jan 20;12 (1):e0170851. PubMed PMID: 26821351; PubMed Central PMCID: PMC4731059. Tasian SK, Casas JA, Posocco D, Gandre-Babbe S, Gagne AL, Liang G, Loh ML, Weiss MJ, French DL, Chou ST. Mutation-specific signaling profiles and kinase inhibitor sensitivities of juvenile myelomonocytic leukemia revealed by induced pluripotent stem cells. Leukemia. 2018 Jun 8. doi: 10.1038/s41375-018-0169-y. [Epub ahead of print] PubMed PMID: 29884903.
BINIMETINIB	Thumar J, Shahbazian D, Aziz SA, Jilaveanu LB, Kluger HM. MEK targeting in N-RAS mutated metastatic melanoma. Mol Cancer. 2014 Mar 4;13:45. doi: 10.1186/1476-4598-13-45. PubMed PMID: 24588908; PubMed Central PMCID: PMC3945937. Ryan MB, Der CJ, Wang-Gillam A, Cox AD. Targeting RAS-mutant cancers: is ERK the key? Trends Cancer. 2015 Nov 1;1(3):183-198. PubMed PMID: 26858988; PubMed Central PMCID: PMC4743050. Hamidi H, Lu M, Chau K, Anderson L, Fejzo M, Ginther C, Linnartz R, Zubel A, Slamon DJ, Finn RS. KRAS mutational subtype and copy number predict in vitro response of human pancreatic cancer cell lines to MEK inhibition. Br J Cancer. 2014 Aug 28. doi: 10.1038/bjc.2014.475. [Epub ahead of print] PubMed PMID: 25167228. Kiessling MK, Curioni-Fontecedro A, Samaras P, Lang S, Scharl M, Aguzzi A, Oldrige DA, Maris JM, Rogler G. Targeting the mTOR Complex by Everolimus in NRAS Mutant Neuroblastoma. PLoS One. 2016 Jan 28;11(1): e0147682. doi: 10.1371/journal.pone.0147682. Erratum in: PLoS One. 2017 Jan 20;12 (1):e0170851. PubMed PMID: 26821351; PubMed Central PMCID: PMC4731059. Sarah E. Woodfield, Linna Zhang, Kathleen A. Scorsone, Yin Liu, and Peter E. Zage, Published online 2016 Mar 1. doi: 10.1186/s12885-016-2199-z, PMCID: PMC4772351, Binimetinib inhibits MEK and is effective against neuroblastoma tumor cells with low NF1 expression
COBIMETINIB	Ryan MB, Der CJ, Wang-Gillam A, Cox AD. Targeting RAS-mutant cancers: is ERK the key? Trends Cancer. 2015 Nov 1;1(3):183-198. PubMed PMID: 26858988; PubMed Central PMCID: PMC4743050. Singh A, Ruan Y, Tippett T, Narendran A. Targeted inhibition of MEK1 by cobimetinib leads to differentiation and apoptosis in neuroblastoma cells. J Exp Clin Cancer Res. 2015 Sep 18;34:104. doi: 10.1186/s13046-015-0222-x. PubMed PMID: 26384788; PubMed Central PMCID: PMC4575431.
PD98059	Reiners JJ Jr, Lee JY, Clift RE, Dudley DT, Myrand SP. PD98059 is an equipotent antagonist of the aryl hydrocarbon receptor and inhibitor of mitogen-activated protein kinase kinase. Mol Pharmacol. 1998 Mar;53(3):438-45. PubMed PMID: 9495809.
ARRY-300	Ryan MB, Der CJ, Wang-Gillam A, Cox AD. Targeting RAS-mutant cancers: is ERK the key? Trends Cancer. 2015 Nov 1;1(3):183-198. PubMed PMID: 26858988; PubMed Central PMCID: PMC4743050.
AS703988	Ryan MB, Der CJ, Wang-Gillam A, Cox AD. Targeting RAS-mutant cancers: is ERK the key? Trends Cancer. 2015 Nov 1;1(3):183-198. PubMed PMID: 26858988; PubMed Central PMCID: PMC4743050.
U0126	Solenkova NV, Solodushko V, Cohen MV, Downey JM. Endogenous adenosine protects preconditioned heart during early minutes of reperfusion by activating Akt. Am J Physiol Heart Circ Physiol. 2006 Jan;290(1):H441-9. Epub 2005 Sep 9. PubMed PMID: 16155103.
WX-554	Ryan MB, Der CJ, Wang-Gillam A, Cox AD. Targeting RAS-mutant cancers: is ERK the key? Trends Cancer. 2015 Nov 1;1(3):183-198. PubMed PMID: 26858988; PubMed Central PMCID: PMC4743050. Akinleye A, Furqan M, Mukhi N, Ravella P, Liu D. MEK and the inhibitors: from bench to bedside. J Hematol Oncol. 2013 Apr 12;6:27. doi: 10.1186/1756-8722-6-27. Review. PubMed PMID: 23587417; PubMed Central PMCID: PMC3626705.
TAK-733	Ryan MB, Der CJ, Wang-Gillam A, Cox AD. Targeting RAS-mutant cancers: is ERK the key? Trends Cancer. 2015 Nov 1;1(3):183-198. PubMed PMID: 26858988; PubMed Central PMCID: PMC4743050. von Euw E, Atefi M, Attar N, Chu C, Zachariah S, Burgess BL, Mok S, Ng C, Wong DJ, Chmielowski B, Lichter DI, Koya RC, McCannel TA, Izmailova E, Ribas A. Antitumor effects of the investigational selective MEK inhibitor TAK733 against cutaneous and uveal melanoma cell lines. Mol Cancer. 2012 Apr 19;11:22. PubMed PMID: 22515704; PubMed Central PMCID: PMC3444881.
RO4987655	Ryan MB, Der CJ, Wang-Gillam A, Cox AD. Targeting RAS-mutant cancers: is ERK the key? Trends Cancer. 2015 Nov 1;1(3):183-198. PubMed PMID: 26858988; PubMed Central PMCID: PMC4743050. Akinleye A, Furqan M, Mukhi N, Ravella P, Liu D. MEK and the inhibitors: from bench to bedside. J Hematol Oncol. 2013 Apr 12;6:27. doi: 10.1186/1756-8722-6-27. Review. PubMed PMID: 23587417; PubMed Central PMCID: PMC3626705. Zimmer L, Barlesi F, Martinez-Garcia M, Dieras V, Schellens JH, Spano JP, Middleton MR, Calvo E, Paz-Ares L, Larkin J, Pacey S, Venturi M, Kraeber-Bodéré F, Tessier JJ, Eberhardt WE, Paques M, Guarin E, Meresse V, Soria JC. Phase I expansion and pharmacodynamic study of the oral MEK inhibitor RO4987655 (CH4987655) in selected patients with advanced cancer with RAS-RAF mutations. Clin Cancer Res. 2014 Aug 15;20(16):4251-61. doi: 10.1158/1078-0432.CCR-14-0341. Epub 2014 Jun 19. PubMed PMID: 24947927.
GDC-0623	

Einsiedlerstrasse 23, 8834 Schindellegi, SWITZERLAND
E-mail: info@realtimeoncology.com **Web:** www.realtimeoncology.com

HATÓANYAG NEVE	REFERENCIA
	Ryan MB, Der CJ, Wang-Gillam A, Cox AD. Targeting RAS-mutant cancers: is ERK the key? Trends Cancer. 2015 Nov 1;1(3):183-198. PubMed PMID: 26858988; PubMed Central PMCID: PMC4743050.
E6201	Kumar V, Schuck EL, Pelletier RD, Farah N, Condon KB, Ye M, Rowbottom C, King BM, Zhang ZY, Saxton PL, Wong YN. Pharmacokinetic characterization of a natural product-inspired novel MEK1 inhibitor E6201 in preclinical species. Cancer Chemother Pharmacol. 2012 Jan;69(1):229-37. doi: 10.1007/s00280-011-1687-8. Epub 2011 Jun 23. PubMed PMID: 21698359.
	Ryan MB, Der CJ, Wang-Gillam A, Cox AD. Targeting RAS-mutant cancers: is ERK the key? Trends Cancer. 2015 Nov 1;1(3):183-198. PubMed PMID: 26858988; PubMed Central PMCID: PMC4743050.
REFAMETINIB	Ryan MB, Der CJ, Wang-Gillam A, Cox AD. Targeting RAS-mutant cancers: is ERK the key? Trends Cancer. 2015 Nov 1;1(3):183-198. PubMed PMID: 26858988; PubMed Central PMCID: PMC4743050.
	Akinleye A, Furqan M, Mukhi N, Ravella P, Liu D. MEK and the inhibitors: from bench to bedside. J Hematol Oncol. 2013 Apr 12;6:27. doi: 10.1186/1756-8722-6-27. Review. PubMed PMID: 23587417; PubMed Central PMCID: PMC3626705.
AZD8330	Cohen RB, Aamdal S, Nyakas M, Cavallin M, Green D, Learoyd M, Smith I, Kurzrock R. A phase I dose-finding, safety and tolerability study of AZD8330 in patients with advanced malignancies. Eur J Cancer. 2013 May;49(7):1521-9. doi: 10.1016/j.ejca.2013.01.013. Epub 2013 Feb 21. PubMed PMID: 23433846.
	Ryan MB, Der CJ, Wang-Gillam A, Cox AD. Targeting RAS-mutant cancers: is ERK the key? Trends Cancer. 2015 Nov 1;1(3):183-198. PubMed PMID: 26858988; PubMed Central PMCID: PMC4743050.
CH5126766	Ishii N, Harada N, Joseph EW, Ohara K, Miura T, Sakamoto H, Matsuda Y, Tomii Y, Tachibana-Kondo Y, Iikura H, Aoki T, Shimma N, Arisawa M, Sowa Y, Poulikakos PI, Rosen N, Aoki Y, Sakai T. Enhanced inhibition of ERK signaling by a novel allosteric MEK inhibitor, CH5126766, that suppresses feedback reactivation of RAF activity. Cancer Res. 2013 Jul 1;73(13):4050-60. doi: 10.1158/0008-5472.CAN-12-3937. Epub 2013 May 10. PubMed PMID: 23667175; PubMed Central PMCID: PMC4115369.
	Ryan MB, Der CJ, Wang-Gillam A, Cox AD. Targeting RAS-mutant cancers: is ERK the key? Trends Cancer. 2015 Nov 1;1(3):183-198. PubMed PMID: 26858988; PubMed Central PMCID: PMC4743050.
SELUMETINIB	Ryan MB, Der CJ, Wang-Gillam A, Cox AD. Targeting RAS-mutant cancers: is ERK the key? Trends Cancer. 2015 Nov 1;1(3):183-198. PubMed PMID: 26858988; PubMed Central PMCID: PMC4743050.
	Irving J, Matheson E, Minto L, Blair H, Case M, Halsey C, Swidenbank I, Ponthan F, Kirschner-Schwabe R, Groeneveld-Krentz S, Hof J, Allan J, Harrison C, Vormoor J, von Stackelberg A, Eckert C. Ras pathway mutations are highly prevalent in relapsed childhood acute lymphoblastic leukaemia, may act as relapse-drivers and confer sensitivity to MEK inhibition. Blood. 2014 Sep 24. pii: blood-2014-04-531871. [Epub ahead of print] PubMed PMID: 25253770.
	Kiessling MK, Curioni-Fontecedro A, Samaras P, Lang S, Scharl M, Aguzzi A, Oldrige DA, Maris JM, Rogler G. Targeting the mTOR Complex by Everolimus in NRAS Mutant Neuroblastoma. PLoS One. 2016 Jan 28;11(1): e0147682. doi: 10.1371/journal.pone.0147682. Erratum in: PLoS One. 2017 Jan 20;12 (1):e0170851. PubMed PMID: 26821351; PubMed Central PMCID: PMC4731059.
	Balmanno K, Chell SD, Gillings AS, Hayat S, Cook SJ. Intrinsic resistance to the MEK1/2 inhibitor AZD6244 (ARRY-142886) is associated with weak ERK1/2 signalling and/or strong PI3K signalling in colorectal cancer cell lines. Int J Cancer. 2009 Nov 15;125(10):2332-41. doi: 10.1002/ijc.24604. PubMed PMID: 19637312.
	Ambrosini G, Pratilas CA, Qin LX, Tadi M, Surriga O, Carvajal RD, Schwartz GK. Identification of unique MEK-dependent genes in GNAQ mutant uveal melanoma involved in cell growth, tumor cell invasion, and MEK resistance. Clin Cancer Res. 2012 Jul 1;18(13):3552-61. doi: 10.1158/1078-0432.CCR-11-3086. Epub 2012 May 1. PubMed PMID: 22550165; PubMed Central PMCID: PMC3433236.
CI-1040	Rinehart J, Adjei AA, Lorusso PM, Waterhouse D, Hecht JR, Natale RB, Hamid O, Varterasian M, Asbury P, Kaldjian EP, Gulyas S, Mitchell DY, Herrera R, Sebolt-Leopold JS, Meyer MB. Multicenter phase II study of the oral MEK inhibitor, CI-1040, in patients with advanced non-small-cell lung, breast, colon, and pancreatic cancer. J Clin Oncol. 2004 Nov 15;22(22):4456-62. Epub 2004 Oct 13. PubMed PMID: 15483017.
TRAMETINIB	Jing J, Greshock J, Holbrook JD, Gilmartin A, Zhang X, McNeil E, Conway T, Moy C, Laquerre S, Bachman K, Wooster R, Degenhardt Y. Comprehensive predictive biomarker analysis for MEK inhibitor GSK1120212. Mol Cancer Ther. 2012 Mar;11(3):720-9. doi: 10.1158/1535-7163.MCT-11-0505. Epub 2011 Dec 14. PubMed PMID: 22169769.
	King JW, Nathan PD. Role of the MEK inhibitor trametinib in the treatment of metastatic melanoma. Future Oncol. 2014 Aug;10(9):1559-70. doi: 10.2217/fon.14.89. PubMed PMID: 25145427.
	Ryan MB, Der CJ, Wang-Gillam A, Cox AD. Targeting RAS-mutant cancers: is ERK the key? Trends Cancer. 2015 Nov 1;1(3):183-198. PubMed PMID: 26858988; PubMed Central PMCID: PMC4743050.
	Laganà A et al. Precision Medicine for Relapsed Multiple Myeloma on the Basis of an Integrative Multiomics Approach. JCO Precision Oncology 2018 :2, 1-17. doi: 10.1200/PO.18.00019
	Ikeda M, Ioka T, Fukutomi A, Morizane C, Kasuga A, Takahashi H, Todaka A, Okusaka T, Creasy CL, Gorman S, Felitsky DJ, Kobayashi M, Zhang F, Furuse J. Efficacy and safety of trametinib in Japanese patients with advanced biliary tract cancers refractory to gemcitabine. Cancer Sci. 2018 Jan;109(1):215-224. doi: 10.1111/cas.13438. Epub 2017 Dec 9. PubMed PMID: 29121415; PubMed Central PMCID: PMC5765304.
REGORAFENIB	Strumberg D, Schultheis B. Regorafenib for cancer. Expert Opin Investig Drugs. 2012 Jun;21(6):879-89. doi: 10.1517 /13543784.2012.684752. Review. PubMed PMID: 22577890.

Einsiedlerstrasse 23, 8834 Schindellegi, SWITZERLAND
E-mail: info@realtimeoncology.com **Web:** www.realtimeoncology.com

HATÓANYAG NEVE	REFERENCIA
	Mross K, Frost A, Steinbild S, Hedbom S, Büchert M, Fasol U, Unger C, Krätzschmar J, Heinig R, Boix O, Christensen O. A phase I dose-escalation study of regorafenib (BAY 73-4506), an inhibitor of oncogenic, angiogenic, and stromal kinases, in patients with advanced solid tumors. Clin Cancer Res. 2012 May 1;18(9):2658-67. doi: 10.1158/1078-0432.CCR-11-1900. Epub 2012 Mar 15. PubMed PMID: 22421192. Eric Van Cutsem, Alberto F. Sobrero, Salvatore Siena, Alfredo Falcone, Marc Ychou, Yves Humblet, Olivier Bouche, Laurent Mineur, Carlo Barone, Antoine Adenis, Josep Tabernero, Takayuki Yoshino, Heinz-Josef Lenz, Richard M. Goldberg, Daniel J. Sargent, Frank Cihon, Andrea Wagner, Dirk Laurent, Axel Grothey. Phase III CORRECT trial of regorafenib in metastatic colorectal cancer (mCRC). Journal of Clinical Oncology, 2012 ASCO Annual Meeting Abstracts. Vol 30, No 15_suppl (May 20 Supplement), 2012: 3502 Yan Y, Grothey A. Molecular profiling in the treatment of colorectal cancer: focus on regorafenib. Onco Targets Ther. 2015 Oct 15;8:2949-57. doi: 10.2147/OTT.S79145. Review. PubMed PMID: 26508880; PubMed Central PMCID: PMC4610887. George S, Feng Y, Von Mehren M, Choy E, Corless CL, Hornick JL, Butrynski JE, Wagner AJ, Solomon S, Morgan JA, Heinrich MC. Prolonged survival and disease control in the academic phase II trial of regorafenib in GIST: Response based on genotype.
CARBOPLATIN	Guo S, Loibl S, von Minckwitz G, Darb-Esfahani S, Lederer B, Denkert C. PIK3CA H1047R Mutation Associated with a Lower Pathological Complete Response Rate in Triple-Negative Breast Cancer Patients Treated with Anthracycline-Taxane-Based Neoadjuvant Chemotherapy. Cancer Res Treat. 2020 Jul;52(3):689-696. doi: 10.4143/crt.2019.497. Epub 2020 Mar 04. PubMed PMID: 32019278; PubMed Central PMCID: PMC7373870. Fouladi M, Gururangan S, Moghrabi A, Phillips P, Gronewold L, Wallace D, Sanford RA, Gajjar A, Kun LE, Heideman R. Carboplatin-based primary chemotherapy for infants and young children with CNS tumors. Cancer. 2009 Jul 15;115(14):3243-53. doi: 10.1002/cncr.24362. PubMed PMID: 19484793; PubMed Central PMCID: PMC4307774.
Anthracycline	Guo S, Loibl S, von Minckwitz G, Darb-Esfahani S, Lederer B, Denkert C. PIK3CA H1047R Mutation Associated with a Lower Pathological Complete Response Rate in Triple-Negative Breast Cancer Patients Treated with Anthracycline-Taxane-Based Neoadjuvant Chemotherapy. Cancer Res Treat. 2020 Jul;52(3):689-696. doi: 10.4143/crt.2019.497. Epub 2020 Mar 04. PubMed PMID: 32019278; PubMed Central PMCID: PMC7373870.
FOLFOX	Jin CH, Wang AH, Chen JM, Li RX, Liu XM, Wang GP, Xing LQ. Observation of curative efficacy and prognosis following combination chemotherapy with celecoxib in the treatment of advanced colorectal cancer. J Int Med Res. 2011;39(6):2129-40. PubMed PMID: 22289528. Wang Q, Shi YL, Zhou K, Wang LL, Yan ZX, Liu YL, Xu LL, Zhao SW, Chu HL, Shi TT, Ma QH, Bi J. PIK3CA mutations confer resistance to first-line chemotherapy in colorectal cancer. Cell Death Dis. 2018 Jul 3;9(7):739. doi: 10.1038/s41419-018-0776-6. PubMed PMID: 29970892; PubMed Central PMCID: PMC6030128.
MELOXICAM	Hamada S, Futamura N, Ikuta K, Urakawa H, Kozawa E, Ishiguro N, Nishida Y. CTNNB1 S45F mutation predicts poor efficacy of meloxicam treatment for desmoid tumors: a pilot study. PLoS One. 2014 May 1;9(5):e96391. doi: 10.1371/journal.pone.0096391. eCollection 2014. PubMed PMID: 24788118; PubMed Central PMCID: PMC4006838.
ABT-737	Wang Z, Fukushima H, Gao D, Inuzuka H, Wan L, Lau AW, Liu P, Wei W. The two faces of FBW7 in cancer drug resistance. Bioessays. 2011 Nov;33(11):851-9. doi: 10.1002/bies.201100101. Review. PubMed PMID: 22006825; PubMed Central PMCID: PMC3364519.
DOXORUBICIN	Ren Y, Chen Z, Chen L, Woods NT, Reuther GW, Cheng JQ, Wang HG, Wu J. Shp2E76K mutant confers cytokine-independent survival of TF-1 myeloid cells by up-regulating Bcl-XL. J Biol Chem. 2007 Dec 14;282(50):36463-73. Epub 2007 Oct 17. PubMed PMID: 17942397; PubMed Central PMCID: PMC3000740. Chen L, Yang L, Yao L, Kuang XY, Zuo WJ, Li S, Qiao F, Liu YR, Cao ZG, Zhou SL, Zhou XY, Yang WT, Shi JX, Huang W, Hu X, Shao ZM. Characterization of PIK3CA and PIK3R1 somatic mutations in Chinese breast cancer patients. Nat Commun. 2018 Apr 10;9(1):1357. doi: 10.1038/s41467-018-03867-9. PubMed PMID: 29636477; PubMed Central PMCID: PMC5893593. Navrkalova V, Sebejova L, Zemanova J, Kminkova J, Kubesova B, Malcikova J, Mraz M, Smardova J, Pavlova S, Doubek M, Brychtova Y, Potesil D, Nemethova V, Mayer J, Pospisilova S, Trbusek M. ATM mutations uniformly lead to ATM dysfunction in chronic lymphocytic leukemia: application of functional test using doxorubicin. Haematologica. 2013 Jul;98(7):1124-31. doi: 10.3324/haematol.2012.081620. Epub 2013 Apr 12. PubMed PMID: 23585524; PubMed Central PMCID: PMC3696617. Chen C, Liu Y, Rappaport AR, Kitzing T, Schultz N, Zhao Z, Shroff AS, Dickins RA, Vakoc CR, Bradner JE, Stock W, LeBeau MM, Shannon KM, Kogan S, Zuber J, Lowe SW. MLL3 is a haploinsufficient 7q tumor suppressor in acute myeloid leukemia. Cancer Cell. 2014 May 12;25(5):652-65. doi: 10.1016/j.ccr.2014.03.016. PubMed PMID: 24794707; PubMed Central PMCID: PMC4206212.
POZIOTINIB	Cha MY, Lee KO, Kim M, Song JY, Lee KH, Park J, Chae YJ, Kim YH, Suh KH, Lee GS, Park SB, Kim MS. Antitumor activity of HM781-36B, a highly effective pan-HER inhibitor in erlotinib-resistant NSCLC and other EGFR-dependent cancer models. Int J Cancer. 2012 May 15;130(10):2445-54. doi: 10.1002/ijc.26276. Epub 2011 Aug 24. PubMed PMID: 21732342.
BMS-690514	Glaser G, Weroha SJ, Becker MA, Hou X, Enderica-Gonzalez S, Harrington SC, Haluska P. Conventional chemotherapy and oncogenic pathway targeting in ovarian carcinosarcoma using a patient-derived tumorgraft. PLoS One. 2015 May 11;10(5):e0126867. doi: 10.1371/journal.pone.0126867. eCollection 2015. PubMed PMID: 25962155; PubMed Central PMCID: PMC4427104. Soria JC, Baselga J, Hanna N, Laurie SA, Bahleda R, Felip E, Calvo E, Armand JP, Shepherd FA, Harbison CT, Berman D, Park JS, Zhang S, Vakkalagadda B, Kurland JF, Pathak AK, Herbst RS. Phase I-IIa study of BMS-690514, an EGFR, HER-2 and -4 and VEGFR-1 to -3 oral tyrosine kinase inhibitor, in patients with advanced or metastatic

Einsiedlerstrasse 23, 8834 Schindellegi, SWITZERLAND
E-mail: info@realtimeoncology.com **Web:** www.realtimeoncology.com

HATÓANYAG NEVE	REFERENCIA
	solid tumours. Eur J Cancer. 2013 May;49(8):1815-24. doi: 10.1016/j.ejca.2013.02.012. Epub 2013 Mar 13. PubMed PMID: 23490650.
BMS-599626	Wong TW, Lee FY, Yu C, Luo FR, Oppenheimer S, Zhang H, Smykla RA, Mastalerz H, Fink BE, Hunt JT, Gavai AV, Vite GD. Preclinical antitumor activity of BMS-599626, a pan-HER kinase inhibitor that inhibits HER1/HER2 homodimer and heterodimer signaling. Clin Cancer Res. 2006 Oct 15;12(20 Pt 1):6186-93. PubMed PMID: 17062696. Axelrod MJ, Mendez RE, Khalil A, Leimgruber SS, Sharlow ER, Capaldo B, Conaway M, Gioeli DG, Weber MJ, Jameson MJ. Synergistic apoptosis in head and neck squamous cell carcinoma cells by co-inhibition of insulin-like growth factor-1 receptor signaling and compensatory signaling pathways. Head Neck. 2015 Dec;37(12):1722-32. doi: 10.1002/hed.23822. Epub 2015 Apr 6. PubMed PMID: 24986420. Soria JC, Cortes J, Massard C, Armand JP, De Andreis D, Ropert S, Lopez E, Catteau A, James J, Marier JF, Beliveau M, Martell RE, Baselga J. Phase I safety, pharmacokinetic and pharmacodynamic trial of BMS-599626 (AC480), an oral pan-HER receptor tyrosine kinase inhibitor, in patients with advanced solid tumors. Ann Oncol. 2012 Feb;23(2):463-71. doi: 10.1093/annonc/mdr137. Epub 2011 May 16. PubMed PMID: 21576284.
TRASTUZUMAB DUOCARMAZINE	Banerji U, van Herpen CML, Saura C, Thistlethwaite F, Lord S, Moreno V, Macpherson IR, Boni V, Rolfo C, de Vries EGE, Rottey S, Geenen J, Eskens F, Gil-Martin M, Mommers EC, Koper NP, Aftimos P. Trastuzumab duocarmazine in locally advanced and metastatic solid tumours and HER2-expressing breast cancer: a phase 1 dose-escalation and dose-expansion study. Lancet Oncol. 2019 Jun 27. pii: S1470-2045(19)30328-6. doi: 10.1016/S1470-2045(19)30328-6. [Epub ahead of print] PubMed PMID: 31257177. Menderes G, Bonazzoli E, Bellone S, Black J, Altwerger G, Masserdotti A, Pettinella F, Zammataro L, Buza N, Hui P, Wong S, Litkouhi B, Ratner E, Silasi DA, Huang GS, Azodi M, Schwartz PE, Santin AD. SYD985, a novel duocarmycin-based HER2-targeting antibody-drug conjugate, shows promising antitumor activity in epithelial ovarian carcinoma with HER2/Neu expression. Gynecol Oncol. 2017 07;146(1):179-186. doi: 10.1016/j.ygyno.2017.04.023. Epub 2017 Aug 01. PubMed PMID: 28473206; PubMed Central PMCID: PMC5533304. SAURA, Cristina, et al. A phase I expansion cohorts study of SYD985 in heavily pretreated patients with HER2-positive or HER2-low metastatic breast cancer. 2018.
MM-302	Miller K, Cortes J, Hurvitz SA, Krop IE, Tripathy D, Verma S, Riahi K, Reynolds JG, Wickham TJ, Molnar I, Yardley DA. HERMIONE: a randomized Phase 2 trial of MM-302 plus trastuzumab versus chemotherapy of physician's choice plus trastuzumab in patients with previously treated, anthracycline-naïve, HER2-positive, locally advanced /metastatic breast cancer. BMC Cancer. 2016 Jun 3;16:352. doi: 10.1186/s12885-016-2385-z. PubMed PMID: 27259714; PubMed Central PMCID: PMC4893300.
ZANIDATAMAB	Funda Meric-Bernstam, Murali Beeram, Jose Ignacio Mayordomo, Diana L. Hanna, Jaffer A. Ajani, Mariela A. Blum Murphy, Rashmi Krishna Murthy, Sarina Anne Piha-Paul, Todd Michael Bauer, Johanna C. Bendell, Anthony B. El-Khoueiry, Heinz-Josef Lenz, Michael F. Press, Nels Royer, Diana Felice Hausman, Erika Paige Hamilton. Single agent activity of ZW25, a HER2-targeted bispecific antibody, in heavily pretreated HER2-expressing cancers. Journal of Clinical Oncology 36, no. 15_suppl (May 20, 2018) 2500-2500. DOI: 10.1200/JCO.2018.36.15_suppl.2500
ARX788	Xichun Hu, Jian Zhang, Dongmei Ji, Gang Xia, Yanping Ji, Gaozhun Xiong, Xuejun Liang. A phase 1 study of ARX788, a HER2-targeting antibody-drug conjugate, in patients with metastatic HER2-positive breast cancer [abstract]. In: Proceedings of the 2019 San Antonio Breast Cancer Symposium; 2019 Dec 10-14; San Antonio, TX. Philadelphia (PA): AACR; Cancer Res 2020;80(4 Suppl):Abstract nr P1-18-16.
ZENOCUTUZUMAB	Maria Alsina, Valentina Boni, Jan H.M. Schellens, Victor Moreno, Kees Bol, Martine Westendorp, L. Andres Sirulnik, Josep Tabernero, and Emiliano Calvo. First-in-human phase 1/2 study of MCLA-128, a full length IgG1 bispecific antibody targeting HER2 and HER3: Final phase 1 data and preliminary activity in HER2+ metastatic breast cancer (MBC). Journal of Clinical Oncology 35, no. 15_suppl (May 20, 2017) 2522-2522. DOI: 10.1200/JCO.2017.35.15_suppl.2522
TRASTUZUMAB DERUXTECAN	Doi T, Shitara K, Naito Y, Shimomura A, Fujiwara Y, Yonemori K, Shimizu C, Shimoi T, Kuboki Y, Matsubara N, Kitano A, Jikoh T, Lee C, Fujisaki Y, Ogitani Y, Yver A, Tamura K. Safety, pharmacokinetics, and antitumour activity of trastuzumab deruxtecan (DS-8201), a HER2-targeting antibody-drug conjugate, in patients with advanced breast and gastric or gastro-oesophageal tumours: a phase 1 dose-escalation study. Lancet Oncol. 2017 Nov;18(11):1512-1522. doi: 10.1016/S1470-2045(17)30604-6. Epub 2017 Oct 13. PubMed PMID: 29037983.
VARLITINIB	http://cancerres.aacrjournals.org/content/77/13_Supplement/2087
ERTUMAXOMAB	Kiewe P, Hasmüller S, Kahlert S, Heinrigs M, Rack B, Marmé A, Korfel A, Jäger M, Lindhofer H, Sommer H, Thiel E, Untch M. Phase I trial of the trifunctional anti-HER2 x anti-CD3 antibody ertumaxomab in metastatic breast cancer. Clin Cancer Res. 2006 May 15;12(10):3085-91. PubMed PMID: 16707606.
MDX-210	Posey JA, Raspet R, Verma U, Deo YM, Keller T, Marshall JL, Hodgson J, Mazumder A, Hawkins MJ. A pilot trial of GM-CSF and MDX-H210 in patients with erbB-2-positive advanced malignancies. J Immunother. 1999 Jul;22(4):371-9. PubMed PMID: 10404439.
PYROTINIB	Ma F, Li Q, Chen S, Zhu W, Fan Y, Wang J, Luo Y, Xing P, Lan B, Li M, Yi Z, Cai R, Yuan P, Zhang P, Li Q, Xu B. Phase I Study and Biomarker Analysis of Pyrotinib, a Novel Irreversible Pan-ErbB Receptor Tyrosine Kinase Inhibitor, in Patients With Human Epidermal Growth Factor Receptor 2-Positive Metastatic Breast Cancer. J Clin Oncol. 2017 May 12:JCO2016696179. doi: 10.1200/JCO.2016.69.6179. [Epub ahead of print] PubMed PMID: 28498781.
TRASTUZUMAB EMTANSINE	Kimberly L. Blackwell, David Miles, Luca Gianni, Ian E. Krop, Manfred Welslau, José Baselga, Mark D. Pegram, Do-Youn Oh, Veronique Dieras, Steven R. Olsen, Liang Fang, Michael W. Lu, Ellie Guardino, Sunil Verma. Primary results from EMILIA, a phase III study of trastuzumab emtansine (T-DM1) versus capecitabine (X) and lapatinib (L) in HER2-positive locally advanced or metastatic breast cancer (MBC) previously treated with trastuzumab (T) and a taxane. DOI: 10.1200/jco.2012.30.18_suppl.lba1 Journal of Clinical Oncology 30, no. 18_suppl
MUBRITINIB	Hamunyela RH, Serafin AM, Akudugu JM. Strong synergism between small molecule inhibitors of HER2, PI3K, mTOR and Bcl-2 in human breast cancer cells. Toxicol In Vitro. 2017 Feb;38:117-123. doi: 10.1016/j.tiv.2016.10.002. Epub 2016 Oct 11. PubMed PMID: 27737796.

Einsiedlerstrasse 23, 8834 Schindellegi, SWITZERLAND
E-mail: info@realtimeoncology.com **Web:** www.realtimeoncology.com

HATÓANYAG NEVE	REFERENCIA
PERTUZUMAB	Sabatier R, Gonçalves A. [Pertuzumab (Perjeta®) approval in HER2-positive metastatic breast cancers]. Bull Cancer. 2014 Jul-Aug;101(7-8):765-71. doi: 10.1684/bdc.2014.1940. French. PubMed PMID: 25091659. Franklin MC, Carey KD, Vajdos FF, Leahy DJ, de Vos AM, Sliwkowski MX. Insights into ErbB signaling from the structure of the ErbB2-pertuzumab complex. Cancer Cell. 2004 Apr;5(4):317-28. PubMed PMID: 15093539.
MARGETUXIMAB	Bang YJ, Giaccone G, Im SA, Oh DY, Bauer TM, Nordstrom JL, Li H, Chichili GR, Moore PA, Hong S, Stewart SJ, Baughman JE, Lechleider RJ, Burris HA. First-in-human phase 1 study of margetuximab (MGAH22), an Fc-modified chimeric monoclonal antibody, in patients with HER2-positive advanced solid tumors. Ann Oncol. 2017 Apr 1;28(4): 855-861. doi: 10.1093/annonc/mdx002. PubMed PMID: 28119295. Nordstrom JL, Gorlatov S, Zhang W, Yang Y, Huang L, Burke S, Li H, Ciccarone V, Zhang T, Stavenhagen J, Koenig S, Stewart SJ, Moore PA, Johnson S, Bonvini E. Anti-tumor activity and toxicokinetics analysis of MGAH22, an anti-HER2 monoclonal antibody with enhanced Fc receptor binding properties. Breast Cancer Res. 2011;13(6):R123. doi: 10.1186/bcr3069. Epub 2011 Nov 30. PubMed PMID: 22129105; PubMed Central PMCID: PMC3326565.
CP-724714	Jani JP, Finn RS, Campbell M, Coleman KG, Connell RD, Currier N, Emerson EO, Floyd E, Harriman S, Kath JC, Morris J, Moyer JD, Pustilnik LR, Rafidi K, Ralston S, Rossi AM, Steyn SJ, Wagner L, Winter SM, Bhattacharya SK. Discovery and pharmacologic characterization of CP-724,714, a selective ErbB2 tyrosine kinase inhibitor. Cancer Res. 2007 Oct 15;67(20):9887-93. PubMed PMID: 17942920.
CANERTINIB	Djerf Severinsson EA, Trinks C, Gréen H, Abdiu A, Hallbeck AL, Stål O, Walz TM. The pan-ErbB receptor tyrosine kinase inhibitor canertinib promotes apoptosis of malignant melanoma in vitro and displays anti-tumor activity in vivo. Biochem Biophys Res Commun. 2011 Oct 28;414(3):563-8. doi: 10.1016/j.bbrc.2011.09.118. Epub 2011 Oct 1. PubMed PMID: 21982771.
TUCATINIB	Yeomans A, Thirdborough SM, Valle-Argos B, Linley A, Krysov S, Hidalgo MS, Leonard E, Ishfaq M, Wagner SD, Willis AE, Steele AJ, Stevenson FK, Forconi F, Coldwell MJ, Packham G. Engagement of the B-cell receptor of chronic lymphocytic leukemia cells drives global and MYC-specific mRNA translation. Blood. 2016 Jan 28;127(4): 449-57. doi: 10.1182/blood-2015-07-660969. Epub 2015 Oct 21. PubMed PMID: 26491071.
VANDETANIB	Sarkar S, Mazumdar A, Dash R, Sarkar D, Fisher PB, Mandal M. ZD6474, a dual tyrosine kinase inhibitor of EGFR and VEGFR-2, inhibits MAPK/ERK and AKT/PI3-K and induces apoptosis in breast cancer cells. Cancer Biol Ther. 2010 Apr 15;9(8):592-603. Epub 2010 Apr 4. PubMed PMID: 20139705. Carlomagno F, Vitagliano D, Guida T, Ciardiello F, Tortora G, Vecchio G, Ryan AJ, Fontanini G, Fusco A, Santoro M. ZD6474, an orally available inhibitor of KDR tyrosine kinase activity, efficiently blocks oncogenic RET kinases. Cancer Res. 2002 Dec 15;62(24):7284-90. PubMed PMID: 12499271. Fox E, Widemann BC, Chuk MK, Marcus L, Aikin A, Whitcomb PO, Merino MJ, Lodish M, Dombi E, Steinberg SM, Wells SA, Balis FM. Vandetanib in children and adolescents with multiple endocrine neoplasia type 2B associated medullary thyroid carcinoma. Clin Cancer Res. 2013 Aug 1;19(15):4239-48. doi: 10.1158/1078-0432.CCR-13-0071. Epub 2013 Jun 13. PubMed PMID: 23766359. Mulligan LM. RET revisited: expanding the oncogenic portfolio. Nat Rev Cancer. 2014 Mar;14(3):173-86. doi: 10.1038 /nrc3680. Review. PubMed PMID: 24561444. Wells SA, Robinson BG, Gagel RF, Dralle H, Fagin JA, Santoro M, Baudin E, Elisei R, Jarzab B, Vasselli JR, Read J, Langmuir P, Ryan AJ, Schlumberger MJ. Vandetanib in patients with locally advanced or metastatic medullary thyroid cancer: a randomized, double-blind phase III trial. J Clin Oncol. 2012 Jan 10;30(2):134-41. doi: 10.1200/JCO. 2011.35.5040. Epub 2011 Sep 24. PubMed PMID: 22025146; PubMed Central PMCID: PMC3675689.
AMIVANTAMAB	Yun J, Lee SH, Kim SY, Jeong SY, Kim JH, Pyo KH, Park CW, Heo SG, Yun MR, Lim S, Lim SM, Hong MH, Kim HR, Thayu M, Curtin JC, Knoblauch RE, Lorenzi MV, Roshak A, Cho BC. Antitumor Activity of Amivantamab (JNJ-61186372), an EGFR-MET Bispecific Antibody, in Diverse Models of EGFR Exon 20 Insertion-Driven NSCLC. Cancer Discov. 2020 Aug;10(8):1194-1209. doi: 10.1158/2159-8290.CD-20-0116. Epub 2020 Oct 15. PubMed PMID: 32414908.
DACOMITINIB	Momeny M, Zarrinrad G, Moghaddaskho F, Poursheikhani A, Sankanian G, Zaghal A, Mirshahvaladi S, Esmaeili F, Eyvani H, Barghi F, Sabourinejad Z, Alishahi Z, Yousefi H, Ghasemi R, Dardaei L, Bashash D, Chahardouli B, Dehpour AR, Tavakkoly-Bazzaz J, Alimoghaddam K, Ghavamzadeh A, Ghaffari SH. Dacomitinib, a pan-inhibitor of ErbB receptors, suppresses growth and invasive capacity of chemoresistant ovarian carcinoma cells. Sci Rep. 2017 Jun 23;7(1):4204. doi: 10.1038/s41598-017-04147-0. PubMed PMID: 28646172; PubMed Central PMCID: PMC5482808. Ramalingam SS, Blackhall F, Krzakowski M, Barrios CH, Park K, Bover I, Seog Heo D, Rosell R, Talbot DC, Frank R, Letrent SP, Ruiz-Garcia A, Taylor I, Liang JQ, Campbell AK, O'Connell J, Boyer M. Randomized phase II study of dacomitinib (PF-00299804), an irreversible pan-human epidermal growth factor receptor inhibitor, versus erlotinib in patients with advanced non-small-cell lung cancer. J Clin Oncol. 2012 Sep 20;30(27):3337-44. doi: 10.1200/JCO. 2011.40.9433. Epub 2012 Jul 2. PubMed PMID: 22753918. Echarri MJ, Lopez-Martin A, Hitt R. Targeted Therapy in Locally Advanced and Recurrent/Metastatic Head and Neck Squamous Cell Carcinoma (LA-R/M HNSCC). Cancers (Basel). 2016 Feb 26;8(3). pii: E27. doi: 10.3390 /cancers8030027. Review. PubMed PMID: 26927178; PubMed Central PMCID: PMC4810111.
NECITUMUMAB	" Kuenen B, Witteveen PO, Ruijter R, Giaccone G, Dontabhaktuni A, Fox F, Katz T, Youssoufian H, Zhu J, Rowinsky EK, Voest EE. A phase I pharmacologic study of necitumumab (IMC-11F8), a fully human IgG1 monoclonal antibody directed against EGFR in patients with advanced solid malignancies. Clin Cancer Res. 2010 Mar 15;16(6):1915-23. doi: 10.1158/1078-0432.CCR-09-2425. Epub 2010 Mar 2. Erratum in: Clin Cancer Res. 2010 Sep 15;16(18):4681. Dosage error in article text. PubMed PMID: 20197484. "

Einsiedlerstrasse 23, 8834 Schindellegi, SWITZERLAND
E-mail: info@realtimeoncology.com **Web:** www.realtimeoncology.com

HATÓANYAG NEVE	REFERENCIA
	Garnock-Jones KP. Necitumumab: First Global Approval. Drugs. 2016 Feb;76(2):283-9. doi: 10.1007/s40265-015-0537-0. PubMed PMID: 26729188.
	Paz-Ares L, Socinski MA, Shahidi J, Hozak RR, Soldatenkova V, Kurek R, Varella-Garcia M, Thatcher N, Hirsch FR. Correlation of EGFR-expression with safety and efficacy outcomes in SQUIRE: a randomized, multicenter, open-label, phase III study of gemcitabine-cisplatin plus necitumumab versus gemcitabine-cisplatin alone in the first-line treatment of patients with stage IV squamous non-small-cell lung cancer. Ann Oncol. 2016 Aug;27(8):1573-9. doi: 10.1093/annonc/mdw214. Epub 2016 May 20. PubMed PMID: 27207107; PubMed Central PMCID: PMC4959928.
PETOSEMTAMAB	Abstract 32: Preclinical evaluation of MCLA-158: A bispecific antibody targeting LGR5 and EGFR using patient-derived colon carcinoma organoids
ZALUTUMUMAB	Saloura V, Cohen EE, Licitra L, Billan S, Dinis J, Lisby S, Gauler TC. An open-label single-arm, phase II trial of zalutumumab, a human monoclonal anti-EGFR antibody, in patients with platinum-refractory squamous cell carcinoma of the head and neck. Cancer Chemother Pharmacol. 2014 Jun;73(6):1227-39. doi: 10.1007/s00280-014-2459-z. Epub 2014 Apr 9. PubMed PMID: 24714973.
	Echarri MJ, Lopez-Martin A, Hitt R. Targeted Therapy in Locally Advanced and Recurrent/Metastatic Head and Neck Squamous Cell Carcinoma (LA-R/M HNSCC). Cancers (Basel). 2016 Feb 26;8(3). pii: E27. doi: 10.3390/cancers8030027. Review. PubMed PMID: 26927178; PubMed Central PMCID: PMC4810111.
SIMOTINIB	He L, Li S, Xie F, Cheng Z, Ran L, Liu X, Yu P. LC-ESI-MS/MS determination of simotinib, a novel epidermal growth factor receptor tyrosine kinase inhibitor: application to a pharmacokinetic study. J Chromatogr B Analyt Technol Biomed Life Sci. 2014 Feb 1;947-948:168-72. doi: 10.1016/j.jchromb.2013.12.021. Epub 2013 Dec 27. PubMed PMID: 24440798.
MATUZUMAB	Schmiedel J, Blaukat A, Li S, Knöchel T, Ferguson KM. Matuzumab binding to EGFR prevents the conformational rearrangement required for dimerization. Cancer Cell. 2008 Apr;13(4):365-73. doi: 10.1016/j.ccr.2008.02.019. PubMed PMID: 18394559; PubMed Central PMCID: PMC2725356.
H 447	Fury MG, Lipton A, Smith KM, Winston CB, Pfister DG. A phase-I trial of the epidermal growth factor receptor directed bispecific antibody MDX-447 without and with recombinant human granulocyte-colony stimulating factor in patients with advanced solid tumors. Cancer Immunol Immunother. 2008 Feb;57(2):155-63. Epub 2007 Jun 30. PubMed PMID: 17602224.
IMGATUZUMAB	Gerdes CA, Nicolini VG, Herter S, van Puijenbroek E, Lang S, Roemmele M, Moessner E, Freytag O, Friess T, Ries CH, Bossenmaier B, Mueller HJ, Umaña P. GA201 (RG7160): a novel, humanized, glycoengineered anti-EGFR antibody with enhanced ADCC and superior in vivo efficacy compared with cetuximab. Clin Cancer Res. 2013 Mar 1;19(5):1126-38. doi: 10.1158/1078-0432.CCR-12-0989. Epub 2012 Dec 3. PubMed PMID: 23209031.
BIBX 1382	Solca FF, Baum A, Langkopf E, Dahmann G, Heider KH, Himmelsbach F, van Meel JC. Inhibition of epidermal growth factor receptor activity by two pyrimidopyrimidine derivatives. J Pharmacol Exp Ther. 2004 Nov;311(2):502-9. Epub 2004 Jun 15. PubMed PMID: 15199094.
PKI 166	Bruns CJ, Solorzano CC, Harbison MT, Ozawa S, Tsan R, Fan D, Abbruzzese J, Traxler P, Buchdunger E, Radinsky R, Fidler IJ. Blockade of the epidermal growth factor receptor signaling by a novel tyrosine kinase inhibitor leads to apoptosis of endothelial cells and therapy of human pancreatic carcinoma. Cancer Res. 2000 Jun 1;60(11):2926-35. PubMed PMID: 10850439.
XILIERTINIB	Ren Y, Zheng J, Fan S, Wang L, Cheng M, Shi D, Zhang W, Tang R, Yu Y, Jiao L, Ni J, Yang H, Cai H, Yin F, Chen Y, Zhou F, Zhang W, Qing W, Su W. Anti-tumor efficacy of theliatinib in esophageal cancer patient-derived xenografts models with epidermal growth factor receptor (EGFR) overexpression and gene amplification. Oncotarget. 2017 Apr 19. doi: 10.18632/oncotarget.17243. [Epub ahead of print] PubMed PMID: 28472779.
TESEVATINIB	Gendreau SB, Ventura R, Keast P, Laird AD, Yakes FM, Zhang W, Bentzien F, Cancilla B, Lutman J, Chu F, Jackman L, Shi Y, Yu P, Wang J, Aftab DT, Jaeger CT, Meyer SM, De Costa A, Engell K, Chen J, Martini JF, Joly AH. Inhibition of the T790M gatekeeper mutant of the epidermal growth factor receptor by EXEL-7647. Clin Cancer Res. 2007 Jun 15;13(12):3713-23. PubMed PMID: 17575237.
NIMOTUZUMAB	"Chen YJ, Chi CW, Su WC, Huang HL. Lapatinib induces autophagic cell death and inhibits growth of human hepatocellular carcinoma. Oncotarget. 2014 Jul 15;5(13):4845-54. PubMed PMID: 24947784; PubMed Central PMCID: PMC4148104."
	" Su D, Jiao SC, Wang LJ, Shi WW, Long YY, Li J, Bai L. Efficacy of nimotuzumab plus gemcitabine usage as first-line treatment in patients with advanced pancreatic cancer. Tumour Biol. 2014 Mar;35(3):2313-8. doi: 10.1007/s13277-013-1306-x. Epub 2013 Oct 19. PubMed PMID: 24142531. "
	"Huang Y, Yu T, Fu X, Chen J, Liu Y, Li C, Xia Y, Zhang Z, Li L. EGFR inhibition prevents in vitro tumor growth of salivary adenoid cystic carcinoma. BMC Cell Biol. 2013 Mar 9;14:13. doi: 10.1186/1471-2121-14-13. PubMed PMID: 23496982; PubMed Central PMCID: PMC3610144."
MEHD7945A	Huang S, Li C, Armstrong EA, Peet CR, Saker J, Amler LC, Sliwkowski MX, Harari PM. Dual targeting of EGFR and HER3 with MEHD7945A overcomes acquired resistance to EGFR inhibitors and radiation. Cancer Res. 2013 Jan 15;73(2):824-33. doi: 10.1158/0008-5472.CAN-12-1611. Epub 2012 Nov 20. PubMed PMID: 23172311.
SAPITINIB	"Barlaam B, Anderton J, Ballard P, Bradbury RH, Hennequin LF, Hickinson DM, Kettle JG, Kirk G, Klinowska T, Lambert-van der Brempt C, Trigwell C, Vincent J, Ogilvie D. Discovery of AZD8931, an Equipotent, Reversible Inhibitor of Signaling by EGFR, HER2, and HER3 Receptors. ACS Med Chem Lett. 2013 May 31;4(8):742-6. doi: 10.1021/ml400146c. eCollection 2013 Aug 8. PubMed PMID: 24900741; PubMed Central PMCID: PMC4027407. "
AEE788	Traxler P, Allegrini PR, Brandt R, Brueggen J, Cozens R, Fabbro D, Grosios K, Lane HA, McSheehy P, Mestan J, Meyer T, Tang C, Wartmann M, Wood J, Caravatti G. AEE788: a dual family epidermal growth factor receptor/ErbB2 and vascular endothelial growth factor receptor tyrosine kinase inhibitor with antitumor and antiangiogenic activity. Cancer Res. 2004 Jul 15;64(14):4931-41. PubMed PMID: 15256466.

Einsiedlerstrasse 23, 8834 Schindellegi, SWITZERLAND
E-mail: info@realtimeoncology.com **Web:** www.realtimeoncology.com

HATÓANYAG NEVE	REFERENCIA
	"Baselga J, Mita AC, Schöffski P, Dumez H, Rojo F, Tabernero J, DiLea C, Mietlowski W, Low C, Huang J, Dugan M, Parker K, Walk E, van Oosterom A, Martinelli E, Takimoto CH. Using pharmacokinetic and pharmacodynamic data in early decision making regarding drug development: a phase I clinical trial evaluating tyrosine kinase inhibitor, AEE788. Clin Cancer Res. 2012 Nov 15;18(22):6364-72. doi: 10.1158/1078-0432.CCR-12-1499. Epub 2012 Sep 26. PubMed PMID: 23014528." "Meco D, Servidei T, Zannonit GF, Martinelli E, Prisco MG, Waure Cd, Riccardi R. Dual Inhibitor AEE78 Reduces Tumor Growth in Preclinical Models of Medulloblastoma. Transl Oncol. 2010 Oct;3(5):326-35. doi: 10.1593/tlo.10163. Epub 2014 Mar 5. PubMed PMID: 24670630."
OSIMERTINIB	Cross DA, Ashton SE, Ghiorghiu S, Eberlein C, Nebhan CA, Spitzler PJ, Orme JP, Finlay MR, Ward RA, Mellor MJ, Hughes G, Rahi A, Jacobs VN, Red Brewer M, Ichihara E, Sun J, Jin H, Ballard P, Al-Kadhimi K, Rowlinson R, Klinowska T, Richmond GH, Cantarini M, Kim DW, Ranson MR, Pao W. AZD9291, an irreversible EGFR TKI, overcomes T790M-mediated resistance to EGFR inhibitors in lung cancer. Cancer Discov. 2014 Sep;4(9):1046-61. doi: 10.1158/2159-8290.CD-14-0337. Epub 2014 Jun 3. PubMed PMID: 24893891. Liao S, Davoli T, Leng Y, Li MZ, Xu Q, Elledge SJ. A genetic interaction analysis identifies cancer drivers that modify EGFR dependency. Genes Dev. 2017 Jan 15;31(2):184-196. doi: 10.1101/gad.291948.116. Epub 2017 Feb 6. PubMed PMID: 28167502; PubMed Central PMCID: PMC5322732.
TRASTUZUMAB	Nahta R, Esteva FJ. HER2 therapy: molecular mechanisms of trastuzumab resistance. Breast Cancer Res. 2006;8(6): 215. Review. PubMed PMID: 17096862; PubMed Central PMCID: PMC1797036. Vu T, Claret FX. Trastuzumab: updated mechanisms of action and resistance in breast cancer. Front Oncol. 2012 Jun 18;2:62. doi: 10.3389/fonc.2012.00062. eCollection 2012. PubMed PMID: 22720269; PubMed Central PMCID: PMC3376449. Kataoka Y, Mukohara T, Shimada H, Saijo N, Hirai M, Minami H. Association between gain-of-function mutations in PIK3CA and resistance to HER2-targeted agents in HER2-amplified breast cancer cell lines. Ann Oncol. 2010 Feb;21 (2):255-62. doi: 10.1093/annonc/mdp304. PubMed PMID: 19633047. Esteva FJ, Guo H, Zhang S, Santa-Maria C, Stone S, Lanchbury JS, Sahin AA, Hortobagyi GN, Yu D. PTEN, PIK3CA, p-AKT, and p-p70S6K status: association with trastuzumab response and survival in patients with HER2-positive metastatic breast cancer. Am J Pathol. 2010 Oct;177(4):1647-56. doi: 10.2353/ajpath.2010.090885. PubMed PMID: 20813970; PubMed Central PMCID: PMC2947262. I Migliaccio, M Gutierrez, M Wu, H Wong, A Pavlick, SG Hilsenbeck, HM Horlings, M Rimawi, K Berns, R Bernards, C Osborne, CL Arteaga and JC Chang. PI3 kinase activation and response to trastuzumab or lapatinib in HER-2 overexpressing locally advanced breast cancer (LABC). Cancer Res 2009;69(2 Suppl):Abstract nr 34.
ERLOTINIB	Akita RW, Sliwkowski MX. Preclinical studies with Erlotinib (Tarceva). Semin Oncol. 2003 Jun;30(3 Suppl 7):15-24. Review. Erratum in: Semin Oncol. 2003 Dec;30(6):826. PubMed PMID: 12840797. " Peters S, Zimmermann S, Adjei AA. Oral epidermal growth factor receptor tyrosine kinase inhibitors for the treatment of non-small cell lung cancer: comparative pharmacokinetics and drug-drug interactions. Cancer Treat Rev. 2014 Sep;40(8):917-26. doi: 10.1016/j.ctrv.2014.06.010. Epub 2014 Jul 1. PubMed PMID: 25027951." Matsumoto Y, Maemondo M, Ishii Y, Okudera K, Demura Y, Takamura K, Kobayashi K, Morikawa N, Gemma A, Ishimoto O, Usui K, Harada M, Miura S, Fujita Y, Sato I, Saijo Y; for the North-East Japan Study Group. A phase II study of erlotinib monotherapy in pre-treated non-small cell lung cancer without EGFR gene mutation who have never/light smoking history: Re-evaluation of EGFR gene status (NEJ006/TCOG0903). Lung Cancer. 2014 Sep 16. pii: S0169-5002(14)00364-X. doi: 10.1016/j.lungcan.2014.08.019. [Epub ahead of print] PubMed PMID: 25249428. Pridham KJ, Varghese RT, Sheng Z. The Role of Class IA Phosphatidylinositol-4,5-Bisphosphate 3-Kinase Catalytic Subunits in Glioblastoma. Front Oncol. 2017 Dec 15;7:312. doi: 10.3389/fonc.2017.00312. eCollection 2017. Review. PubMed PMID: 29326882; PubMed Central PMCID: PMC5736525. Whale AD, Colman L, Lensun L, Rogers HL, Shuttleworth SJ. Functional characterization of a novel somatic oncogenic mutation of PIK3CB. Signal Transduct Target Ther. 2017 Dec 22;2:17063. doi: 10.1038/sigtrans.2017.63. eCollection 2017. PubMed PMID: 29279775; PubMed Central PMCID: PMC5740215.
JNJ-26483327	Gijsen M, King P, Perera T, Parker PJ, Harris AL, Larijani B, Kong A. HER2 phosphorylation is maintained by a PKB negative feedback loop in response to anti-HER2 herceptin in breast cancer. PLoS Biol. 2010 Dec 21;8(12): e1000563. doi: 10.1371/journal.pbio.1000563. Erratum in: PLoS Biol. 2016 Mar;14(3):e1002414. PubMed PMID: 21203579; PubMed Central PMCID: PMC3006345. Konings IR, de Jonge MJ, Burger H, van der Gaast A, van Beijsterveldt LE, Winkler H, Verweij J, Yuan Z, Hellemans P, Eskens FA. Phase I and pharmacological study of the broad-spectrum tyrosine kinase inhibitor JNJ-26483327 in patients with advanced solid tumours. Br J Cancer. 2010 Sep 28;103(7):987-92. doi: 10.1038/sj.bjc.6605867. Epub 2010 Sep 7. PubMed PMID: 20823884; PubMed Central PMCID: PMC2965873.
AFATINIB	Li D, Ambrogio L, Shimamura T, Kubo S, Takahashi M, Chirieac LR, Padera RF, Shapiro GI, Baum A, Himmelsbach F, Rettig WJ, Meyerson M, Solca F, Greulich H, Wong KK. BIBW2992, an irreversible EGFR/HER2 inhibitor highly effective in preclinical lung cancer models. Oncogene. 2008 Aug 7;27(34):4702-11. doi: 10.1038/onc.2008.109. Epub 2008 Apr 14. PubMed PMID: 18408761; PubMed Central PMCID: PMC2748240. Eskens FA, Mom CH, Planting AS, Gietema JA, Amelsberg A, Huisman H, van Doorn L, Burger H, Stopfer P, Verweij J, de Vries EG. A phase I dose escalation study of BIBW 2992, an irreversible dual inhibitor of epidermal growth

Einsiedlerstrasse 23, 8834 Schindellegi, SWITZERLAND
E-mail: info@realtimeoncology.com **Web:** www.realtimeoncology.com

HATÓANYAG NEVE	REFERENCIA
	factor receptor 1 (EGFR) and 2 (HER2) tyrosine kinase in a 2-week on, 2-week off schedule in patients with advanced solid tumours. Br J Cancer. 2008 Jan 15;98(1):80-5. Epub 2007 Nov 20. PubMed PMID: 18026190; PubMed Central PMCID: PMC2359721. " Yu HA, Riely GJ. Second-generation epidermal growth factor receptor tyrosine kinase inhibitors in lung cancers. J Natl Compr Canc Netw. 2013 Feb 1;11(2):161-9. PubMed PMID: 23411383; PubMed Central PMCID: PMC3673302." Echarri MJ, Lopez-Martin A, Hitt R. Targeted Therapy in Locally Advanced and Recurrent/Metastatic Head and Neck Squamous Cell Carcinoma (LA-R/M HNSCC). Cancers (Basel). 2016 Feb 26;8(3). pii: E27. doi: 10.3390 /cancers8030027. Review. PubMed PMID: 26927178; PubMed Central PMCID: PMC4810111. Schuler M, Awada A, Harter P, Canon JL, Possinger K, Schmidt M, De Grève J, Neven P, Dirix L, Jonat W, Beckmann MW, Schütte J, Fasching PA, Gottschalk N, Besse-Hammer T, Fleischer F, Wind S, Uttenreuther-Fischer M, Piccart M, Harbeck N. A phase II trial to assess efficacy and safety of afatinib in extensively pretreated patients with HER2-negative metastatic breast cancer. Breast Cancer Res Treat. 2012 Aug;134(3):1149-59. doi: 10.1007/s10549-012-2126-1. Epub 2012 Jul 5. PubMed PMID: 22763464; PubMed Central PMCID: PMC3409367.
EPERTINIB	Spicer J, Baird R, Suder A, Cresti N, Corbacho JG, Hogarth L, Frenkel E, Matsumoto S, Kawabata I, Donaldson K, Posner J, Sarker D, Jodrell D, Plummer R. Phase 1 dose-escalation study of S-222611, an oral reversible dual tyrosine kinase inhibitor of EGFR and HER2, in patients with solid tumours. Eur J Cancer. 2015 Jan;51(2):137-45. doi: 10.1016/j.ejca.2014.11.003. Epub 2014 Nov 27. PubMed PMID: 25434923.
TAK-285	Meng X, Li Y, Tang H, Mao W, Yang H, Wang X, Ding X, Xie S. Drug response to HER2 gatekeeper T798M mutation in HER2-positive breast cancer. Amino Acids. 2016 Feb;48(2):487-97. doi: 10.1007/s00726-015-2102-2. Epub 2015 Oct 6. PubMed PMID: 26439378. Ishikawa T, Seto M, Banno H, Kawakita Y, Oorui M, Taniguchi T, Ohta Y, Tamura T, Nakayama A, Miki H, Kamiguchi H, Tanaka T, Habuka N, Sogabe S, Yano J, Aertgeerts K, Kamiyama K. Design and synthesis of novel human epidermal growth factor receptor 2 (HER2)/epidermal growth factor receptor (EGFR) dual inhibitors bearing a pyrrolo[3,2-d]pyrimidine scaffold. J Med Chem. 2011 Dec 8;54(23):8030-50. doi: 10.1021/jm2008634. Epub 2011 Nov 4. PubMed PMID: 22003817.
NERATINIB	Li D, Ambrogio L, Shimamura T, Kubo S, Takahashi M, Chirieac LR, Padera RF, Shapiro GI, Baum A, Himmelsbach F, Rettig WJ, Meyerson M, Solca F, Greulich H, Wong KK. BIBW2992, an irreversible EGFR/HER2 inhibitor highly effective in preclinical lung cancer models. Oncogene. 2008 Aug 7;27(34):4702-11. doi: 10.1038/onc.2008.109. Epub 2008 Apr 14. PubMed PMID: 18408761; PubMed Central PMCID: PMC2748240. Rabindran SK, Discafani CM, Rosfjord EC, Baxter M, Floyd MB, Golas J, Hallett WA, Johnson BD, Nilakantan R, Overbeek E, Reich MF, Shen R, Shi X, Tsou HR, Wang YF, Wissner A. Antitumor activity of HKI-272, an orally active, irreversible inhibitor of the HER-2 tyrosine kinase. Cancer Res. 2004 Jun 1;64(11):3958-65. PubMed PMID: 15173008. Wong KK, Fracasso PM, Bukowski RM, Lynch TJ, Munster PN, Shapiro GI, Jänne PA, Eder JP, Naughton MJ, Ellis MJ, Jones SF, Mekhail T, Zacharchuk C, Vermette J, Abbas R, Quinn S, Powell C, Burris HA. A phase I study with neratinib (HKI-272), an irreversible pan ErbB receptor tyrosine kinase inhibitor, in patients with solid tumors. Clin Cancer Res. 2009 Apr 1;15(7):2552-8. doi: 10.1158/1078-0432.CCR-08-1978. Epub 2009 Mar 24. PubMed PMID: 19318484.
PELITINIB	Li D, Ambrogio L, Shimamura T, Kubo S, Takahashi M, Chirieac LR, Padera RF, Shapiro GI, Baum A, Himmelsbach F, Rettig WJ, Meyerson M, Solca F, Greulich H, Wong KK. BIBW2992, an irreversible EGFR/HER2 inhibitor highly effective in preclinical lung cancer models. Oncogene. 2008 Aug 7;27(34):4702-11. doi: 10.1038/onc.2008.109. Epub 2008 Apr 14. PubMed PMID: 18408761; PubMed Central PMCID: PMC2748240.
CUDC-101	Galloway TJ, Wirth LJ, Colevas AD, Gilbert J, Bauman JE, Saba NF, Raben D, Mehra R, Ma AW, Atoyan R, Wang J, Burtness B, Jimeno A. A Phase I Study of CUDC-101, a Multitarget Inhibitor of HDACs, EGFR, and HER2, in Combination with Chemoradiation in Patients with Head and Neck Squamous Cell Carcinoma. Clin Cancer Res. 2015 Apr 1;21(7):1566-73. doi: 10.1158/1078-0432.CCR-14-2820. Epub 2015 Jan 8. PubMed PMID: 25573383. Cai X, Zhai HX, Wang J, Forrester J, Qu H, Yin L, Lai CJ, Bao R, Qian C. Discovery of 7-(4-(3-ethynylphenylamino)-7-methoxyquinazolin-6-yloxy)-N-hydroxyheptanamide (CUDc-101) as a potent multi-acting HDAC, EGFR, and HER2 inhibitor for the treatment of cancer. J Med Chem. 2010 Mar 11;53(5):2000-9. doi: 10.1021/jm901453q. PubMed PMID: 20143778.
AV-412	Suzuki T, Fujii A, Ohya J, Nakamura H, Fujita F, Koike M, Fujita M. Antitumor activity of a dual epidermal growth factor receptor and ErbB2 kinase inhibitor MP-412 (AV-412) in mouse xenograft models. Cancer Sci. 2009 Aug;100 (8):1526-31. doi: 10.1111/j.1349-7006.2009.01197.x. Epub 2009 May 13. PubMed PMID: 19459856. Suzuki T, Fujii A, Ohya J, Nakamura H, Fujita F, Koike M, Fujita M. Antitumor activity of a dual epidermal growth factor receptor and ErbB2 kinase inhibitor MP-412 (AV-412) in mouse xenograft models. Cancer Sci. 2009 Aug;100 (8):1526-31. doi: 10.1111/j.1349-7006.2009.01197.x. Epub 2009 May 13. PubMed PMID: 19459856.
ALLITINIB	Zhang J, Cao J, Li J, Zhang Y, Chen Z, Peng W, Sun S, Zhao N, Wang J, Zhong D, Zhang X, Zhang J. A phase I study of AST1306, a novel irreversible EGFR and HER2 kinase inhibitor, in patients with advanced solid tumors. J Hematol Oncol. 2014 Mar 11;7:22. doi: 10.1186/1756-8722-7-22. PubMed PMID: 24612546; PubMed Central PMCID: PMC4007625. Silva-Oliveira RJ, Silva VA, Martinho O, Cruvinel-Carloni A, Melendez ME, Rosa MN, de Paula FE, de Souza Viana L, Carvalho AL, Reis RM. Cytotoxicity of allitinib, an irreversible anti-EGFR agent, in a large panel of human cancer-derived cell lines: KRAS mutation status as a predictive biomarker. Cell Oncol (Dordr). 2016 Jun;39(3):253-63. doi: 10.1007/s13402-016-0270-z. Epub 2016 Feb 26. PubMed PMID: 26920031.
GEFITINIB	Murray S, Bobos M, Angouridakis N, Nikolaou A, Linardou H, Razis E, Fountzilas G. Screening for EGFR Mutations in Patients with Head and Neck Cancer Treated with Gefitinib on a Compassionate-Use Program: A Hellenic

Einsiedlerstrasse 23, 8834 Schindellegi, SWITZERLAND
E-mail: info@realtimeoncology.com **Web:** www.realtimeoncology.com

HATÓANYAG NEVE	REFERENCIA
	Cooperative Oncology Group Study. J Oncol. 2010;2010:709678. doi: 10.1155/2010/709678. Epub 2011 Jan 3. PubMed PMID: 21274259; PubMed Central PMCID: PMC3022192. Oizumi S, Kobayashi K, Inoue A, Maemondo M, Sugawara S, Yoshizawa H, Isobe H, Harada M, Kinoshita I, Okinaga S, Kato T, Harada T, Gemma A, Saijo Y, Yokomizo Y, Morita S, Hagiwara K, Nukiwa T. Quality of life with gefitinib in patients with EGFR-mutated non-small cell lung cancer: quality of life analysis of North East Japan Study Group 002 Trial. Oncologist. 2012;17(6):863-70. doi: 10.1634/theoncologist.2011-0426. Epub 2012 May 11. PubMed PMID: 22581822; PubMed Central PMCID: PMC3380886. Moasser MM, Basso A, Averbuch SD, Rosen N. The tyrosine kinase inhibitor ZD1839 ("Iressa") inhibits HER2-driven signaling and suppresses the growth of HER2-overexpressing tumor cells. Cancer Res. 2001 Oct 1;61(19):7184-8. PubMed PMID: 11585753. Bell DW, Lynch TJ, Haserlat SM, Harris PL, Okimoto RA, Brannigan BW, Sgroi DC, Muir B, Riemenschneider MJ, Iacona RB, Krebs AD, Johnson DH, Giaccone G, Herbst RS, Manegold C, Fukuoka M, Kris MG, Baselga J, Ochs JS, Haber DA. Epidermal growth factor receptor mutations and gene amplification in non-small-cell lung cancer: molecular analysis of the IDEAL/INTACT gefitinib trials. J Clin Oncol. 2005 Nov 1;23(31):8081-92. Epub 2005 Oct 3. PubMed PMID: 16204011. Arteaga CL, Johnson DH. Tyrosine kinase inhibitors-ZD1839 (Iressa). Curr Opin Oncol. 2001 Nov;13(6):491-8. Review. PubMed PMID: 11673690.
PANITUMUMAB	Vanderbilt Medical Center, Nashville, TN; Kansas City Cancer Center, Overland Park, KS; Hematology Oncology Associates, Port S. Lucie, FL; Utah Cancer Specialists, Salt Lake City, UT; Tennessee Oncology, Nashville, TN; UCLA School of Medicine, Los Angeles, CA; Amgen, Inc., Thousand Oaks, CA. Panitumumab antitumor activity in patients (pts) with metastatic colorectal cancer (mCRC) expressing 10% epidermal growth factor receptor (EGFr). J Clin Oncol (Meeting Abstracts) June 2006 vol. 24 no. 18_suppl 3548. Stephenson JJ, Gregory C, Burris H, Larson T, Verma U, Cohn A, Crawford J, Cohen RB, Martin J, Lum P, Yang X, Amado RG. An open-label clinical trial evaluating safety and pharmacokinetics of two dosing schedules of panitumumab in patients with solid tumors. Clin Colorectal Cancer. 2009 Jan;8(1):29-37. doi: 10.3816/CCC.2009.n.005. PubMed PMID: 19203894. Yamaguchi T, Iwasa S, Nagashima K, Ikezawa N, Hamaguchi T, Shoji H, Honma Y, Takashima A, Okita N, Kato K, Yamada Y, Shimada Y. Comparison of Panitumumab Plus Irinotecan and Cetuximab Plus Irinotecan for KRAS Wild-type Metastatic Colorectal Cancer. Anticancer Res. 2016 Jul;36(7):3531-6. PubMed PMID: 27354619. Ibrahim EM, Abouelkhair KM. Clinical outcome of panitumumab for metastatic colorectal cancer with wild-type KRAS status: a meta-analysis of randomized clinical trials. Med Oncol. 2011 Dec;28 Suppl 1:S310-7. doi: 10.1007/s12032-010-9760-4. Epub 2011 Jan 9. PubMed PMID: 21221853. Echarri MJ, Lopez-Martin A, Hitt R. Targeted Therapy in Locally Advanced and Recurrent/Metastatic Head and Neck Squamous Cell Carcinoma (LA-R/M HNSCC). Cancers (Basel). 2016 Feb 26;8(3). pii: E27. doi: 10.3390/cancers8030027. Review. PubMed PMID: 26927178; PubMed Central PMCID: PMC4810111.
CETUXIMAB	Kwon J, Yoon HJ, Kim JH, Lee TS, Song IH, Lee HW, Kang MC, Park JH. Cetuximab inhibits cisplatin-induced activation of EGFR signaling in esophageal squamous cell carcinoma. Oncol Rep. 2014 Sep;32(3):1188-92. doi: 10.3892/or.2014.3302. Epub 2014 Jul 3. PubMed PMID: 24993015. Zhang X, Xu J, Liu H, Yang L, Liang J, Xu N, Bai Y, Wang J, Shen L. Predictive biomarkers for the efficacy of cetuximab combined with cisplatin and capecitabine in advanced gastric or esophagogastric junction adenocarcinoma: a prospective multicenter phase 2 trial. Med Oncol. 2014 Oct;31(10):226. doi: 10.1007/s12032-014-0226-y. Epub 2014 Sep 19. PubMed PMID: 25234930. Hata A, Katakami N, Kitajima N. Successful cetuximab therapy after failure of panitumumab rechallenge in a patient with metastatic colorectal cancer: restoration of drug sensitivity after anti-EGFR monoclonal antibody-free interval. J Gastrointest Cancer. 2014 Dec;45(4):506-7. doi: 10.1007/s12029-014-9624-9. PubMed PMID: 24880984. Barni S, Ghilardi M, Borgonovo K, Cabiddu M, Zaniboni A, Petrelli F. Cetuximab/irinotecan-chemotherapy in KRAS wild-type pretreated metastatic colorectal cancer: a pooled analysis and review of literature. Rev Recent Clin Trials. 2013 Jun;8(2):101-9. Review. PubMed PMID: 23859115. Yamaguchi T, Iwasa S, Nagashima K, Ikezawa N, Hamaguchi T, Shoji H, Honma Y, Takashima A, Okita N, Kato K, Yamada Y, Shimada Y. Comparison of Panitumumab Plus Irinotecan and Cetuximab Plus Irinotecan for KRAS Wild-type Metastatic Colorectal Cancer. Anticancer Res. 2016 Jul;36(7):3531-6. PubMed PMID: 27354619.
OXALIPLATIN	Choi YY, Kim H, Shin SJ, Kim HY, Lee J, Yang HK, Kim WH, Kim YW, Kook MC, Park YK, Kim HH, Lee HS, Lee KH, Gu MJ, Choi SH, Hong S, Kim JW, Hyung WJ, Noh SH, Cheong JH. Microsatellite Instability and Programmed Cell Death-Ligand 1 Expression in Stage II/III Gastric Cancer: Post Hoc Analysis of the CLASSIC Randomized Controlled study. Ann Surg. 2019 08;270(2):309-316. doi: 10.1097/SLA.0000000000002803. PubMed PMID: 29727332.
CAPECITABINE	Bennouna J, Lang I, Valladares-Ayerbes M, Boer K, Adenis A, Escudero P, Kim TY, Pover GM, Morris CD, Douillard JY. A Phase II, open-label, randomised study to assess the efficacy and safety of the MEK1/2 inhibitor AZD6244 (ARRY-142886) versus capecitabine monotherapy in patients with colorectal cancer who have failed one or two prior chemotherapeutic regimens. Invest New Drugs. 2011 Oct;29(5):1021-8. doi: 10.1007/s10637-010-9392-8. PubMed PMID: 20127139.

Einsiedlerstrasse 23, 8834 Schindellegi, SWITZERLAND
E-mail: info@realtimeoncology.com **Web:** www.realtimeoncology.com

HATÓANYAG NEVE	REFERENCIA
	Choi YY, Kim H, Shin SJ, Kim HY, Lee J, Yang HK, Kim WH, Kim YW, Kook MC, Park YK, Kim HH, Lee HS, Lee KH, Gu MJ, Choi SH, Hong S, Kim JW, Hyung WJ, Noh SH, Cheong JH. Microsatellite Instability and Programmed Cell Death-Ligand 1 Expression in Stage II/III Gastric Cancer: Post Hoc Analysis of the CLASSIC Randomized Controlled study. Ann Surg. 2019 08;270(2):309-316. doi: 10.1097/SLA.0000000000002803. PubMed PMID: 29727332.
CISPLATIN	D'Andrea AD. The Fanconi Anemia/BRCA signaling pathway: disruption in cisplatin-sensitive ovarian cancers. Cell Cycle. 2003 Jul-Aug;2(4):290-2. Review. PubMed PMID: 12851475. Santarpia L, Iwamoto T, Di Leo A, Hayashi N, Bottai G, Stampfer M, André F, Turner NC, Symmans WF, Hortobágyi GN, Pusztai L, Bianchini G. DNA repair gene patterns as prognostic and predictive factors in molecular breast cancer subtypes. Oncologist. 2013;18(10):1063-73. doi: 10.1634/theoncologist.2013-0163. Epub 2013 Sep 26. PubMed PMID: 24072219; PubMed Central PMCID: PMC3805146. Moreno T et al., ARID2 deficiency promotes tumor progression and is associated with higher sensitivity to PARP inhibition in lung cancer. bioRxiv 2020.01.10.898726; doi: https://doi.org/10.1101/2020.01.10.898726 Bui N, Huang JK, Bojorquez-Gomez A, Licon K, Sanchez KS, Tang SN, Beckett AN, Wang T, Zhang W, Shen JP, Kreisberg JF, Ideker T. Disruption of NSD1 in Head and Neck Cancer Promotes Favorable Chemotherapeutic Responses Linked to Hypomethylation. Mol Cancer Ther. 2018 Jul;17(7):1585-1594. doi: 10.1158/1535-7163.MCT-17-0937. Epub 2018 Apr 10. PubMed PMID: 29636367; PubMed Central PMCID: PMC6030464. Tian Z, Yao G, Song H, Zhou Y, Geng J. IGF2R expression is associated with the chemotherapy response and prognosis of patients with advanced NSCLC. Cell Physiol Biochem. 2014;34(5):1578-88. doi: 10.1159/000366361. Epub 2014 Oct 31. PubMed PMID: 25402559.
EPIRUBICIN	Smyth EC, Wotherspoon A, Peckitt C, Gonzalez D, Hulkki-Wilson S, Eltahir Z, Fassan M, Rugge M, Valeri N, Okines A, Hewish M, Allum W, Stenning S, Nankivell M, Langley R, Cunningham D. Mismatch Repair Deficiency, Microsatellite Instability, and Survival: An Exploratory Analysis of the Medical Research Council Adjuvant Gastric Infusional Chemotherapy (MAGIC) Trial. JAMA Oncol. 2017 Sep 01;3(9):1197-1203. doi: 10.1001/jamaoncol.2016.6762. PubMed PMID: 28241187; PubMed Central PMCID: PMC5824280.
5-FLUOROURACIL	An W, Nadeau SA, Mohapatra BC, Feng D, Zutshi N, Storck MD et al., Loss of Cbl and Cbl-b ubiquitin ligases abrogates hematopoietic stem cell quiescence and sensitizes leukemic disease to chemotherapy. Oncotarget. 2015 Apr 30;6(12):10498-509. PubMed PMID: 25871390 Wang Q, Shi YL, Zhou K, Wang LL, Yan ZX, Liu YL, Xu LL, Zhao SW, Chu HL, Shi TT, Ma QH, Bi J. PIK3CA mutations confer resistance to first-line chemotherapy in colorectal cancer. Cell Death Dis. 2018 Jul 3;9(7):739. doi: 10.1038/s41419-018-0776-6. PubMed PMID: 29970892; PubMed Central PMCID: PMC6030128. Tsai CY, Lin TA, Huang SC, Hsu JT, Yeh CN, Chen TC, Chiu CT, Chen JS, Yeh TS. Is Adjuvant Chemotherapy Necessary for Patients with Deficient Mismatch Repair Gastric Cancer?-Autophagy Inhibition Matches the Mismatched. Oncologist. 2020 07;25(7):e1021-e1030. doi: 10.1634/theoncologist.2019-0419. Epub 2020 Dec 14. PubMed PMID: 32058649; PubMed Central PMCID: PMC7356708. Smyth EC, Wotherspoon A, Peckitt C, Gonzalez D, Hulkki-Wilson S, Eltahir Z, Fassan M, Rugge M, Valeri N, Okines A, Hewish M, Allum W, Stenning S, Nankivell M, Langley R, Cunningham D. Mismatch Repair Deficiency, Microsatellite Instability, and Survival: An Exploratory Analysis of the Medical Research Council Adjuvant Gastric Infusional Chemotherapy (MAGIC) Trial. JAMA Oncol. 2017 Sep 01;3(9):1197-1203. doi: 10.1001/jamaoncol.2016.6762. PubMed PMID: 28241187; PubMed Central PMCID: PMC5824280.

BIOMARKEREK ÉS DRIVEREK	REFERENCIA
MSI-H	Silva VW, Askan G, Daniel TD, Lowery M, Klimstra DS, Abou-Alfa GK, Shia J. Biliary carcinomas: pathology and the role of DNA mismatch repair deficiency. Chin Clin Oncol. 2016 Oct;5(5):62. doi: 10.21037/cco.2016.10.04. Review. PubMed PMID: 27829276. (7) U.S. Food and Drug Administration. KEYTRUDA (Pembrolizumab) approval letter, May 2017. www.accessdata.fda.gov/drugsatfda_docs/label/2017/125514s014lbl.pdf. Dec G, Romanowicz-Makowska H, Smolarz B, Kulig A. Microsatellite instability (MSI) analysis in patients with endometrial cancer. Pol J Pathol. 2005;56(1):15-9. PubMed PMID: 15921009. Altavilla G, Fassan M, Busatto G, Orsolan M, Giacomelli L. Microsatellite instability and hMLH1 and hMSH2 expression in renal tumors. Oncol Rep. 2010 Oct;24(4):927-32. PubMed PMID: 20811672. Segev Y, Pal T, Rosen B, McLaughlin JR, Sellers TA, Risch HA, Zhang S, Sun P, Narod SA, Schildkraut J. Risk factors for ovarian cancers with and without microsatellite instability. Int J Gynecol Cancer. 2014 May;24(4):664-9. doi: 10.1097/IGC.0000000000000134. PubMed PMID: 24755492.
TMB-H	Morse CB, Elvin JA, Gay LM, Liao JB. Elevated tumor mutational burden and prolonged clinical response to anti-PD-L1 antibody in platinum-resistant recurrent ovarian cancer. Gynecol Oncol Rep. 2017 Jun 27;21:78-80. doi: 10.1016/j.gore.2017.06.013. eCollection 2017 Aug. PubMed PMID: 28736741; PubMed Central PMCID: PMC5510487. Goodman AM, Sokol ES, Frampton GM, Lippman SM, Kurzrock R. Microsatellite-Stable Tumors with High Mutational Burden Benefit from Immunotherapy. Cancer Immunol Res. 2019 10;7(10):1570-1573. doi: 10.1158/2326-6066.CIR-19-0149. Epub 2019 Oct 12. PubMed PMID: 31405947; PubMed Central PMCID: PMC6774837.

Einsiedlerstrasse 23, 8834 Schindellegi, SWITZERLAND
E-mail: info@realtimeoncology.com **Web:** www.realtimeoncology.com

BIOMARKEREK ÉS DRIVEREK	REFERENCIA
	ALVA, Ajjai Shivaram, et al. Pembrolizumab (P) in patients (pts) with metastatic breast cancer (MBC) with high tumor mutational burden (HTMB): Results from the Targeted Agent and Profiling Utilization Registry (TAPUR) Study. 2019. Goodman AM, Kato S, Bazhenova L, Patel SP, Frampton GM, Miller V, Stephens PJ, Daniels GA, Kurzrock R. Tumor Mutational Burden as an Independent Predictor of Response to Immunotherapy in Diverse Cancers. Mol Cancer Ther. 2017 Nov;16(11):2598-2608. doi: 10.1158/1535-7163.MCT-17-0386. Epub 2017 Aug 23. PubMed PMID: 28835386; PubMed Central PMCID: PMC5670009. Schrock AB, Ouyang C, Sandhu J, Sokol E, Jin D, Ross JS, Miller VA, Lim D, Amanam I, Chao J, Catenacci D, Cho M, Braiteh F, Klempner SJ, Ali SM, Fakih M. Tumor mutational burden is predictive of response to immune checkpoint inhibitors in MSI-high metastatic colorectal cancer. Ann Oncol. 2019 Apr 30. pii: mdz134. doi: 10.1093/annonc/mdz134. [Epub ahead of print] PubMed PMID: 31038663.
ER protein overexpression	Zhang Y, Zhao D, Gong C, Zhang F, He J, Zhang W, Zhao Y, Sun J. Prognostic role of hormone receptors in endometrial cancer: a systematic review and meta-analysis. World J Surg Oncol. 2015 Jun 25;13:208. doi: 10.1186/s12957-015-0619-1. Review. PubMed PMID: 26108802; PubMed Central PMCID: PMC4511445. Kleine W, Maier T, Geyer H, Pfleiderer A. Estrogen and progesterone receptors in endometrial cancer and their prognostic relevance. Gynecol Oncol. 1990 Jul;38(1):59-65. PubMed PMID: 2141316. Harding M, Cowan S, Hole D, Cassidy L, Kitchener H, Davis J, Leake R. Estrogen and progesterone receptors in ovarian cancer. Cancer. 1990 Feb 1;65(3):486-91. PubMed PMID: 2297640. Yokoyama Y, Mizunuma H. Recurrent epithelial ovarian cancer and hormone therapy. World J Clin Cases. 2013 Sep 16;1(6):187-90. doi: 10.12998/wjcc.v1.i6.187. PubMed PMID: 24303498; PubMed Central PMCID: PMC3845958. Lee YR, Park J, Yu HN, Kim JS, Youn HJ, Jung SH. Up-regulation of PI3K/Akt signaling by 17beta-estradiol through activation of estrogen receptor-alpha, but not estrogen receptor-beta, and stimulates cell growth in breast cancer cells. Biochem Biophys Res Commun. 2005 Nov 4;336(4):1221-6. PubMed PMID: 16169518.
PTEN-R130Q	Wellcome Trust Sanger Institute NCBI ClinVar Wellcome Trust Sanger Institute NCBI ClinVar Wellcome Trust Sanger Institute
FBXW7-R479Q	Wellcome Trust Sanger Institute Wellcome Trust Sanger Institute Wellcome Sanger Institute Wellcome Trust Sanger Institute Wellcome Sanger Institute
CTNNB1-T41A	Wellcome Trust Sanger Institute Wellcome Trust Sanger Institute Wellcome Trust Sanger Institute Wellcome Trust Sanger Institute Wellcome Trust Sanger Institute
PIK3CA-E81K	Wellcome Trust Sanger Institute https://cancer.sanger.ac.uk/cosmic/mutation/overview?id=20477959&merge=750 Wellcome Trust Sanger Institute Wellcome Trust Sanger Institute Wellcome Trust Sanger Institute
ATM-S214fs*16	Wellcome Trust Sanger Institute Wellcome Trust Sanger Institute Wellcome Trust Sanger Institute

Einsiedlerstrasse 23, 8834 Schindellegi, SWITZERLAND
E-mail: info@realtimeoncology.com **Web:** www.realtimeoncology.com

BIOMARKEREK ÉS DRIVEREK	REFERENCIA
	Wellcome Trust Sanger Institute
	Wellcome Trust Sanger Institute
CDH1-I594fs*19	NCBI ClinVar
	Wellcome Trust Sanger Institute
	Wellcome Trust Sanger Institute
	Wellcome Trust Sanger Institute
	Wellcome Trust Sanger Institute
RECQL4-L339fs*20	NCBI ClinVar Database
	Wellcome Trust Sanger Institute
	NCBI ClinVar
	Wellcome trust sanger Institute
	Wellcome Sanger Institute
MRE11-R364*	NCBI ClinVar
	NCBI ClinVar
	Wellcome Sanger Institute
	Wellcome Trust Sanger Institute
	Wellcome Trust Sanger Institute
IL2RG-R226C	NCBI ClinVar
PIK3CB-L1049R	Pridham KJ, Varghese RT, Sheng Z. The Role of Class IA Phosphatidylinositol-4,5-Bisphosphate 3-Kinase Catalytic Subunits in Glioblastoma. Front Oncol. 2017 Dec 15;7:312. doi: 10.3389/fonc.2017.00312. eCollection 2017. Review. PubMed PMID: 29326882; PubMed Central PMCID: PMC5736525.
	Wellcome Trust Sanger Institute
	https://cancer.sanger.ac.uk/cosmic/mutation/overview?id=57280906
	Wellcome Sanger Institute
	NCBI ClinVar
ATM-I1581fs*20	Wellcome Trust Sanger Institute
	Wellcome Trust Sanger Institute
	Wellcome Sanger Institute
	Wellcome Trust Sanger Institute
	Wellcome Sanger Institute
CIC-R507C	NCBI ClinVar
	Wellcome Sanger Institute
	Wellcome Trust Sanger Institute
	Wellcome Trust Sanger Institute
	https://cancer.sanger.ac.uk/cosmic/search?q=CIC+Q427H
TSC2-I475T	Wellcome Trust Sanger Institute
	https://www.ncbi.nlm.nih.gov/clinvar/variation/582899/
	NCBI ClinVar
	NCBI ClinVar Database

Einsiedlerstrasse 23, 8834 Schindellegi, SWITZERLAND
E-mail: info@realtimeoncology.com **Web:** www.realtimeoncology.com

BIOMARKEREK ÉS DRIVEREK	REFERENCIA
	NCBI ClinVar Database
CTNNB1-Q26*	Wellcome Trust Sanger Institute
	Wellcome Trust Sanger Institute
	Wellcome Trust Sanger Institute
	Wellcome Trust Sanger Institute
	Cho J, Kim SY, Kim YJ, Sim MH, Kim ST, Kim NKD, Kim K, Park W, Kim JH, Jang KT, Lee J. Emergence of CTNNB1 mutation at acquired resistance to KIT inhibitor in metastatic melanoma. Clin Transl Oncol. 2017 Oct;19(10):1247-1252. doi: 10.1007/s12094-017-1662-x. Epub 2017 Apr 18. PubMed PMID: 28421416.
CTNNB1-496-1G>T	Wellcome Trust Sanger Institute
	Wellcome Trust Sanger Institute
	Austinat M, Dunsch R, Wittekind C, Tannapfel A, Gebhardt R, Gaunitz F. Correlation between beta-catenin mutations and expression of Wnt-signaling target genes in hepatocellular carcinoma. Mol Cancer. 2008 Feb 18;7:21. doi: 10.1186/1476-4598-7-21. PubMed PMID: 18282277; PubMed Central PMCID: PMC2287186.
	Wellcome Trust Sanger Institute
	Wellcome Trust Sanger Institute
ALK-M830L	Wellcome Trust Sanger Institute
	Wellcome Trust Sanger Institute
	Wellcome Trust Sanger Institute
	Kumar A, Shanthi V, Ramanathan K. Computational Investigation and Experimental Validation of Crizotinib Resistance Conferred by C1156Y Mutant Anaplastic Lymphoma Kinase. Mol Inform. 2015 Feb;34(2-3):105-14. doi: 10.1002/minf.201400070. Epub 2015 Jan 30. PubMed PMID: 27490033.
	Wellcome Trust Sanger Institute
ARID1A-F2141fs*59	Wellcome Trust Sanger Institute
	Wellcome Trust Sanger Institute
	http://cancer.sanger.ac.uk/cosmic/search?q=arid1a+R1528*
	Wellcome Trust Sanger Institute
	Wellcome Trust Sanger Institute
ARID1A-Q1519fs*8	Wellcome Trust Sanger Institute
	LOVD database
	Wellcome Trust Sanger Institute
	Wellcome Trust Sanger Institute
	Wellcome Sanger Institute
ARID1A-Y551fs*68	Ticha I, Hojny J, Michalkova R, Kodet O, Krkavcova E, Hajkova N, Nemejcova K, Bartu M, Jaksa R, Dura M, Kanwal M, Martinikova AS, Macurek L, Zemankova P, Kleibl Z, Dundr P. A comprehensive evaluation of pathogenic mutations in primary cutaneous melanomas, including the identification of novel loss-of-function variants. Sci Rep. 2019 11 19;9(1):17050. doi: 10.1038/s41598-019-53636-x. Epub 2019 Jun 19. PubMed PMID: 31745173; PubMed Central PMCID: PMC6863855.
	Wellcome Trust Sanger Institute
	NCBI ClinVar
	NCBI ClinVar
	LOVD database
RAD51D-P65L	NCBI ClinVar
	NCBI ClinVar
	NCBI ClinVar

Einsiedlerstrasse 23, 8834 Schindellegi, SWITZERLAND
E-mail: info@realtimeoncology.com **Web:** www.realtimeoncology.com

BIOMARKEREK ÉS DRIVEREK	REFERENCIA
	Wellcome Sanger Institute Wickramanayake A, Bernier G, Pennil C, Casadei S, Agnew KJ, Stray SM, Mandell J, Garcia RL, Walsh T, King MC, Swisher EM. Loss of function germline mutations in RAD51D in women with ovarian carcinoma. Gynecol Oncol. 2012 Dec;127(3):552-5. doi: 10.1016/j.ygyno.2012.09.009. Epub 2012 Sep 14. Erratum in: Gynecol Oncol. 2014 Jan; 132(1):260. Wickramanyake, Anneka [corrected to Wickramanayake, Anneka]. PubMed PMID: 22986143; PubMed Central PMCID: PMC3905744.
KMT2C-L4419P	Wellcome Sanger Institute Wellcome Trust Sanger Institute https://cancer.sanger.ac.uk/cosmic/mutation/overview?id=3304628 Wellcome Trust Sanger Institute Wellcome Trust Sanger Institute
TET2-L1276fs*24	Wellcome Trust Sanger Institute https://web.expasy.org/variant_pages/VAR_058189.html https://cancer.sanger.ac.uk/cosmic/mutation/overview?id=7269706 Wellcome Sanger Institute Wellcome Trust Sanger Institute
FAT1-S1782N	https://cancer.sanger.ac.uk/cosmic/mutation/overview?id=1173044 Wellcome Trust Sanger Institute Wellcome Sanger Institute Wellcome Trust Sanger Institute NCBI ClinVar Database
FAT1-L3946P	Wellcome Sanger Institute Leiden Open Variation Database Wellcome Trust Sanger Institute Wellcome Sanger Institute Wellcome Trust Sanger Institute
FAT1-M3869T	Wellcome Sanger Institute Wellcome Trust Sanger Institute Wellcome Trust Sanger Institute Leiden Open Variation Database https://cancer.sanger.ac.uk/cosmic/mutation/overview?id=1173044
SOX9-L60V	Wellcome Trust Sanger Institute Wellcome Trust Sanger Institute NCBI ClinVar Prévostel C, Rammah-Bouazza C, Trauchessec H, Canterel-Thouennon L, Busson M, Ychou M, Blache P. SOX9 is an atypical intestinal tumor suppressor controlling the oncogenic Wnt/ß-catenin signaling. Oncotarget. 2016 Dec 13; 7(50):82228-82243. doi: 10.18632/oncotarget.10573. PubMed PMID: 27429045; PubMed Central PMCID: PMC5347687. Javier BM, Yaeger R, Wang L, Sanchez-Vega F, Zehir A, Middha S, Sadowska J, Vakiani E, Shia J, Klimstra D, Ladanyi M, Iacobuzio-Donahue CA, Hechtman JF. Recurrent, truncating SOX9 mutations are associated with SOX9 overexpression, KRAS mutation, and TP53 wild type status in colorectal carcinoma. Oncotarget. 2016 Aug 9;7(32): 50875-50882. doi: 10.18632/oncotarget.9682. PubMed PMID: 27248473; PubMed Central PMCID: PMC5239443.
DNMT3A-Q110fs*14	NCBI ClinVar Wellcome Sanger Institute

Einsiedlerstrasse 23, 8834 Schindellegi, SWITZERLAND
E-mail: info@realtimeoncology.com **Web:** www.realtimeoncology.com

BIOMARKEREK ÉS DRIVEREK	REFERENCIA
	Wellcome Sanger Institute
	Wellcome Trust Sanger Institute
	Wellcome Sanger Institute
PTPN11-R386K	Wellcome Trust Sanger Institute
	Wellcome Sanger Institute
	Wellcome Trust Sanger Institute
	Wellcome Trust Sanger Institute
	Wellcome Trust Sanger Institute
GNAS-A36V	Wellcome Trust Sanger Institute
	Wellcome Sanger Institute
	Wellcome Trust Sanger Institute
	Wellcome Trust Sanger Institute
	Wellcome Trust Sanger Institute
CBL-E196fs*16	Angona A, Fernández-Rodríguez C, Alvarez-Larrán A, Camacho L, Longarón R, Torres E, Pairet S, Besses C, Bellosillo B. Molecular characterisation of triple negative essential thrombocythaemia patients by platelet analysis and targeted sequencing. Blood Cancer J. 2016 Aug 26;6(8):e463. doi: 10.1038/bcj.2016.75. PubMed PMID: 27564461; PubMed Central PMCID: PMC5022184.
	Wellcome Sanger Institute
	Wellcome Trust Sanger Institute
	Wellcome Sanger Institute
	Wellcome Sanger Institute
SMARCA4-Q1195H	http://cancer.sanger.ac.uk/cosmic/mutation/overview?id=6784850
	Wellcome Trust Sanger Institute
	Wellcome Trust Sanger Institute
	Wellcome Sanger Institute
	http://cancer.sanger.ac.uk/cosmic/search?q=SMARCA4+K588del
FH-A104T	Wellcome Sanger Institute
	Wellcome Trust Sanger Institute
	https://www.ncbi.nlm.nih.gov/clinvar/variation/42095/
	Wellcome Sanger Institute
	NCBI ClinVar
MED12-R431L	Wellcome Sanger Institute
	NCBI ClinVar
	Wellcome Trust Sanger Institute
	NCBI ClinVar
	Piscuoglio S, Murray M, Fusco N, Marchiò C, Loo FL, Martelotto LG, Schultheis AM, Akram M, Weigelt B, Brogi E, Reis-Filho JS. MED12 somatic mutations in fibroadenomas and phyllodes tumours of the breast. Histopathology. 2015 Nov;67(5):719-29. doi: 10.1111/his.12712. Epub 2015 Dec 24. PubMed PMID: 25855048; PubMed Central PMCID: PMC4996373.
EPHA7-I473V	Wellcome Trust Sanger Institute
	Wellcome Trust Sanger Institute

Einsiedlerstrasse 23, 8834 Schindellegi, SWITZERLAND
E-mail: info@realtimeoncology.com **Web:** www.realtimeoncology.com

BIOMARKEREK ÉS DRIVEREK	REFERENCIA
	https://www.ncbi.nlm.nih.gov/projects/SNP/snp_ref.cgi?rs=151105732 Wellcome Sanger Institute Wellcome Sanger Institute
TGFBR2-Q334H	https://www.ncbi.nlm.nih.gov/clinvar/variation/161394/ NCBI ClinVar https://cancer.sanger.ac.uk/cosmic/mutation/overview?id=6475910 Wellcome Trust Sanger Insitute Zimmermann MT, Urrutia R, Oliver GR, Blackburn PR, Cousin MA, Bozeck NJ, Klee EW. Molecular modeling and molecular dynamic simulation of the effects of variants in the TGFBR2 kinase domain as a paradigm for interpretation of variants obtained by next generation sequencing. PLoS One. 2017 Feb 9;12(2):e0170822. doi: 10.1371/journal.pone.0170822. eCollection 2017. PubMed PMID: 28182693; PubMed Central PMCID: PMC5300139.
KDM5C-R68fs*5	Wellcome Trust Sanger Institute Wellcome Trust Sanger Institute Wellcome Sanger Institute Wellcome Sanger Institute NCBI ClinVar Database
CARD11-R555fs*45	https://cancer.sanger.ac.uk/cosmic/mutation/overview?id=46512555 NCBI ClinVar Database Chan W, Schaffer TB, Pomerantz JL. A quantitative signaling screen identifies CARD11 mutations in the CARD and LATCH domains that induce Bcl10 ubiquitination and human lymphoma cell survival. Mol Cell Biol. 2013 Jan;33(2): 429-43. doi: 10.1128/MCB.00850-12. Epub 2012 Nov 12. PubMed PMID: 23149938; PubMed Central PMCID: PMC3554118. Wellcome Trust Sanger Institute Wellcome Sanger Insitute
NSD1-M1531fs*43	Wellcome Sanger Institute Wellcome Trust Sanger Institute Wellcome trust Sanger Institute Wellcome Trust Sanger Institute Wellcome Sanger Institute
NSD1-F1799fs*22	Wellcome Trust Sanger Institute Wellcome trust Sanger Institute Wellcome Trust Sanger Institute Wellcome Trust Sanger Institute NCBI ClinVar
XRCC2-K267fs*?	Wellcome Sanger Institute Mohamed FZ, Hussien YM, AlBakry MM, Mohamed RH, Said NM. Role of DNA repair and cell cycle control genes in ovarian cancer susceptibility. Mol Biol Rep. 2013 May;40(5):3757-68. doi: 10.1007/s11033-012-2452-8. Epub 2013 Jan 1. PubMed PMID: 23277402. NCBI ClinVar NCBI ClinVar Database Leiden Open Variation Database
CARD11-R404M	

Einsiedlerstrasse 23, 8834 Schindellegi, SWITZERLAND
E-mail: info@realtimeoncology.com **Web:** www.realtimeoncology.com

BIOMARKEREK ÉS DRIVEREK	REFERENCIA
	Yang YK, Yang C, Chan W, Wang Z, Deibel KE, Pomerantz JL. Molecular Determinants of Scaffold-induced Linear Ubiquitinylation of B Cell Lymphoma/Leukemia 10 (Bcl10) during T Cell Receptor and Oncogenic Caspase Recruitment Domain-containing Protein 11 (CARD11) Signaling. J Biol Chem. 2016 Dec 09;291(50):25921-25936. doi: 10.1074/jbc.M116.754028. Epub 2016 Feb 24. PubMed PMID: 27777308; PubMed Central PMCID: PMC5207066.
	Leiden Open Variation Database
	Wellcome Trust Sanger Institute
	Wellcome Trust Sanger Institute
	Chan W, Schaffer TB, Pomerantz JL. A quantitative signaling screen identifies CARD11 mutations in the CARD and LATCH domains that induce Bcl10 ubiquitination and human lymphoma cell survival. Mol Cell Biol. 2013 Jan;33(2): 429-43. doi: 10.1128/MCB.00850-12. Epub 2012 Nov 12. PubMed PMID: 23149938; PubMed Central PMCID: PMC3554118.
ARID2-D1758G	Wellcome Trust Sanger Institute
	Wellcome Trust Sanger Institute
	Wellcome Trust Sanger Institute
	Wellcome Sanger Institute
	Wellcome Trust Sanger Institute
CDK12-G1271fs*23	Wellcome Trust Sanger Institute
	Wellcome Sanger Institute
	Wellcome Trust Sanger Institute
	Wellcome Trust Sanger Institute
	Wellcome Trust Sanger Institute
CDK12-A1174S	Wellcome Sanger Institute
	Wellcome Trust Sanger Institute
	Wellcome Sanger Institute
	Wellcome Sanger Institute
	Wellcome Trust Sanger Institute
ARAF-S157N	Wellcome Sanger Institute
	Imielinski M, Greulich H, Kaplan B, Araujo L, Amann J, Horn L, Schiller J, Villalona-Calero MA, Meyerson M, Carbone DP. Oncogenic and sorafenib-sensitive ARAF mutations in lung adenocarcinoma. J Clin Invest. 2014 Apr;124(4): 1582-6. doi: 10.1172/JCI72763. Epub 2014 Feb 24. PubMed PMID: 24569458; PubMed Central PMCID: PMC3973082.
	Nelson DS, Quispel W, Badalian-Very G, van Halteren AG, van den Bos C, Bovée JV, Tian SY, Van Hummelen P, Ducar M, MacConaill LE, Egeler RM, Rollins BJ. Somatic activating ARAF mutations in Langerhans cell histiocytosis. Blood. 2014 May 15;123(20):3152-5. doi: 10.1182/blood-2013-06-511139. Epub 2014 Mar 20. PubMed PMID: 24652991.
TP53BP1-H964R	Wellcome Trust Sanger Institute
	NCBI ClinVar
	Nicolas E, Arora S, Zhou Y, Serebriiskii IG, Andrake MD, Handorf ED, Bodian DL, Vockley JG, Dunbrack RL, Ross EA, Egleston BL, Hall MJ, Golemis EA, Giri VN, Daly MB. Systematic evaluation of underlying defects in DNA repair as an approach to case-only assessment of familial prostate cancer. Oncotarget. 2015 Nov 24;6(37):39614-33. doi: 10.18632/oncotarget.5554. PubMed PMID: 26485759; PubMed Central PMCID: PMC4741850.
	Wellcome Trust Sanger Institute
	http://snpeffect.switchlab.org/mutation/TP53B_HUMAN/VAR_022180
IGF2R-D1317fs*5	https://cancer.sanger.ac.uk/cosmic/mutation/overview?id=33703705
	Wellcome Trust Sanger Institute

Einsiedlerstrasse 23, 8834 Schindellegi, SWITZERLAND
E-mail: info@realtimeoncology.com **Web:** www.realtimeoncology.com

BIOMARKEREK ÉS DRIVEREK	REFERENCIA
	Wellcome Sanger Institute
	Wellcome Sanger Institute
	NCBI ClinVar
JAK2-C68R	Wellcome Trust Sanger Institute
	Wellcome Trust Sanger Institute
	Wellcome Sanger Institute
	Wellcome Trust Sanger Institute
	Wellcome Trust Sanger Institute
IGF2R-W53R	Wellcome Sanger Institute
	Wellcome Sanger Institute
	Wellcome Sanger Institute
	https://cancer.sanger.ac.uk/cosmic/mutation/overview?id=33703705
	Wellcome Trust Sanger Institute
PAX5-A322fs*11	Wellcome Trust Sanger Institute
	Wellcome Trust Sanger Institute
	Wellcome Trust Sanger Institute
	Shim YJ, Ha J-S, Do Y-R, Kim HS. Whole-Exome Sequencing in Korean Children with Acute Lymphoblastic Leukemia. Blood. 2015 Dec 3;126(23):4994–4994.
	Wellcome Trust Sanger Institute
FANCF-G357D	https://www.ncbi.nlm.nih.gov/clinvar/variation/134349/
	Wellcome Trust Sanger Institute
	https://databases.lovd.nl/shared/variants/FANCF?search_position_c_start=959&search_position_c_start_intron=0&search_position_c_end=959&search_position_c_end_intron=0&search_vot_clean_dna_change=%3D%22959C%3ET%22&search_transcriptid=00007725
	Wellcome Trust Sanger Institute
	NCBI ClinVar
CTCF-E691fs*30	Wellcome Trust Sanger Institute
	NCBI ClinVar
	Wellcome Sanger Institute
	Wellcome Trust Sanger Institute
	LOVD database
ESRP1-S625G	Wellcome Trust Sanger Institute
	Leiden Open Variation Database
	Wellcome Trust Sanger Institute
	NCBI ClinVar
	Wellcome Sanger Institute
EPHA3-T115N	Wellcome Trust Sanger Institute
	Wellcome Trust Sanger Institute
	Wellcome Trust Sanger Institute
	Wellcome Trust Sanger Institute

Einsiedlerstrasse 23, 8834 Schindellegi, SWITZERLAND
E-mail: info@realtimeoncology.com **Web:** www.realtimeoncology.com

BIOMARKEREK ÉS DRIVEREK	REFERENCIA
	Wellcome Trust Sanger Institute
PPP2R2A-Y189*	Shouse G, de Necochea-Campion R, Mirshahidi S, Liu X, Chen CS. Novel B55-PP2A mutations in AML promote AKT T308 phosphorylation and sensitivity to AKT inhibitor-induced growth arrest. Oncotarget. 2016 Sep 20;7(38):61081-61092. doi: 10.18632/oncotarget.11209. PubMed PMID: 27531894; PubMed Central PMCID: PMC5308637.
ERBB4-G1109S	Wellcome Trust Sanger Institute
	Wellcome Sanger Institute
	Wellcome Trust Sanger Institute
	Wellcome Sanger Institute
	Wellcome Sanger Institute
WNK2-P1381fs*11	Wellcome Trust Sanger Institute
	Wellcome Trust Sanger Institute
	Wellcome Trust Sanger Institute
	NCBI ClinVar
	Wellcome Sanger Institute
LAMA2-R185C	Wellcome Trust Sanger Institute
	Wellcome Trust Sanger Institute
	Wellcome Trust Sanger Institute
	https://www.ncbi.nlm.nih.gov/clinvar/variation/92968/
	Wellcome Sanger Institute
DMD-S3343fs*34	LOVD
	NCBI ClinVar
	Wellcome Sanger Institute
	Wellcome Sanger Institute
	Wellcome Sanger Institute
DMD-R1957Q	Wellcome Sanger Institute
	Wellcome Trust Sanger Institute
	Wellcome Sanger Institute
	NCBI ClinVar
	NCBI ClinVar
PMS1-N489I	Spugnesi L, Gabriele M, Scarpitta R, Tancredi M, Maresca L, Gambino G, Collavoli A, Aretini P, Bertolini I, Salvadori B, Landucci E, Fontana A, Rossetti E, Roncella M, Naccarato GA, Caligo MA. Germline mutations in DNA repair genes may predict neoadjuvant therapy response in triple negative breast patients. Genes Chromosomes Cancer. 2016 Dec;55(12):915-924. doi: 10.1002/gcc.22389. Epub 2016 Jul 26. PubMed PMID: 27328445.
	Wellcome Sanger Institute
	https://web.expasy.org/variant_pages/VAR_014877.html
	NCBI ClinVar
	NCBI ClinVar
PMS1-G417fs*6	https://web.expasy.org/variant_pages/VAR_014877.html
	NCBI ClinVar
	Spugnesi L, Gabriele M, Scarpitta R, Tancredi M, Maresca L, Gambino G, Collavoli A, Aretini P, Bertolini I, Salvadori B, Landucci E, Fontana A, Rossetti E, Roncella M, Naccarato GA, Caligo MA. Germline mutations in DNA repair genes may predict neoadjuvant therapy response in triple negative breast patients. Genes Chromosomes Cancer. 2016 Dec;55(12):915-924. doi: 10.1002/gcc.22389. Epub 2016 Jul 26. PubMed PMID: 27328445.

Einsiedlerstrasse 23, 8834 Schindellegi, SWITZERLAND
E-mail: info@realtimeoncology.com **Web:** www.realtimeoncology.com

BIOMARKEREK ÉS DRIVEREK	REFERENCIA
	Wellcome Sanger Institute
	NCBI ClinVar
ZRSR2-P383A	Wellcome Trust Sanger Institute
	Wellcome Sanger Institute
	Eisfeld AK, Kohlschmidt J, Mims A, Nicolet D, Walker CJ, Blachly JS, Carroll AJ, Papaioannou D, Kolitz JE, Powell BE, Stone RM, de la Chapelle A, Byrd JC, Mrózek K, Bloomfield CD. Additional gene mutations may refine the 2017 European LeukemiaNet classification in adult patients with de novo acute myeloid leukemia aged <60 years. Leukemia. 2020 May 27;:. doi: 10.1038/s41375-020-0872-3. Epub 2020 Aug 27. PubMed PMID: 32461631.
ZMYM3-C723F	Wellcome Sanger Institute
	Wellcome Trust Sanger Institute
	Wellcome Trust Sanger Institute
	Wellcome Trust Sanger institute
	Wellcome Trust Sanger Institute
SLX4-P1004L	Wellcome Trust Sanger Institute
	Wellcome Sanger Institute
	NCBI ClinVar
	NCBI ClinVar
	Wellcome Sanger Institute
CSMD3-S3630Y	Wellcome Trust Sanger Institute
	Wellcome Sanger Institute
	Wellcome Sanger Institute
	Wellcome Trust Sanger Institute
	Wellcome Sanger Institute
SCN11A-K491fs*5	Wellcome Sanger Institute
SAMD9L-K21fs*3	Wellcome Sanger Institute
	Wellcome Sanger Institute
	Wellcome Trust Sanger Institute
	LOVD Database
	Wellcome Sanger Institute
TAF1-R855C	Wellcome Trust Sanger Institute
	Wellcome Trust Sanger Institute
	NCBI ClinVar
	Leiden Open Variation Database
	Kimura J, Nguyen ST, Liu H, Taira N, Miki Y, Yoshida K. A functional genome-wide RNAi screen identifies TAF1 as a regulator for apoptosis in response to genotoxic stress. Nucleic Acids Res. 2008 Sep;36(16):5250-9. doi: 10.1093/nar/gkn506. Epub 2008 Feb 06. PubMed PMID: 18684994; PubMed Central PMCID: PMC2532742.
SLIT2-K904fs*13	NCBI ClinVar
	Wellcome Sanger Institute
	https://cancer.sanger.ac.uk/cosmic/mutation/overview?id=69285153
	Hwang DY, Kohl S, Fan X, Vivante A, Chan S, Dworschak GC, Schulz J, van Eerde AM, Hilger AC, Gee HY, Pennimpede T, Herrmann BG, van de Hoek G, Renkema KY, Schell C, Huber TB, Reutter HM, Soliman NA, Stajic N, Bogdanovic R, Kehinde EO, Lifton RP, Tasic V, Lu W, Hildebrandt F. Mutations of the SLIT2-ROBO2 pathway genes SLIT2 and SRGAP1 confer risk for congenital anomalies of the kidney and urinary tract. Hum Genet. 2015 Aug;134

Einsiedlerstrasse 23, 8834 Schindellegi, SWITZERLAND
E-mail: info@realtimeoncology.com **Web:** www.realtimeoncology.com

BIOMARKEREK ÉS DRIVEREK	REFERENCIA
	(8):905-16. doi: 10.1007/s00439-015-1570-5. Epub 2015 May 31. PubMed PMID: 26026792; PubMed Central PMCID: PMC4497857.
	Wellcome Trust Sanger Institute
CDC27-K319fs*24	Wellcome Trust Sanger Institute
	Wellcome Sanger Institute
	http://snpeffect.switchlab.org/mutation/CDC27_HUMAN/VAR_014489
	Qiu L, Wu J, Pan C, Tan X, Lin J, Liu R, Chen S, Geng R, Huang W. Downregulation of CDC27 inhibits the proliferation of colorectal cancer cells via the accumulation of p21Cip1/Waf1. Cell Death Dis. 2016 Jan 28;7:e2074. doi: 10.1038/cddis.2015.402. PubMed PMID: 26821069; PubMed Central PMCID: PMC4816181.
DDX11-S407R	Wellcome Trust Sanger Institute
	https://databases.lovd.nl/shared/variants/DDX11/unique
	Wellcome Trust Sanger Institute
	https://cancer.sanger.ac.uk/cosmic/mutation/overview?id=43939475&merge=3954641
	Wellcome Trust Sanger Institute
BAZ2B-N2000S	Wellcome Sanger Institute
	Wellcome Trust Sanger Institute
	Wellcome Trust Sanger Institute
	Wellcome Trust Sanger Institute
	Wellcome Trust Sanger Institute
THSD7B-P642A	Wellcome Sanger Institute
	Wellcome Trust Sanger Institute
	Wellcome Sanger Institute
	Wellcome Sanger Institute
	Wellcome Sanger Institute
GLI1-G162D	Wellcome Sanger Institute
	Wellcome Trust Sanger Institute
	Wellcome Sanger Institute
	https://cancer.sanger.ac.uk/cosmic/search?q=GLI1+R372H
	Wellcome Sanger Institute
ADGRB3-E227A	Wellcome Sanger Institute
	Wellcome Trust Sanger Institute
	Wellcome Trust Sanger Institute
	Wellcome Sanger Institute
	Wellcome Trust Sanger Institute
ZBED4-V241I	Wellcome Trust Sanger Institute
	Wellcome Sanger Institute
	Wellcome Sanger Institute
	Wellcome Trust Sanger Institute
RPTOR-V1192I	Wellcome Sanger Institute
	Wellcome Trust Sanger Institute

Einsiedlerstrasse 23, 8834 Schindellegi, SWITZERLAND
E-mail: info@realtimeoncology.com **Web:** www.realtimeoncology.com

Oncompass Report

A Realtime Oncology Molecular Treatment Calculator számításaival

AZONOSÍTÓ	431898
NÉV	Anonymous

BIOMARKEREK ÉS DRIVEREK	REFERENCIA
	Wellcome Sanger Institute
SMAD2-R410G	Wellcome Sanger Institute
	Wellcome Trust Sanger Institute
SEC16A-P9L	Wellcome Sanger Institute
GATA2-G273fs*53	Wellcome Sanger Institute
TRIO-L2277*	Wellcome Sanger Institute
AKAP9-P1381L	Wellcome Sanger Institute
AKAP9-R434W	Wellcome Sanger Institute
KMT2C-K339N	Wellcome Trust Sanger Institute
	Lu YW, Zhang HF, Liang R, Xie ZR, Luo HY, Zeng YJ, Xu Y, Wang LM, Kong XY, Wang KH. Colorectal Cancer Genetic Heterogeneity Delineated by Multi-Region Sequencing. PLoS One. 2016 Mar 29;11(3):e0152673. doi: 10.1371/journal.pone.0152673. eCollection 2016. PubMed PMID: 27023146; PubMed Central PMCID: PMC4811559.
	LOVD database
BCR-D1106N	Wellcome Trust Sanger Institute
	https://web.expasy.org/variant_pages/VAR_041891.html
PREX2-S977L	Wellcome Trust Sanger Institute
	NCBI ClinVar

TARGET GÉNEK	REFERENCIA
PD-1 vad típus	Chang L, Chang M, Chang HM, Chang F. Microsatellite Instability: A Predictive Biomarker for Cancer Immunotherapy. Appl Immunohistochem Mol Morphol. 2018 Feb;26(2):e15-e21. doi: 10.1097/PAI.0000000000000575. PubMed PMID: 28877075.
	Gatalica Z, Vranic S, Xiu J, Swensen J, Reddy S. High microsatellite instability (MSI-H) colorectal carcinoma: a brief review of predictive biomarkers in the era of personalized medicine. Fam Cancer. 2016 Jul;15(3):405-12. doi: 10.1007/s10689-016-9884-6. Review. PubMed PMID: 26875156; PubMed Central PMCID: PMC4901118.
	Yu Y. Molecular classification and precision therapy of cancer: immune checkpoint inhibitors. Front Med. 2017 Dec 5. doi: 10.1007/s11684-017-0581-0. [Epub ahead of print] PubMed PMID: 29209918.
	Nowicki TS, Hu-Lieskovan S, Ribas A. Mechanisms of Resistance to PD-1 and PD-L1 Blockade. Cancer J. 2018 Jan/Feb;24(1):47-53. doi: 10.1097/PPO.0000000000000303. Review. PubMed PMID: 29360728; PubMed Central PMCID: PMC5785093.
	Heong V, Ngoi N, Tan DS. Update on immune checkpoint inhibitors in gynecological cancers. J Gynecol Oncol. 2017 Mar;28(2):e20. doi: 10.3802/jgo.2017.28.e20. Epub 2016 Dec 14. Review. PubMed PMID: 28028993; PubMed Central PMCID: PMC5323287.
CD274 vad típus	Goodman AM, Sokol ES, Frampton GM, Lippman SM, Kurzrock R. Microsatellite-Stable Tumors with High Mutational Burden Benefit from Immunotherapy. Cancer Immunol Res. 2019 10;7(10):1570-1573. doi: 10.1158/2326-6066.CIR-19-0149. Epub 2019 Oct 12. PubMed PMID: 31405947; PubMed Central PMCID: PMC6774837.
	Lin Shen, Jian Li, Yanhong Deng, Weijie Zhang, Aiping Zhou, Weijian Guo, Jianwei Yang, Ying Yuan, Liangjun Zhu, Shukui Qin, Silong Xiang, Haolan Lu, John Gong, Ting Xu, David Liu. Envafolimab (KN035) in advanced tumors with mismatch-repair deficiency. DOI: 10.1200/JCO.2020.38.15_suppl.3021 Journal of Clinical Oncology 38, no. 15_suppl (May 20, 2020) 3021-3021.
	Goodman AM, Kato S, Bazhenova L, Patel SP, Frampton GM, Miller V, Stephens PJ, Daniels GA, Kurzrock R. Tumor Mutational Burden as an Independent Predictor of Response to Immunotherapy in Diverse Cancers. Mol Cancer Ther. 2017 Nov;16(11):2598-2608. doi: 10.1158/1535-7163.MCT-17-0386. Epub 2017 Aug 23. PubMed PMID: 28835386; PubMed Central PMCID: PMC5670009.
	Xu YP, Lv L, Liu Y, Smith MD, Li WC, Tan XM, Cheng M, Li Z, Bovino M, Aubé J, Xiong Y. Tumor suppressor TET2 promotes cancer immunity and immunotherapy efficacy. J Clin Invest. 2019 Jul 16;130:4316-4331. doi: 10.1172/JCI129317. PubMed PMID: 31310587; PubMed Central PMCID: PMC6763236.
	Schrock AB, Ouyang C, Sandhu J, Sokol E, Jin D, Ross JS, Miller VA, Lim D, Amanam I, Chao J, Catenacci D, Cho M, Braiteh F, Klempner SJ, Ali SM, Fakih M. Tumor mutational burden is predictive of response to immune checkpoint inhibitors in MSI-high metastatic colorectal cancer. Ann Oncol. 2019 Apr 30. pii: mdz134. doi: 10.1093/annonc/mdz134. [Epub ahead of print] PubMed PMID: 31038663.
CTLA4 vad típus	Zhang Z, Wu HX, Lin WH, Wang ZX, Yang LP, Zeng ZL, Luo HY. EPHA7 mutation as a predictive biomarker for immune checkpoint inhibitors in multiple cancers. BMC Med. 2021 Feb 02;19(1):26. doi: 10.1186/s12916-020-01899-x. Epub 2021 Feb 02. PubMed PMID: 33526018.

Einsiedlerstrasse 23, 8834 Schindellegi, SWITZERLAND
E-mail: info@realtimeoncology.com **Web:** www.realtimeoncology.com

TARGET GÉNEK	REFERENCIA
	Xiao Y, Freeman GJ. The microsatellite instable subset of colorectal cancer is a particularly good candidate for checkpoint blockade immunotherapy. Cancer Discov. 2015 Jan;5(1):16-8. doi: 10.1158/2159-8290.CD-14-1397. PubMed PMID: 25583798; PubMed Central PMCID: PMC4295637. Spranger S, Bao R, Gajewski TF. Melanoma-intrinsic -catenin signalling prevents anti-tumour immunity. Nature. 2015 Jul 09;523(7559):231-5. doi: 10.1038/nature14404. Epub 2015 Dec 11. PubMed PMID: 25970248. Samstein RM, Lee CH, Shoushtari AN, Hellmann MD, Shen R, Janjigian YY, Barron DA, Zehir A, Jordan EJ, Omuro A, Kaley TJ, Kendall SM, Motzer RJ, Hakimi AA, Voss MH, Russo P, Rosenberg J, Iyer G, Bochner BH, Bajorin DF, Al-Ahmadie HA, Chaft JE, Rudin CM, Riely GJ, Baxi S, Ho AL, Wong RJ, Pfister DG, Wolchok JD, Barker CA, Gutin PH, Brennan CW, Tabar V, Mellinghoff IK, DeAngelis LM, Ariyan CE, Lee N, Tap WD, Gounder MM, D'Angelo SP, Saltz L, Stadler ZK, Scher HI, Baselga J, Razavi P, Klebanoff CA, Yaeger R, Segal NH, Ku GY, DeMatteo RP, Ladanyi M, Rizvi NA, Berger MF, Riaz N, Solit DB, Chan TA, Morris LGT. Tumor mutational load predicts survival after immunotherapy across multiple cancer types. Nat Genet. 2019 Feb;51(2):202-206. doi: 10.1038/s41588-018-0312-8. Epub 2019 Jan 14. PubMed PMID: 30643254; PubMed Central PMCID: PMC6365097.
WRN vad típus	Chan EM, Shibue T, McFarland JM, Gaeta B, Ghandi M, Dumont N, Gonzalez A, McPartlan JS, Li T, Zhang Y, Bin Liu J, Lazaro JB, Gu P, Piett CG, Apffel A, Ali SO, Deasy R, Keskula P, Ng RWS, Roberts EA, Reznichenko E, Leung L, Alimova M, Schenone M, Islam M, Maruvka YE, Liu Y, Roper J, Raghavan S, Giannakis M, Tseng YY, Nagel ZD, D'Andrea A, Root DE, Boehm JS, Getz G, Chang S, Golub TR, Tsherniak A, Vazquez F, Bass AJ. WRN helicase is a synthetic lethal target in microsatellite unstable cancers. Nature. 2019 04;568(7753):551-556. doi: 10.1038/s41586-019-1102-x. Epub 2019 Oct 10. PubMed PMID: 30971823; PubMed Central PMCID: PMC6580861. van Wietmarschen N, Sridharan S, Nathan WJ, Tubbs A, Chan EM, Callen E, Wu W, Belinky F, Tripathi V, Wong N, Foster K, Noorbakhsh J, Garimella K, Cruz-Migoni A, Sommers JA, Huang Y, Borah AA, Smith JT, Kalfon J, Kesten N, Fugger K, Walker RL, Dolzhenko E, Eberle MA, Hayward BE, Usdin K, Freudenreich CH, Brosh RM, West SC, McHugh PJ, Meltzer PS, Bass AJ, Nussenzweig A. Repeat expansions confer WRN dependence in microsatellite-unstable cancers. Nature. 2020 Sep 30;:. doi: 10.1038/s41586-020-2769-8. Epub 2020 Oct 30. PubMed PMID: 32999459.
IDO1 vad típus	Xiao Y, Freeman GJ. The microsatellite instable subset of colorectal cancer is a particularly good candidate for checkpoint blockade immunotherapy. Cancer Discov. 2015 Jan;5(1):16-8. doi: 10.1158/2159-8290.CD-14-1397. PubMed PMID: 25583798; PubMed Central PMCID: PMC4295637.
LAG3 vad típus	Xiao Y, Freeman GJ. The microsatellite instable subset of colorectal cancer is a particularly good candidate for checkpoint blockade immunotherapy. Cancer Discov. 2015 Jan;5(1):16-8. doi: 10.1158/2159-8290.CD-14-1397. PubMed PMID: 25583798; PubMed Central PMCID: PMC4295637.
ESR1 vad típus	Manso L, Mourón S, Tress M, Gómez-López G, Morente M, Ciruelos E, Rubio-Camarillo M, Rodriguez-Peralto JL, Pujana MA, Pisano DG, Quintela-Fandino M. Analysis of Paired Primary-Metastatic Hormone-Receptor Positive Breast Tumors (HRPBC) Uncovers Potential Novel Drivers of Hormonal Resistance. PLoS One. 2016 May 19;11(5): e0155840. doi: 10.1371/journal.pone.0155840. eCollection 2016. PubMed PMID: 27195705; PubMed Central PMCID: PMC4873174. Maggi LB Jr, Weber JD. Targeting PTEN-defined breast cancers with a one-two punch. Breast Cancer Res. 2015 Apr 8;17:51. doi: 10.1186/s13058-015-0566-3. PubMed PMID: 25888162; PubMed Central PMCID: PMC4389304. Fu X, Creighton CJ, Biswal NC, Kumar V, Shea M, Herrera S, Contreras A, Gutierrez C, Wang T, Nanda S, Giuliano M, Morrison G, Nardone A, Karlin KL, Westbrook TF, Heiser LM, Anur P, Spellman P, Guichard SM, Smith PD, Davies BR, Klinowska T, Lee AV, Mills GB, Rimawi MF, Hilsenbeck SG, Gray JW, Joshi A, Osborne CK, Schiff R. Overcoming endocrine resistance due to reduced PTEN levels in estrogen receptor-positive breast cancer by co-targeting mammalian target of rapamycin, protein kinase B, or mitogen-activated protein kinase kinase. Breast Cancer Res. 2014 Sep 11;16(5):430. doi: 10.1186/s13058-014-0430-x. PubMed PMID: 25212826; PubMed Central PMCID: PMC4303114. Ciruelos Gil EM. Targeting the PI3K/AKT/mTOR pathway in estrogen receptor-positive breast cancer. Cancer Treat Rev. 2014 Aug;40(7):862-71. doi: 10.1016/j.ctrv.2014.03.004. Epub 2014 Mar 26. Review. PubMed PMID: 24774538. Yokoyama Y, Mizunuma H. Recurrent epithelial ovarian cancer and hormone therapy. World J Clin Cases. 2013 Sep 16;1(6):187-90. doi: 10.12998/wjcc.v1.i6.187. PubMed PMID: 24303498; PubMed Central PMCID: PMC3845958.
MTOR vad típus	Lee YR, Park J, Yu HN, Kim JS, Youn HJ, Jung SH. Up-regulation of PI3K/Akt signaling by 17beta-estradiol through activation of estrogen receptor-alpha, but not estrogen receptor-beta, and stimulates cell growth in breast cancer cells. Biochem Biophys Res Commun. 2005 Nov 4;336(4):1221-6. PubMed PMID: 16169518. Jardim DL, Wheler JJ, Hess K, Tsimberidou AM, Zinner R, Janku F, Subbiah V, Naing A, Piha-Paul SA, Westin SN, Roy-Chowdhuri S, Meric-Bernstam F, Hong DS. FBXW7 mutations in patients with advanced cancers: clinical and molecular characteristics and outcomes with mTOR inhibitors. PLoS One. 2014 Feb 19;9(2):e89388. doi: 10.1371/journal.pone.0089388. PubMed PMID: 24586741; PubMed Central PMCID: PMC3929689. Patel M, Gomez NC, McFadden AW, Moats-Staats BM, Wu S, Rojas A, Sapp T, Simon JM, Smith SV, Kaiser-Rogers K, Davis IJ. PTEN deficiency mediates a reciprocal response to IGFI and mTOR inhibition. Mol Cancer Res. 2014 Nov; 12(11):1610-20. doi: 10.1158/1541-7786.MCR-14-0006. Epub 2014 Jul 3. PubMed PMID: 24994750; PubMed Central PMCID: PMC4233155. Yardley DA, Noguchi S, Pritchard KI, Burris HA 3rd, Baselga J, Gnant M, Hortobagyi GN, Campone M, Pistilli B, Piccart M, Melichar B, Petrakova K, Arena FP, Erdkamp F, Harb WA, Feng W, Cahana A, Taran T, Lebwohl D, Rugo HS. Everolimus plus exemestane in postmenopausal patients with HR(+) breast cancer: BOLERO-2 final progression-free survival analysis. Adv Ther. 2013 Oct;30(10):870-84. doi: 10.1007/s12325-013-0060-1. Epub 2013 Oct 25. Erratum in: Adv Ther. 2014 Sep;31(9):1008-9. PubMed PMID: 24158787; PubMed Central PMCID: PMC3898123.

Einsiedlerstrasse 23, 8834 Schindellegi, SWITZERLAND
E-mail: info@realtimeoncology.com **Web:** www.realtimeoncology.com

TARGET GÉNEK	REFERENCIA
	Liu Y, Huang Y, Wang Z, Huang Y, Li X, Louie A, Wei G, Mao JH. Temporal mTOR inhibition protects Fbxw7-deficient mice from radiation-induced tumor development. Aging (Albany NY). 2013 Feb;5(2):111-9. PubMed PMID: 23454868; PubMed Central PMCID: PMC3616198.
PIK3CA vad típus	Lee YR, Park J, Yu HN, Kim JS, Youn HJ, Jung SH. Up-regulation of PI3K/Akt signaling by 17beta-estradiol through activation of estrogen receptor-alpha, but not estrogen receptor-beta, and stimulates cell growth in breast cancer cells. Biochem Biophys Res Commun. 2005 Nov 4;336(4):1221-6. PubMed PMID: 16169518. Telford BJ, Chen A, Beetham H, Frick J, Brew TP, Gould CM, Single A, Godwin T, Simpson KJ, Guilford P. Synthetic Lethal Screens Identify Vulnerabilities in GPCR Signaling and Cytoskeletal Organization in E-Cadherin-Deficient Cells. Mol Cancer Ther. 2015 May;14(5):1213-23. doi: 10.1158/1535-7163.MCT-14-1092. Epub 2015 Mar 16. PubMed PMID: 25777964. Li D, Lo W, Rudloff U. Merging perspectives: genotype-directed molecular therapy for hereditary diffuse gastric cancer (HDGC) and E-cadherin-EGFR crosstalk. Clin Transl Med. 2018 Feb 22;7(1):7. doi: 10.1186/s40169-018-0184-7. PubMed PMID: 29468433; PubMed Central PMCID: PMC5821620. DeGraffenried LA, Fulcher L, Friedrichs WE, Grünwald V, Ray RB, Hidalgo M. Reduced PTEN expression in breast cancer cells confers susceptibility to inhibitors of the PI3 kinase/Akt pathway. Ann Oncol. 2004 Oct;15(10):1510-6. PubMed PMID: 15367412. Ciruelos Gil EM. Targeting the PI3K/AKT/mTOR pathway in estrogen receptor-positive breast cancer. Cancer Treat Rev. 2014 Aug;40(7):862-71. doi: 10.1016/j.ctrv.2014.03.004. Epub 2014 Mar 26. Review. PubMed PMID: 24774538.
AKT1 vad típus	Lee YR, Park J, Yu HN, Kim JS, Youn HJ, Jung SH. Up-regulation of PI3K/Akt signaling by 17beta-estradiol through activation of estrogen receptor-alpha, but not estrogen receptor-beta, and stimulates cell growth in breast cancer cells. Biochem Biophys Res Commun. 2005 Nov 4;336(4):1221-6. PubMed PMID: 16169518. Li J, Davies BR, Han S, Zhou M, Bai Y, Zhang J, Xu Y, Tang L, Wang H, Liu YJ, Yin X, Ji Q, Yu DH. The AKT inhibitor AZD5363 is selectively active in PI3KCA mutant gastric cancer, and sensitizes a patient-derived gastric cancer xenograft model with PTEN loss to Taxotere. J Transl Med. 2013 Oct 2;11:241. doi: 10.1186/1479-5876-11-241. PubMed PMID: 24088382; PubMed Central PMCID: PMC3850695. Conley-LaComb MK, Saliganan A, Kandagatla P, Chen YQ, Cher ML, Chinni SR. PTEN loss mediated Akt activation promotes prostate tumor growth and metastasis via CXCL12/CXCR4 signaling. Mol Cancer. 2013 Jul 31;12(1):85. doi: 10.1186/1476-4598-12-85. PubMed PMID: 23902739; PubMed Central PMCID: PMC3751767. Telford BJ, Chen A, Beetham H, Frick J, Brew TP, Gould CM, Single A, Godwin T, Simpson KJ, Guilford P. Synthetic Lethal Screens Identify Vulnerabilities in GPCR Signaling and Cytoskeletal Organization in E-Cadherin-Deficient Cells. Mol Cancer Ther. 2015 May;14(5):1213-23. doi: 10.1158/1535-7163.MCT-14-1092. Epub 2015 Mar 16. PubMed PMID: 25777964. Samartzis EP, Gutsche K, Dedes KJ, Fink D, Stucki M, Imesch P. Loss of ARID1A expression sensitizes cancer cells to PI3K- and AKT-inhibition. Oncotarget. 2014 Jul 30;5(14):5295-303. PubMed PMID: 24979463; PubMed Central PMCID: PMC4170604.
CDK4 vad típus	Murphy CG, Dickler MN. The Role of CDK4/6 Inhibition in Breast Cancer. Oncologist. 2015 May;20(5):483-90. doi: 10.1634/theoncologist.2014-0443. Epub 2015 Apr 15. Review. PubMed PMID: 25876993; PubMed Central PMCID: PMC4425391.
CDK6 vad típus	Murphy CG, Dickler MN. The Role of CDK4/6 Inhibition in Breast Cancer. Oncologist. 2015 May;20(5):483-90. doi: 10.1634/theoncologist.2014-0443. Epub 2015 Apr 15. Review. PubMed PMID: 25876993; PubMed Central PMCID: PMC4425391.
PARP1 vad típus	Stoepker C, Faramarz A, Rooimans MA, van Mil SE, Balk JA, Velleuer E, Ameziane N, Te Riele H, de Winter JP. DNA helicases FANCM and DDX11 are determinants of PARP inhibitor sensitivity. DNA Repair (Amst). 2015 Feb;26:54-64. doi: 10.1016/j.dnarep.2014.12.003. Epub 2014 Dec 24. PubMed PMID: 25583207. Wang C, Jette N, Moussienko D, Bebb DG, Lees-Miller SP. ATM-Deficient Colorectal Cancer Cells Are Sensitive to the PARP Inhibitor Olaparib. Transl Oncol. 2017 Apr;10(2):190-196. doi: 10.1016/j.tranon.2017.01.007. Epub 2017 Feb 6. PubMed PMID: 28182994; PubMed Central PMCID: PMC5299208. Hurley RM, Wahner Hendrickson AE, Visscher DW, Ansell P, Harrell MI, Wagner JM, Negron V, Goergen KM, Maurer MJ, Oberg AL, Meng XW, Flatten KS, De Jonge MJA, Van Herpen CD, Gietema JA, Koornstra RHT, Jager A, den Hollander MW, Dudley M, Shepherd SP, Swisher EM, Kaufmann SH. 53BP1 as a potential predictor of response in PARP inhibitor-treated homologous recombination-deficient ovarian cancer. Gynecol Oncol. 2019 04;153(1):127-134. doi: 10.1016/j.ygyno.2019.01.015. Epub 2019 Jun 25. PubMed PMID: 30686551; PubMed Central PMCID: PMC6430710. Koppensteiner R, Samartzis EP, Noske A, von Teichman A, Dedes I, Gwerder M, Imesch P, Ikenberg K, Moch H, Fink D, Stucki M, Dedes KJ. Effect of MRE11 loss on PARP-inhibitor sensitivity in endometrial cancer in vitro. PLoS One. 2014 Jun 13;9(6):e100041. doi: 10.1371/journal.pone.0100041. eCollection 2014. PubMed PMID: 24927325; PubMed Central PMCID: PMC4057395. Santarpia L, Iwamoto T, Di Leo A, Hayashi N, Bottai G, Stampfer M, André F, Turner NC, Symmans WF, Hortobágyi GN, Pusztai L, Bianchini G. DNA repair gene patterns as prognostic and predictive factors in molecular breast cancer subtypes. Oncologist. 2013;18(10):1063-73. doi: 10.1634/theoncologist.2013-0163. Epub 2013 Sep 26. PubMed PMID: 24072219; PubMed Central PMCID: PMC3805146.
PIK3CB vad típus	Greshock J. Abstract IA17: Exploiting the synthetic lethal properties of selective PI3K- inhibition in PTEN deficient cells with GSK2636771. Mol Cancer Ther. 2013 May 1;12(5 Supplement):IA17–IA17.

Einsiedlerstrasse 23, 8834 Schindellegi, SWITZERLAND
E-mail: info@realtimeoncology.com **Web:** www.realtimeoncology.com

TARGET GÉNEK	REFERENCIA
	Xu PF, Yang JA, Liu JH, Yang X, Liao JM, Yuan FE, Liu BH, Chen QX. PI3K inhibitor AZD6482 exerts antiproliferative activity and induces apoptosis in human glioblastoma cells. Oncol Rep. 2019 Jan;41(1):125-132. doi: 10.3892/or.2018.6845. Epub 2018 Nov 02. PubMed PMID: 30542720; PubMed Central PMCID: PMC6278584. Telford BJ, Chen A, Beetham H, Frick J, Brew TP, Gould CM, Single A, Godwin T, Simpson KJ, Guilford P. Synthetic Lethal Screens Identify Vulnerabilities in GPCR Signaling and Cytoskeletal Organization in E-Cadherin-Deficient Cells. Mol Cancer Ther. 2015 May;14(5):1213-23. doi: 10.1158/1535-7163.MCT-14-1092. Epub 2015 Mar 16. PubMed PMID: 25777964. Li D, Lo W, Rudloff U. Merging perspectives: genotype-directed molecular therapy for hereditary diffuse gastric cancer (HDGC) and E-cadherin-EGFR crosstalk. Clin Transl Med. 2018 Feb 22;7(1):7. doi: 10.1186/s40169-018-0184-7. PubMed PMID: 29468433; PubMed Central PMCID: PMC5821620. Costa HA, Leitner MG, Sos ML, Mavrantoni A, Rychkova A, Johnson JR, Newton BW, Yee MC, De La Vega FM, Ford JM, Krogan NJ, Shokat KM, Oliver D, Halaszovich CR, Bustamante CD. Discovery and functional characterization of a neomorphic PTEN mutation. Proc Natl Acad Sci U S A. 2015 Nov 10;112(45):13976-81. doi: 10.1073/pnas.1422504112. Epub 2015 Oct 26. PubMed PMID: 26504226; PubMed Central PMCID: PMC4653168.
ALK vad típus	Telford BJ, Chen A, Beetham H, Frick J, Brew TP, Gould CM, Single A, Godwin T, Simpson KJ, Guilford P. Synthetic Lethal Screens Identify Vulnerabilities in GPCR Signaling and Cytoskeletal Organization in E-Cadherin-Deficient Cells. Mol Cancer Ther. 2015 May;14(5):1213-23. doi: 10.1158/1535-7163.MCT-14-1092. Epub 2015 Mar 16. PubMed PMID: 25777964. Li D, Lo W, Rudloff U. Merging perspectives: genotype-directed molecular therapy for hereditary diffuse gastric cancer (HDGC) and E-cadherin-EGFR crosstalk. Clin Transl Med. 2018 Feb 22;7(1):7. doi: 10.1186/s40169-018-0184-7. PubMed PMID: 29468433; PubMed Central PMCID: PMC5821620. O'donohue T et al. TPX-0005 (Repotrectinib), a next-generation ALK/ROS1/NTRK1–3 inhibitor, has potent antiproliferative and anti-tumor activity as monotherapy and in combination with chemotherapy in neuroblastoma cell lines and pediatric patient derived xenograft models. VOLUME 138, SUPPLEMENT 2, S16-S17, OCTOBER 01, 2020 Fontana D, Ceccon M, Gambacorti-Passerini C, Mologni L. Activity of second-generation ALK inhibitors against crizotinib-resistant mutants in an NPM-ALK model compared to EML4-ALK. Cancer Med. 2015 Jul;4(7):953-65. doi: 10.1002/cam4.413. Epub 2015 Feb 26. PubMed PMID: 25727400; PubMed Central PMCID: PMC4529334. Guan J, Tucker ER, Wan H, Chand D, Danielson LS, Ruuth K, El Wakil A, Witek B, Jamin Y, Umapathy G, Robinson SP, Johnson TW, Smeal T, Martinsson T, Chesler L, Palmer RH, Hallberg B. The ALK inhibitor PF-06463922 is effective as a single agent in neuroblastoma driven by expression of ALK and MYCN. Dis Model Mech. 2016 Sep 1;9(9):941-52. doi: 10.1242/dmm.024448. Epub 2016 Jul 7. PubMed PMID: 27483357; PubMed Central PMCID: PMC5047689.
CTNNB1 vad típus	Jiang W, He T, Liu S, Zheng Y, Xiang L, Pei X, Wang Z, Yang H. The PIK3CA E542K and E545K mutations promote glycolysis and proliferation via induction of the -catenin/SIRT3 signaling pathway in cervical cancer. J Hematol Oncol. 2018 Dec 14;11(1):139. doi: 10.1186/s13045-018-0674-5. PubMed PMID: 30547809; PubMed Central PMCID: PMC6293652. Bahrami A, Amerizadeh F, ShahidSales S, Khazaei M, Ghayour-Mobarhan M, Sadeghnia HR, Maftouh M, Hassanian SM, Avan A. Therapeutic Potential of Targeting Wnt/-Catenin Pathway in Treatment of Colorectal Cancer: Rational and Progress. J Cell Biochem. 2017 Aug;118(8):1979-1983. doi: 10.1002/jcb.25903. Epub 2017 Apr 25. Review. PubMed PMID: 28109136.
ATM vad típus	McCabe N, Hanna C, Walker SM, Gonda D, Li J, Wikstrom K, Savage KI, Butterworth KT, Chen C, Harkin DP, Prise KM, Kennedy RD. Mechanistic Rationale to Target PTEN-Deficient Tumor Cells with Inhibitors of the DNA Damage Response Kinase ATM. Cancer Res. 2015 Jun 1;75(11):2159-65. doi: 10.1158/0008-5472.CAN-14-3502. Epub 2015 Apr 13. PubMed PMID: 25870146.
NOTCH1 vad típus	Aydin IT, Melamed RD, Adams SJ, Castillo-Martin M, Demir A, Bryk D, Brunner G, Cordon-Cardo C, Osman I, Rabadan R, Celebi JT. FBXW7 mutations in melanoma and a new therapeutic paradigm. J Natl Cancer Inst. 2014 May 16;106(6):dju107. doi: 10.1093/jnci/dju107. PubMed PMID: 24838835; PubMed Central PMCID: PMC4081626.
MCL1 vad típus	Wang Z, Fukushima H, Gao D, Inuzuka H, Wan L, Lau AW, Liu P, Wei W. The two faces of FBW7 in cancer drug resistance. Bioessays. 2011 Nov;33(11):851-9. doi: 10.1002/bies.201100101. Review. PubMed PMID: 22006825; PubMed Central PMCID: PMC3364519.
TTK vad típus	Zaman GJR, de Roos JADM, Libouban MAA, Prinsen MBW, de Man J, Buijsman RC, Uitdehaag JCM. TTK Inhibitors as a Targeted Therapy for CTNNB1 (-catenin) Mutant Cancers. Mol Cancer Ther. 2017 Nov;16(11):2609-2617. doi: 10.1158/1535-7163.MCT-17-0342. Epub 2017 Jul 27. PubMed PMID: 28751540.
AKT2 vad típus	Li J, Davies BR, Han S, Zhou M, Bai Y, Zhang J, Xu Y, Tang L, Wang H, Liu YJ, Yin X, Ji Q, Yu DH. The AKT inhibitor AZD5363 is selectively active in PI3KCA mutant gastric cancer, and sensitizes a patient-derived gastric cancer xenograft model with PTEN loss to Taxotere. J Transl Med. 2013 Oct 2;11:241. doi: 10.1186/1479-5876-11-241. PubMed PMID: 24088382; PubMed Central PMCID: PMC3850695. Beaver JA, Gustin JP, Yi KH, Rajpurohit A, Thomas M, Gilbert SF, Rosen DM, Ho Park B, Lauring J. PIK3CA and AKT1 mutations have distinct effects on sensitivity to targeted pathway inhibitors in an isogenic luminal breast cancer model system. Clin Cancer Res. 2013 Oct 1;19(19):5413-22. doi: 10.1158/1078-0432.CCR-13-0884. Epub 2013 Jul 25. PubMed PMID: 23888070; PubMed Central PMCID: PMC3805128.
AKT3 vad típus	

Einsiedlerstrasse 23, 8834 Schindellegi, SWITZERLAND
E-mail: info@realtimeoncology.com **Web:** www.realtimeoncology.com

TARGET GÉNEK	REFERENCIA
	Li J, Davies BR, Han S, Zhou M, Bai Y, Zhang J, Xu Y, Tang L, Wang H, Liu YJ, Yin X, Ji Q, Yu DH. The AKT inhibitor AZD5363 is selectively active in PI3KCA mutant gastric cancer, and sensitizes a patient-derived gastric cancer xenograft model with PTEN loss to Taxotere. J Transl Med. 2013 Oct 2;11:241. doi: 10.1186/1479-5876-11-241. PubMed PMID: 24088382; PubMed Central PMCID: PMC3850695.
JAK2 vad típus	Telford BJ, Chen A, Beetham H, Frick J, Brew TP, Gould CM, Single A, Godwin T, Simpson KJ, Guilford P. Synthetic Lethal Screens Identify Vulnerabilities in GPCR Signaling and Cytoskeletal Organization in E-Cadherin-Deficient Cells. Mol Cancer Ther. 2015 May;14(5):1213-23. doi: 10.1158/1535-7163.MCT-14-1092. Epub 2015 Mar 16. PubMed PMID: 25777964. Tasian SK, Casas JA, Posocco D, Gandre-Babbe S, Gagne AL, Liang G, Loh ML, Weiss MJ, French DL, Chou ST. Mutation-specific signaling profiles and kinase inhibitor sensitivities of juvenile myelomonocytic leukemia revealed by induced pluripotent stem cells. Leukemia. 2018 Jun 8. doi: 10.1038/s41375-018-0169-y. [Epub ahead of print] PubMed PMID: 29884903. Purandare AV, McDevitt TM, Wan H, You D, Penhallow B, Han X, Vuppugalla R, Zhang Y, Ruepp SU, Trainor GL, Lombardo L, Pedicord D, Gottardis MM, Ross-Macdonald P, de Silva H, Hosbach J, Emanuel SL, Blat Y, Fitzpatrick E, Taylor TL, McIntyre KW, Michaud E, Mulligan C, Lee FY, Woolfson A, Lasho TL, Pardanani A, Tefferi A, Lorenzi MV. Characterization of BMS-911543, a functionally selective small-molecule inhibitor of JAK2. Leukemia. 2012 Feb;26 (2):280-8. doi: 10.1038/leu.2011.292. Epub 2011 Oct 21. PubMed PMID: 22015772.
ATR vad típus	Perkhofer L, Schmitt A, Romero Carrasco MC, Ihle M, Hampp S, Ruess DA, Hessmann E, Russell R, Lechel A, Azoitei N, Lin Q, Liebau S, Hohwieler M, Bohnenberger H, Lesina M, Algül H, Gieldon L, Schröck E, Gaedcke J, Wagner M, Wiesmüller L, Sipos B, Seufferlein T, Reinhardt HC, Frappart PO, Kleger A. ATM Deficiency Generating Genomic Instability Sensitizes Pancreatic Ductal Adenocarcinoma Cells to Therapy-Induced DNA Damage. Cancer Res. 2017 Oct 15;77(20):5576-5590. doi: 10.1158/0008-5472.CAN-17-0634. Epub 2017 Aug 8. PubMed PMID: 28790064. Lücking U, Wortmann L, Wengner AM, Lefranc J, Lienau P, Briem H, Siemeister G, Bömer U, Denner K, Schäfer M, Koppitz M, Eis K, Bartels F, Bader B, Bone W, Moosmayer D, Holton SJ, Eberspächer U, Grudzinska-Goebel J, Schatz C, Deeg G, Mumberg D, von Nussbaum F. Damage Incorporated: Discovery of the Potent, Highly Selective, Orally Available ATR Inhibitor BAY 1895344 with Favorable Pharmacokinetic Properties and Promising Efficacy in Monotherapy and in Combination Treatments in Preclinical Tumor Models. J Med Chem. 2020 Jul 09;63(13):7293-7325. doi: 10.1021/acs.jmedchem.0c00369. Epub 2020 Jul 28. PubMed PMID: 32502336. Reaper PM, Griffiths MR, Long JM, Charrier JD, Maccormick S, Charlton PA, Golec JM, Pollard JR. Selective killing of ATM- or p53-deficient cancer cells through inhibition of ATR. Nat Chem Biol. 2011 Apr 13;7(7):428-30. doi: 10.1038 /nchembio.573. PubMed PMID: 21490603.
ABL1 vad típus	Telford BJ, Chen A, Beetham H, Frick J, Brew TP, Gould CM, Single A, Godwin T, Simpson KJ, Guilford P. Synthetic Lethal Screens Identify Vulnerabilities in GPCR Signaling and Cytoskeletal Organization in E-Cadherin-Deficient Cells. Mol Cancer Ther. 2015 May;14(5):1213-23. doi: 10.1158/1535-7163.MCT-14-1092. Epub 2015 Mar 16. PubMed PMID: 25777964. Sourbier C, Ricketts CJ, Matsumoto S, Crooks DR, Liao PJ, Mannes PZ, Yang Y, Wei MH, Srivastava G, Ghosh S, Chen V, Vocke CD, Merino M, Srinivasan R, Krishna MC, Mitchell JB, Pendergast AM, Rouault TA, Neckers L, Linehan WM. Targeting ABL1-mediated oxidative stress adaptation in fumarate hydratase-deficient cancer. Cancer Cell. 2014 Dec 8;26(6):840-850. doi: 10.1016/j.ccell.2014.10.005. PubMed PMID: 25490448; PubMed Central PMCID: PMC4386283.
JAK1 vad típus	Telford BJ, Chen A, Beetham H, Frick J, Brew TP, Gould CM, Single A, Godwin T, Simpson KJ, Guilford P. Synthetic Lethal Screens Identify Vulnerabilities in GPCR Signaling and Cytoskeletal Organization in E-Cadherin-Deficient Cells. Mol Cancer Ther. 2015 May;14(5):1213-23. doi: 10.1158/1535-7163.MCT-14-1092. Epub 2015 Mar 16. PubMed PMID: 25777964. Tasian SK, Casas JA, Posocco D, Gandre-Babbe S, Gagne AL, Liang G, Loh ML, Weiss MJ, French DL, Chou ST. Mutation-specific signaling profiles and kinase inhibitor sensitivities of juvenile myelomonocytic leukemia revealed by induced pluripotent stem cells. Leukemia. 2018 Jun 8. doi: 10.1038/s41375-018-0169-y. [Epub ahead of print] PubMed PMID: 29884903.
ROS1 vad típus	Telford BJ, Chen A, Beetham H, Frick J, Brew TP, Gould CM, Single A, Godwin T, Simpson KJ, Guilford P. Synthetic Lethal Screens Identify Vulnerabilities in GPCR Signaling and Cytoskeletal Organization in E-Cadherin-Deficient Cells. Mol Cancer Ther. 2015 May;14(5):1213-23. doi: 10.1158/1535-7163.MCT-14-1092. Epub 2015 Mar 16. PubMed PMID: 25777964. Li D, Lo W, Rudloff U. Merging perspectives: genotype-directed molecular therapy for hereditary diffuse gastric cancer (HDGC) and E-cadherin-EGFR crosstalk. Clin Transl Med. 2018 Feb 22;7(1):7. doi: 10.1186/s40169-018-0184-7. PubMed PMID: 29468433; PubMed Central PMCID: PMC5821620. Bajrami I, Marlow R, van de Ven M, Brough R, Pemberton HN, Frankum J, Song F, Rafiq R, Konde A, Krastev DB, Menon M, Campbell J, Gulati A, Kumar R, Pettitt SJ, Gurden MD, Cardenosa ML, Chong I, Gazinska P, Wallberg F, Sawyer EJ, Martin LA, Dowsett M, Linardopoulos S, Natrajan R, Ryan CJ, Derksen PWB, Jonkers J, Tutt ANJ, Ashworth A, Lord CJ. E-Cadherin/ROS1 Inhibitor Synthetic Lethality in Breast Cancer. Cancer Discov. 2018 Apr;8(4): 498-515. doi: 10.1158/2159-8290.CD-17-0603. PubMed PMID: 29610289.
AURKC vad típus	Telford BJ, Chen A, Beetham H, Frick J, Brew TP, Gould CM, Single A, Godwin T, Simpson KJ, Guilford P. Synthetic Lethal Screens Identify Vulnerabilities in GPCR Signaling and Cytoskeletal Organization in E-Cadherin-Deficient Cells. Mol Cancer Ther. 2015 May;14(5):1213-23. doi: 10.1158/1535-7163.MCT-14-1092. Epub 2015 Mar 16. PubMed PMID: 25777964. Li D, Lo W, Rudloff U. Merging perspectives: genotype-directed molecular therapy for hereditary diffuse gastric cancer (HDGC) and E-cadherin-EGFR crosstalk. Clin Transl Med. 2018 Feb 22;7(1):7. doi: 10.1186/s40169-018-0184-7. PubMed PMID: 29468433; PubMed Central PMCID: PMC5821620.

Einsiedlerstrasse 23, 8834 Schindellegi, SWITZERLAND
E-mail: info@realtimeoncology.com **Web:** www.realtimeoncology.com

Oncompass Report

A Realtime Oncology Molecular Treatment Calculator számításaival

AZONOSÍTÓ	431898
NÉV	Anonymous

TARGET GÉNEK	REFERENCIA
AURKB vad típus	Telford BJ, Chen A, Beetham H, Frick J, Brew TP, Gould CM, Single A, Godwin T, Simpson KJ, Guilford P. Synthetic Lethal Screens Identify Vulnerabilities in GPCR Signaling and Cytoskeletal Organization in E-Cadherin-Deficient Cells. Mol Cancer Ther. 2015 May;14(5):1213-23. doi: 10.1158/1535-7163.MCT-14-1092. Epub 2015 Mar 16. PubMed PMID: 25777964. Li D, Lo W, Rudloff U. Merging perspectives: genotype-directed molecular therapy for hereditary diffuse gastric cancer (HDGC) and E-cadherin-EGFR crosstalk. Clin Transl Med. 2018 Feb 22;7(1):7. doi: 10.1186/s40169-018-0184-7. PubMed PMID: 29468433; PubMed Central PMCID: PMC5821620.
PIK3CG vad típus	Telford BJ, Chen A, Beetham H, Frick J, Brew TP, Gould CM, Single A, Godwin T, Simpson KJ, Guilford P. Synthetic Lethal Screens Identify Vulnerabilities in GPCR Signaling and Cytoskeletal Organization in E-Cadherin-Deficient Cells. Mol Cancer Ther. 2015 May;14(5):1213-23. doi: 10.1158/1535-7163.MCT-14-1092. Epub 2015 Mar 16. PubMed PMID: 25777964. Li D, Lo W, Rudloff U. Merging perspectives: genotype-directed molecular therapy for hereditary diffuse gastric cancer (HDGC) and E-cadherin-EGFR crosstalk. Clin Transl Med. 2018 Feb 22;7(1):7. doi: 10.1186/s40169-018-0184-7. PubMed PMID: 29468433; PubMed Central PMCID: PMC5821620.
AURKA vad típus	Telford BJ, Chen A, Beetham H, Frick J, Brew TP, Gould CM, Single A, Godwin T, Simpson KJ, Guilford P. Synthetic Lethal Screens Identify Vulnerabilities in GPCR Signaling and Cytoskeletal Organization in E-Cadherin-Deficient Cells. Mol Cancer Ther. 2015 May;14(5):1213-23. doi: 10.1158/1535-7163.MCT-14-1092. Epub 2015 Mar 16. PubMed PMID: 25777964. Li D, Lo W, Rudloff U. Merging perspectives: genotype-directed molecular therapy for hereditary diffuse gastric cancer (HDGC) and E-cadherin-EGFR crosstalk. Clin Transl Med. 2018 Feb 22;7(1):7. doi: 10.1186/s40169-018-0184-7. PubMed PMID: 29468433; PubMed Central PMCID: PMC5821620.
PIK3CD vad típus	Telford BJ, Chen A, Beetham H, Frick J, Brew TP, Gould CM, Single A, Godwin T, Simpson KJ, Guilford P. Synthetic Lethal Screens Identify Vulnerabilities in GPCR Signaling and Cytoskeletal Organization in E-Cadherin-Deficient Cells. Mol Cancer Ther. 2015 May;14(5):1213-23. doi: 10.1158/1535-7163.MCT-14-1092. Epub 2015 Mar 16. PubMed PMID: 25777964. Li D, Lo W, Rudloff U. Merging perspectives: genotype-directed molecular therapy for hereditary diffuse gastric cancer (HDGC) and E-cadherin-EGFR crosstalk. Clin Transl Med. 2018 Feb 22;7(1):7. doi: 10.1186/s40169-018-0184-7. PubMed PMID: 29468433; PubMed Central PMCID: PMC5821620.
PDGFRB vad típus	Telford BJ, Chen A, Beetham H, Frick J, Brew TP, Gould CM, Single A, Godwin T, Simpson KJ, Guilford P. Synthetic Lethal Screens Identify Vulnerabilities in GPCR Signaling and Cytoskeletal Organization in E-Cadherin-Deficient Cells. Mol Cancer Ther. 2015 May;14(5):1213-23. doi: 10.1158/1535-7163.MCT-14-1092. Epub 2015 Mar 16. PubMed PMID: 25777964.
BCL2 vad típus	Telford BJ, Chen A, Beetham H, Frick J, Brew TP, Gould CM, Single A, Godwin T, Simpson KJ, Guilford P. Synthetic Lethal Screens Identify Vulnerabilities in GPCR Signaling and Cytoskeletal Organization in E-Cadherin-Deficient Cells. Mol Cancer Ther. 2015 May;14(5):1213-23. doi: 10.1158/1535-7163.MCT-14-1092. Epub 2015 Mar 16. PubMed PMID: 25777964.
NTRK1 vad típus	Telford BJ, Chen A, Beetham H, Frick J, Brew TP, Gould CM, Single A, Godwin T, Simpson KJ, Guilford P. Synthetic Lethal Screens Identify Vulnerabilities in GPCR Signaling and Cytoskeletal Organization in E-Cadherin-Deficient Cells. Mol Cancer Ther. 2015 May;14(5):1213-23. doi: 10.1158/1535-7163.MCT-14-1092. Epub 2015 Mar 16. PubMed PMID: 25777964.
FGFR1 vad típus	Telford BJ, Chen A, Beetham H, Frick J, Brew TP, Gould CM, Single A, Godwin T, Simpson KJ, Guilford P. Synthetic Lethal Screens Identify Vulnerabilities in GPCR Signaling and Cytoskeletal Organization in E-Cadherin-Deficient Cells. Mol Cancer Ther. 2015 May;14(5):1213-23. doi: 10.1158/1535-7163.MCT-14-1092. Epub 2015 Mar 16. PubMed PMID: 25777964.
PDGFRA vad típus	Telford BJ, Chen A, Beetham H, Frick J, Brew TP, Gould CM, Single A, Godwin T, Simpson KJ, Guilford P. Synthetic Lethal Screens Identify Vulnerabilities in GPCR Signaling and Cytoskeletal Organization in E-Cadherin-Deficient Cells. Mol Cancer Ther. 2015 May;14(5):1213-23. doi: 10.1158/1535-7163.MCT-14-1092. Epub 2015 Mar 16. PubMed PMID: 25777964.
JAK3 vad típus	Telford BJ, Chen A, Beetham H, Frick J, Brew TP, Gould CM, Single A, Godwin T, Simpson KJ, Guilford P. Synthetic Lethal Screens Identify Vulnerabilities in GPCR Signaling and Cytoskeletal Organization in E-Cadherin-Deficient Cells. Mol Cancer Ther. 2015 May;14(5):1213-23. doi: 10.1158/1535-7163.MCT-14-1092. Epub 2015 Mar 16. PubMed PMID: 25777964.
SRC vad típus	Telford BJ, Chen A, Beetham H, Frick J, Brew TP, Gould CM, Single A, Godwin T, Simpson KJ, Guilford P. Synthetic Lethal Screens Identify Vulnerabilities in GPCR Signaling and Cytoskeletal Organization in E-Cadherin-Deficient Cells. Mol Cancer Ther. 2015 May;14(5):1213-23. doi: 10.1158/1535-7163.MCT-14-1092. Epub 2015 Mar 16. PubMed PMID: 25777964.
NPY5R vad típus	Telford BJ, Chen A, Beetham H, Frick J, Brew TP, Gould CM, Single A, Godwin T, Simpson KJ, Guilford P. Synthetic Lethal Screens Identify Vulnerabilities in GPCR Signaling and Cytoskeletal Organization in E-Cadherin-Deficient Cells. Mol Cancer Ther. 2015 May;14(5):1213-23. doi: 10.1158/1535-7163.MCT-14-1092. Epub 2015 Mar 16. PubMed PMID: 25777964.
CDK2 vad típus	Telford BJ, Chen A, Beetham H, Frick J, Brew TP, Gould CM, Single A, Godwin T, Simpson KJ, Guilford P. Synthetic Lethal Screens Identify Vulnerabilities in GPCR Signaling and Cytoskeletal Organization in E-Cadherin-Deficient Cells. Mol Cancer Ther. 2015 May;14(5):1213-23. doi: 10.1158/1535-7163.MCT-14-1092. Epub 2015 Mar 16. PubMed PMID: 25777964.
CDK1 vad típus	Telford BJ, Chen A, Beetham H, Frick J, Brew TP, Gould CM, Single A, Godwin T, Simpson KJ, Guilford P. Synthetic Lethal Screens Identify Vulnerabilities in GPCR Signaling and Cytoskeletal Organization in E-Cadherin-Deficient Cells. Mol Cancer Ther. 2015 May;14(5):1213-23. doi: 10.1158/1535-7163.MCT-14-1092. Epub 2015 Mar 16. PubMed PMID: 25777964.
RET vad típus	

TARGET GÉNEK	REFERENCIA
	Telford BJ, Chen A, Beetham H, Frick J, Brew TP, Gould CM, Single A, Godwin T, Simpson KJ, Guilford P. Synthetic Lethal Screens Identify Vulnerabilities in GPCR Signaling and Cytoskeletal Organization in E-Cadherin-Deficient Cells. Mol Cancer Ther. 2015 May;14(5):1213-23. doi: 10.1158/1535-7163.MCT-14-1092. Epub 2015 Mar 16. PubMed PMID: 25777964.
GBF1 vad típus	Telford BJ, Chen A, Beetham H, Frick J, Brew TP, Gould CM, Single A, Godwin T, Simpson KJ, Guilford P. Synthetic Lethal Screens Identify Vulnerabilities in GPCR Signaling and Cytoskeletal Organization in E-Cadherin-Deficient Cells. Mol Cancer Ther. 2015 May;14(5):1213-23. doi: 10.1158/1535-7163.MCT-14-1092. Epub 2015 Mar 16. PubMed PMID: 25777964.
MET vad típus	Telford BJ, Chen A, Beetham H, Frick J, Brew TP, Gould CM, Single A, Godwin T, Simpson KJ, Guilford P. Synthetic Lethal Screens Identify Vulnerabilities in GPCR Signaling and Cytoskeletal Organization in E-Cadherin-Deficient Cells. Mol Cancer Ther. 2015 May;14(5):1213-23. doi: 10.1158/1535-7163.MCT-14-1092. Epub 2015 Mar 16. PubMed PMID: 25777964.
HMGCR vad típus	Single, Andrew, Augustine Chen, Bryony Telford, Henry Beetham, and Parry Guilford. "Abstract B41: Statins show synthetic lethality in E-cadherin-deficient cells and are synergistic with SRC and HDAC inhibitors." (2017): B41-B41.
EZH2 vad típus	Chan-Penebre E, Armstrong K, Drew A, Grassian AR, Feldman I, Knutson SK, Kuplast-Barr K, Roche M, Campbell J, Ho P, Copeland RA, Chesworth R, Smith JJ, Keilhack H, Ribich SA. Selective Killing of SMARCA2- and SMARCA4-deficient Small Cell Carcinoma of the Ovary, Hypercalcemic Type Cells by Inhibition of EZH2: In Vitro and In Vivo Preclinical Models. Mol Cancer Ther. 2017 05;16(5):850-860. doi: 10.1158/1535-7163.MCT-16-0678. Epub 2017 Oct 14. PubMed PMID: 28292935. Kim KH, Kim W, Howard TP, Vazquez F, Tsherniak A, Wu JN, Wang W, Haswell JR, Walensky LD, Hahn WC, Orkin SH, Roberts CW. SWI/SNF-mutant cancers depend on catalytic and non-catalytic activity of EZH2. Nat Med. 2015 Dec;21(12):1491-6. doi: 10.1038/nm.3968. Epub 2015 Nov 9. PubMed PMID: 26552009; PubMed Central PMCID: PMC4886303. Bitler BG, Aird KM, Garipov A, Li H, Amatangelo M, Kossenkov AV, Schultz DC, Liu Q, Shih IeM, Conejo-Garcia JR, Speicher DW, Zhang R. Synthetic lethality by targeting EZH2 methyltransferase activity in ARID1A-mutated cancers. Nat Med. 2015 Mar;21(3):231-8. doi: 10.1038/nm.3799. Epub 2015 Feb 16. PubMed PMID: 25686104; PubMed Central PMCID: PMC4352133.
ARAF vad típus	Nelson DS, Quispel W, Badalian-Very G, van Halteren AG, van den Bos C, Bovée JV, Tian SY, Van Hummelen P, Ducar M, MacConaill LE, Egeler RM, Rollins BJ. Somatic activating ARAF mutations in Langerhans cell histiocytosis. Blood. 2014 May 15;123(20):3152-5. doi: 10.1182/blood-2013-06-511139. Epub 2014 Mar 20. PubMed PMID: 24652991.
KDM1A vad típus	Soldi R, Ghosh Halder T, Weston A, Thode T, Drenner K, Lewis R, Kaadige MR, Srivastava S, Daniel Ampanattu S, Rodriguez Del Villar R, Lang J, Vankayalapati H, Weissman B, Trent JM, Hendricks WPD, Sharma S. The novel reversible LSD1 inhibitor SP-2577 promotes anti-tumor immunity in SWItch/Sucrose-NonFermentable (SWI/SNF) complex mutated ovarian cancer. PLoS One. 2020;15(7):e0235705. doi: 10.1371/journal.pone.0235705. Epub 2020 Oct 10. PubMed PMID: 32649682; PubMed Central PMCID: PMC7351179.
YES1 vad típus	Miller RE, Brough R, Bajrami I, Williamson CT, McDade S, Campbell J, Kigozi A, Rafiq R, Pemberton H, Natrajan R, Joel J, Astley H, Mahoney C, Moore JD, Torrance C, Gordan JD, Webber JT, Levin RS, Shokat KM, Bandyopadhyay S, Lord CJ, Ashworth A. Synthetic Lethal Targeting of ARID1A-Mutant Ovarian Clear Cell Tumors with Dasatinib. Mol Cancer Ther. 2016 Jul;15(7):1472-84. doi: 10.1158/1535-7163.MCT-15-0554. Epub 2016 Jun 30. PubMed PMID: 27364904.
CD33 vad típus	Burd A, Levine RL, Ruppert AS, Mims AS, Borate U, Stein EM, Patel P, Baer MR, Stock W, Deininger M, Blum W, Schiller G, Olin R, Litzow M, Foran J, Lin TL, Ball B, Boyiadzis M, Traer E, Odenike O, Arellano M, Walker A, Duong VH, Kovacsovics T, Collins R, Shoben AB, Heerema NA, Foster MC, Vergilio JA, Brennan T, Vietz C, Severson E, Miller M, Rosenberg L, Marcus S, Yocum A, Chen T, Stefanos M, Druker B, Byrd JC. Precision medicine treatment in acute myeloid leukemia using prospective genomic profiling: feasibility and preliminary efficacy of the Beat AML Master Trial. Nat Med. 2020 Oct 26;:. doi: 10.1038/s41591-020-1089-8. Epub 2020 Nov 26. PubMed PMID: 33106665.
ERBB4 vad típus	Lau C, Killian KJ, Samuels Y, Rudloff U. ERBB4 mutation analysis: emerging molecular target for melanoma treatment. Methods Mol Biol. 2014;1102:461-80. doi: 10.1007/978-1-62703-727-3_24. PubMed PMID: 24258993; PubMed Central PMCID: PMC5125540. Britten CD. Targeting ErbB receptor signaling: a pan-ErbB approach to cancer. Mol Cancer Ther. 2004 Oct;3(10): 1335-42. Review. PubMed PMID: 15486201.
BRD4 vad típus	Chen C, Liu Y, Rappaport AR, Kitzing T, Schultz N, Zhao Z, Shroff AS, Dickins RA, Vakoc CR, Bradner JE, Stock W, LeBeau MM, Shannon KM, Kogan S, Zuber J, Lowe SW. MLL3 is a haploinsufficient 7q tumor suppressor in acute myeloid leukemia. Cancer Cell. 2014 May 12;25(5):652-65. doi: 10.1016/j.ccr.2014.03.016. PubMed PMID: 24794707; PubMed Central PMCID: PMC4206212.
DOT1L vad típus	Rau RE, Rodriguez BA, Luo M, Jeong M, Rosen A, Rogers JH, Campbell CT, Daigle SR, Deng L, Song Y, Sweet S, Chevassut T, Andreeff M, Kornblau SM, Li W, Goodell MA. DOT1L as a therapeutic target for the treatment of DNMT3A-mutant acute myeloid leukemia. Blood. 2016 Aug 18;128(7):971-81. doi: 10.1182/blood-2015-11-684225. Epub 2016 Jun 22. PubMed PMID: 27335278; PubMed Central PMCID: PMC4990856.
LYN vad típus	Roger Belizaire, Sebastian H.J. Koochaki, Namrata D. Udeshi, Alexis Vedder, Lei Sun, Tanya Svinkina, Christina Hartigan, Caroline Stanclift, Monica Schenone, Steven A. Carr, Eric Padron, Benjamin L. Ebert. CBL mutations promote activation of PI3K/AKT signaling via LYN kinase. doi: https://doi.org/10.1101/2020.04.13.038448
PRKACA vad típus	http://www.fasebj.org/content/31/1_Supplement/lb527.short
CHEK1 vad típus	Paculová H, Kramara J, Šimečková Š, Fedr R, Souček K, Hylse O, Paruch K, Svoboda M, Mistrík M, Kohoutek J. BRCA1 or CDK12 loss sensitizes cells to CHK1 inhibitors. Tumour Biol. 2017 Oct;39(10):1010428317727479. doi: 10.1177/1010428317727479. PubMed PMID: 29025359.
COX2 vad típus	

Einsiedlerstrasse 23, 8834 Schindellegi, SWITZERLAND
E-mail: info@realtimeoncology.com **Web:** www.realtimeoncology.com

TARGET GÉNEK	REFERENCIA
	Frey MR, Hilliard VC, Mullane MT, Polk DB. ErbB4 promotes cyclooxygenase-2 expression and cell survival in colon epithelial cells. Lab Invest. 2010 Oct;90(10):1415-24. doi: 10.1038/labinvest.2010.117. Epub 2010 Jun 28. PubMed PMID: 20585313; PubMed Central PMCID: PMC2947587.

DRIVER ÉS TARGET GÉNEK LEÍRÁSA

DRIVER GÉNEK

Név	Leírás
ABCC2	Mediates hepatobiliary excretion of numerous organic anions. May function as a cellular cisplatin transporter.
ALK	Neuronal orphan receptor tyrosine kinase that is essentially and transiently expressed in specific regions of the central and peripheral nervous systems and plays an important role in the genesis and differentiation of the nervous system. Transduces signals from ligands at the cell surface, through specific activation of the mitogen-activated protein kinase (MAPK) pathway. Phosphorylates almost exclusively at the first tyrosine of the Y-x-x-x-Y-Y motif. Following activation by ligand, ALK induces tyrosine phosphorylation of CBL, FRS2, IRS1 and SHC1, as well as of the MAP kinases MAPK1/ERK2 and MAPK3/ERK1. Acts as a receptor for ligands pleiotrophin (PTN), a secreted growth factor, and midkine (MDK), a PTN-related factor, thus participating in PTN and MDK signal transduction. PTN-binding induces MAPK pathway activation, which is important for the anti-apoptotic signaling of PTN and regulation of cell proliferation. MDK-binding induces phosphorylation of the ALK target insulin receptor substrate (IRS1), activates mitogen-activated protein kinases (MAPKs) and PI3-kinase, resulting also in cell proliferation induction. Drives NF-kappa-B activation, probably through IRS1 and the activation of the AKT serine/threonine kinase. Recruitment of IRS1 to activated ALK and the activation of NF-kappa-B are essential for the autocrine growth and survival signaling of MDK.
ARAF	Involved in the transduction of mitogenic signals from the cell membrane to the nucleus. May also regulate the TOR signaling cascade. Isoform 2: Serves as a positive regulator of myogenic differentiation by inducing cell cycle arrest, the expression of myogenin and other muscle-specific proteins, and myotube formation.
ARID1A	Involved in transcriptional activation and repression of select genes by chromatin remodeling (alteration of DNA-nucleosome topology). Binds DNA non-specifically. Belongs to the neural progenitors-specific chromatin remodeling complex (npBAF complex) and the neuron-specific chromatin remodeling complex (nBAF complex). During neural development a switch from a stem/progenitor to a post-mitotic chromatin remodeling mechanism occurs as neurons exit the cell cycle and become committed to their adult state. The transition from proliferating neural stem/progenitor cells to post-mitotic neurons requires a switch in subunit composition of the npBAF and nBAF complexes. As neural progenitors exit mitosis and differentiate into neurons, npBAF complexes which contain ACTL6A/BAF53A and PHF10/BAF45A, are exchanged for homologous alternative ACTL6B/BAF53B and DPF1 /BAF45B or DPF3/BAF45C subunits in neuron-specific complexes (nBAF). The npBAF complex is essential for the self-renewal/proliferative capacity of the multipotent neural stem cells. The nBAF complex along with CREST plays a role regulating the activity of genes essential for dendrite growth (By similarity).
ARID2	Involved in transcriptional activation and repression of select genes by chromatin remodeling (alteration of DNA-nucleosome topology). Required for the stability of the SWI/SNF chromatin remodeling complex SWI/SNF-B (PBAF). May be involved in targeting the complex to different genes. May be involved in regulating transcriptional activation of cardiac genes.
ATM	Serine/threonine protein kinase which activates checkpoint signaling upon double strand breaks (DSBs), apoptosis and genotoxic stresses such as ionizing ultraviolet A light (UVA), thereby acting as a DNA damage sensor. Recognizes the substrate consensus sequence [ST]-Q. Phosphorylates Ser-139 of histone variant H2AX/H2AFX at double strand breaks (DSBs), thereby regulating DNA damage response mechanism. Also plays a role in pre-B cell allelic exclusion, a process leading to expression of a single immunoglobulin heavy chain allele to enforce clonality and monospecific recognition by the B-cell antigen receptor (BCR) expressed on individual B-lymphocytes. After the introduction of DNA breaks by the RAG complex on one immunoglobulin allele, acts by mediating a repositioning of the second allele to pericentromeric heterochromatin, preventing accessibility to the RAG complex and recombination of the second allele. Also involved in signal transduction and cell cycle control. May function as a tumor suppressor. Necessary for activation of ABL1 and SAPK. Phosphorylates DYRK2, CHEK2, p53/TP53, FANCD2, NFKBIA, BRCA1, CTIP, nibrin (NBN), TERF1, RAD9 and DCLRE1C. May play a role in vesicle and/or protein transport. Could play a role in T-cell development, gonad and neurological function. Plays a role in replication-dependent histone mRNA degradation. Binds DNA ends. Phosphorylation of DYRK2 in nucleus in response to genotoxic stress prevents its MDM2-mediated ubiquitination and subsequent proteasome degradation. Phosphorylates ATF2 which stimulates its function in DNA damage response.
ATP4A	Catalyzes the hydrolysis of ATP coupled with the exchange of H+ and K+ ions across the plasma membrane. Responsible for acid production in the stomach.
BAZ2B	May play a role in transcriptional regulation interacting with ISWI.
BCORL1	Transcriptional corepressor. May specifically inhibit gene expression when recruited to promoter regions by sequence-specific DNA-binding proteins such as BCL6. This repression may be mediated at least in part by histone deacetylase activities which can associate with this corepressor.
CARD11	Involved in the costimulatory signal essential for T-cell receptor (TCR)-mediated T-cell activation. Its binding to DPP4 induces T-cell proliferation and NF-kappa-B activation in a T-cell receptor/CD3-dependent manner. Activates NF-kappa-B via BCL10 and IKK. Stimulates the phosphorylation of BCL10
CBL	Adapter protein that functions as a negative regulator of many signaling pathways that are triggered by activation of cell surface receptors. Acts as an E3 ubiquitin-protein ligase, which accepts ubiquitin from specific E2 ubiquitin-conjugating enzymes, and then transfers it to substrates promoting their degradation by the proteasome. Recognizes activated receptor tyrosine kinases, including KIT, FLT1, FGFR1, FGFR2, PDGFRA, PDGFRB, EGFR, CSF1R, EPHA8 and KDR and terminates signaling. Recognizes membrane-bound HCK, SRC and other kinases of the SRC family and mediates their ubiquitination and degradation. Participates in signal transduction in hematopoietic cells. Plays an important role in the regulation of osteoblast differentiation and apoptosis. Essential for osteoclastic bone resorption. The Tyr-731 phosphorylated form induces the activation and recruitment of

Einsiedlerstrasse 23, 8834 Schindellegi, SWITZERLAND
E-mail: info@realtimeoncology.com **Web:** www.realtimeoncology.com

DRIVER ÉS TARGET GÉNEK LEÍRÁSA

DRIVER GÉNEK

Név	Leírás
	phosphatidylinositol 3-kinase to the cell membrane in a signaling pathway that is critical for osteoclast function. May be functionally coupled with the E2 ubiquitin-protein ligase UB2D3.
CCNE1	Essential for the control of the cell cycle at the G1/S (start) transition.
CDH1	Cadherins are calcium-dependent cell adhesion proteins. They preferentially interact with themselves in a homophilic manner in connecting cells; cadherins may thus contribute to the sorting of heterogeneous cell types. CDH1 is involved in mechanisms regulating cell-cell adhesions, mobility and proliferation of epithelial cells. Has a potent invasive suppressor role. It is a ligand for integrin alpha-E/beta-7. E-Cad/CTF2 promotes non-amyloidogenic degradation of Abeta precursors. Has a strong inhibitory effect on APP C99 and C83 production.
CDK12	Cyclin-dependent kinase that phosphorylates the C-terminal domain (CTD) of the large subunit of RNA polymerase II (POLR2A), thereby acting as a key regulator of transcription elongation. Regulates the expression of genes involved in DNA repair and is required for the maintenance of genomic stability. Preferentially phosphorylates Ser-5 in CTD repeats that are already phosphorylated at Ser-7, but can also phosphorylate Ser-2. Required for RNA splicing, possibly by phosphorylating SRSF1/SF2. Involved in regulation of MAP kinase activity, possibly leading to affect the response to estrogen inhibitors.
CIC	Transcriptional repressor which may play a role in development of the central nervous system (CNS)
CSMD3	Involved in dendrite development.
CTCF	Chromatin binding factor that binds to DNA sequence specific sites. Involved in transcriptional regulation by binding to chromatin insulators and preventing interaction between promoter and nearby enhancers and silencers. Acts as transcriptional repressor binding to promoters of vertebrate MYC gene and BAG1 gene. Also binds to the PLK and PIM1 promoters. Acts as a transcriptional activator of APP. Regulates APOA1/C3/A4/A5 gene cluster and controls MHC class II gene expression. Plays an essential role in oocyte and preimplantation embryo development by activating or repressing transcription. Seems to act as tumor suppressor. Plays a critical role in the epigenetic regulation. Participates in the allele-specific gene expression at the imprinted IGF2/H19 gene locus. On the maternal allele, binding within the H19 imprinting control region (ICR) mediates maternally inherited higher-order chromatin conformation to restrict enhancer access to IGF2. Plays a critical role in gene silencing over considerable distances in the genome. Preferentially interacts with unmethylated DNA, preventing spreading of CpG methylation and maintaining methylation-free zones. Inversely, binding to target sites is prevented by CpG methylation. Plays a important role in chromatin remodeling. Can dimerize when it is bound to different DNA sequences, mediating long-range chromatin looping. Mediates interchromosomal association between IGF2/H19 and WSB1/NF1 and may direct distant DNA segments to a common transcription factory. Causes local loss of histone acetylation and gain of histone methylation in the beta-globin locus, without affecting transcription. When bound to chromatin, it provides an anchor point for nucleosomes positioning. Seems to be essential for homologous X-chromosome pairing. May participate with Tsix in establishing a regulatable epigenetic switch for X chromosome inactivation. May play a role in preventing the propagation of stable methylation at the escape genes from X- inactivation. Involved in sister chromatid cohesion. Associates with both centromeres and chromosomal arms during metaphase and required for cohesin localization to CTCF sites. Regulates asynchronous replication of IGF2/H19.
CTNNB1	Key downstream component of the canonical Wnt signaling pathway. In the absence of Wnt, forms a complex with AXIN1, AXIN2, APC, CSNK1A1 and GSK3B that promotes phosphorylation on N-terminal Ser and Thr residues and ubiquitination of CTNNB1 via BTRC and its subsequent degradation by the proteasome. In the presence of Wnt ligand, CTNNB1 is not ubiquitinated and accumulates in the nucleus, where it acts as a coactivator for transcription factors of the TCF/LEF family, leading to activate Wnt responsive genes. Involved in the regulation of cell adhesion. Acts as a negative regulator of centrosome cohesion. Involved in the CDK2/PTPN6/CTNNB1/CEACAM1 pathway of insulin internalization. Blocks anoikis of malignant kidney and intestinal epithelial cells and promotes their anchorage-independent growth by down-regulating DAPK2. Disrupts PML function and PML-NB formation by inhibiting RANBP2-mediated sumoylation of PML (PubMed:17524503, PubMed:18077326, PubMed:18086858, PubMed:18957423, PubMed:21262353, PubMed:22647378, PubMed:22699938, PubMed:22155184). Promotes neurogenesis by maintaining sympathetic neuroblasts within the cell cycle (By similarity).
DDX11	DNA-dependent ATPase and ATP-dependent DNA helicase that participates in various functions in genomic stability, including DNA replication, DNA repair and heterochromatin organization as well as in ribosomal RNA synthesis (PubMed:10648783, PubMed:21854770, PubMed:23797032, PubMed:26089203, PubMed:26503245). Its double-stranded DNA helicase activity requires either a minimal 5'-single-stranded tail length of approximately 15 nt (flap substrates) or 10 nt length single-stranded gapped DNA substrates of a partial duplex DNA structure for helicase loading and translocation along DNA in a 5' to 3' direction (PubMed:18499658, PubMed:22102414). The helicase activity is capable of displacing duplex regions up to 100 bp, which can be extended up to 500 bp by the replication protein A (RPA) or the cohesion CTF18-replication factor C (Ctf18-RFC) complex activities (PubMed: 18499658). Shows also ATPase- and helicase activities on substrates that mimic key DNA intermediates of replication, repair and homologous recombination reactions, including forked duplex, anti-parallel G-quadruplex and three-stranded D-loop DNA molecules (PubMed:22102414, PubMed:26503245). Plays a role in DNA double-strand break (DSB) repair at the DNA replication fork during DNA replication recovery from DNA damage (PubMed: 23797032). Recruited with TIMELESS factor upon DNA-replication stress response at DNA replication fork to preserve replication fork progression, and hence ensure DNA replication fidelity (PubMed:26503245). Cooperates also with TIMELESS factor during DNA replication to regulate proper sister chromatid cohesion and mitotic chromosome segregation (PubMed:17105772, PubMed:18499658, PubMed:20124417, PubMed:23116066, PubMed: 23797032). Stimulates 5'-single-stranded DNA flap endonuclease activity of FEN1 in an ATP- and helicase-independent manner; and hence it may contribute in Okazaki fragment processing at DNA replication fork during lagging strand DNA synthesis (PubMed:18499658). Its ability to function at DNA replication fork is modulated by its binding to long non-coding RNA (lncRNA) cohesion regulator non-coding RNA DDX11-AS1/CONCR, which is able to increase both DDX11 ATPase activity and binding to DNA replicating regions (PubMed:27477908). Plays also a role in heterochromatin organization (PubMed:21854770). Involved in rRNA transcription activation through binding to active hypomethylated rDNA gene loci by recruiting UBTF and the RNA polymerase Pol I transcriptional machinery (PubMed:26089203). Plays a role in embryonic development and prevention of aneuploidy (By similarity). Involved in melanoma cell proliferation and survival (PubMed:23116066). Associates with chromatin at DNA replication fork regions (PubMed:27477908). Binds to single- and double-stranded DNAs (PubMed:9013641, PubMed:18499658, PubMed:22102414).

Einsiedlerstrasse 23, 8834 Schindellegi, SWITZERLAND
E-mail: info@realtimeoncology.com **Web:** www.realtimeoncology.com

DRIVER ÉS TARGET GÉNEK LEÍRÁSA

DRIVER GÉNEK

Név	Leírás
DMD	Anchors the extracellular matrix to the cytoskeleton via F-actin. Ligand for dystroglycan. Component of the dystrophin-associated glycoprotein complex which accumulates at the neuromuscular junction (NMJ) and at a variety of synapses in the peripheral and central nervous systems and has a structural function in stabilizing the sarcolemma. Also implicated in signaling events and synaptic transmission.
DNMT3A	Required for genome-wide de novo methylation and is essential for the establishment of DNA methylation patterns during development. DNA methylation is coordinated with methylation of histones. It modifies DNA in a non-processive manner and also methylates non-CpG sites. May preferentially methylate DNA linker between 2 nucleosomal cores and is inhibited by histone H1. Plays a role in paternal and maternal imprinting. Required for methylation of most imprinted loci in germ cells. Acts as a transcriptional corepressor for ZBTB18. Recruited to trimethylated Lys-36 of histone H3 (H3K36me3) sites. Can actively repress transcription through the recruitment of HDAC activity.
ELMO1	Involved in cytoskeletal rearrangements required for phagocytosis of apoptotic cells and cell motility. Acts in association with DOCK1 and CRK. Was initially proposed to be required in complex with DOCK1 to activate Rac Rho small GTPases. May enhance the guanine nucleotide exchange factor (GEF) activity of DOCK1.
EPHA3	Receptor tyrosine kinase which binds promiscuously membrane-bound ephrin family ligands residing on adjacent cells, leading to contact-dependent bidirectional signaling into neighboring cells. The signaling pathway downstream of the receptor is referred to as forward signaling while the signaling pathway downstream of the ephrin ligand is referred to as reverse signaling. Highly promiscuous for ephrin-A ligands it binds preferentially EFNA5. Upon activation by EFNA5 regulates cell-cell adhesion, cytoskeletal organization and cell migration. Plays a role in cardiac cells migration and differentiation and regulates the formation of the atrioventricular canal and septum during development probably through activation by EFNA1. Involved in the retinotectal mapping of neurons. May also control the segregation but not the guidance of motor and sensory axons during neuromuscular circuit development.
EPHA7	Receptor tyrosine kinase which binds promiscuously GPI-anchored ephrin-A family ligands residing on adjacent cells, leading to contact-dependent bidirectional signaling into neighboring cells. The signaling pathway downstream of the receptor is referred to as forward signaling while the signaling pathway downstream of the ephrin ligand is referred to as reverse signaling. Among GPI-anchored ephrin-A ligands, EFNA5 is a cognate /functional ligand for EPHA7 and their interaction regulates brain development modulating cell-cell adhesion and repulsion. Has a repellent activity on axons and is for instance involved in the guidance of corticothalamic axons and in the proper topographic mapping of retinal axons to the colliculus. May also regulate brain development through a caspase(CASP3)-dependent proapoptotic activity. Forward signaling may result in activation of components of the ERK signaling pathway including MAP2K1, MAP2K2, MAPK1 AND MAPK3 which are phosphorylated upon activation of EPHA7.
ERBB4	Tyrosine-protein kinase that plays an essential role as cell surface receptor for neuregulins and EGF family members and regulates development of the heart, the central nervous system and the mammary gland, gene transcription, cell proliferation, differentiation, migration and apoptosis. Required for normal cardiac muscle differentiation during embryonic development, and for postnatal cardiomyocyte proliferation. Required for normal development of the embryonic central nervous system, especially for normal neural crest cell migration and normal axon guidance. Required for mammary gland differentiation, induction of milk proteins and lactation. Acts as cell-surface receptor for the neuregulins NRG1, NRG2, NRG3 and NRG4 and the EGF family members BTC, EREG and HBEGF. Ligand binding triggers receptor dimerization and autophosphorylation at specific tyrosine residues that then serve as binding sites for scaffold proteins and effectors. Ligand specificity and signaling is modulated by alternative splicing, proteolytic processing, and by the formation of heterodimers with other ERBB family members, thereby creating multiple combinations of intracellular phosphotyrosines that trigger ligand- and context-specific cellular responses. Mediates phosphorylation of SHC1 and activation of the MAP kinases MAPK1/ERK2 and MAPK3 /ERK1. Isoform JM-A CYT-1 and isoform JM-B CYT-1 phosphorylate PIK3R1, leading to the activation of phosphatidylinositol 3-kinase and AKT1 and protect cells against apoptosis. Isoform JM-A CYT-1 and isoform JM-B CYT-1 mediate reorganization of the actin cytoskeleton and promote cell migration in response to NRG1. Isoform JM-A CYT-2 and isoform JM-B CYT-2 lack the phosphotyrosine that mediates interaction with PIK3R1, and hence do not phosphorylate PIK3R1, do not protect cells against apoptosis, and do not promote reorganization of the actin cytoskeleton and cell migration. Proteolytic processing of isoform JM-A CYT-1 and isoform JM-A CYT-2 gives rise to the corresponding soluble intracellular domains (4ICD) that translocate to the nucleus, promote nuclear import of STAT5A, activation of STAT5A, mammary epithelium differentiation, cell proliferation and activation of gene expression. The ERBB4 soluble intracellular domains (4ICD) colocalize with STAT5A at the CSN2 promoter to regulate transcription of milk proteins during lactation. The ERBB4 soluble intracellular domains can also translocate to mitochondria and promote apoptosis.
ESR1	Nuclear hormone receptor. The steroid hormones and their receptors are involved in the regulation of eukaryotic gene expression and affect cellular proliferation and differentiation in target tissues. Ligand-dependent nuclear transactivation involves either direct homodimer binding to a palindromic estrogen response element (ERE) sequence or association with other DNA-binding transcription factors, such as AP-1/c-Jun, c-Fos, ATF-2, Sp1 and Sp3, to mediate ERE-independent signaling. Ligand binding induces a conformational change allowing subsequent or combinatorial association with multiprotein coactivator complexes through LXXLL motifs of their respective components. Mutual transrepression occurs between the estrogen receptor (ER) and NF-kappa-B in a cell-type specific manner. Decreases NF-kappa-B DNA-binding activity and inhibits NF-kappa-B-mediated transcription from the IL6 promoter and displace RELA/p65 and associated coregulators from the promoter. Recruited to the NF-kappa-B response element of the CCL2 and IL8 promoters and can displace CREBBP. Present with NF-kappa-B components RELA/p65 and NFKB1/p50 on ERE sequences. Can also act synergistically with NF-kappa-B to activate transcription involving respective recruitment adjacent response elements; the function involves CREBBP. Can activate the transcriptional activity of TFF1. Also mediates membrane-initiated estrogen signaling involving various kinase cascades. Isoform 3 is involved in activation of NOS3 and endothelial nitric oxide production. Isoforms lacking one or several functional domains are thought to modulate transcriptional activity by competitive ligand or DNA binding and/or heterodimerization with the full length receptor. Essential for MTA1-mediated transcriptional regulation of BRCA1 and BCAS3. Isoform 3 can bind to ERE and inhibit isoform 1.
ESRP1	

Einsiedlerstrasse 23, 8834 Schindellegi, SWITZERLAND
E-mail: info@realtimeoncology.com **Web:** www.realtimeoncology.com

DRIVER ÉS TARGET GÉNEK LEÍRÁSA

DRIVER GÉNEK

Név	Leírás
	mRNA splicing factor that regulates the formation of epithelial cell-specific isoforms. Specifically regulates the expression of FGFR2-IIIb, an epithelial cell-specific isoform of FGFR2. Also regulates the splicing of CD44, CTNND1, ENAH, 3 transcripts that undergo changes in splicing during the epithelial-to-mesenchymal transition (EMT). Acts by directly binding specific sequences in mRNAs. Binds the GU-rich sequence motifs in the ISE/ISS-3, a cis-element regulatory region present in the mRNA of FGFR2.
FANCF	DNA repair protein that may operate in a postreplication repair or a cell cycle checkpoint function. May be implicated in interstrand DNA cross-link repair and in the maintenance of normal chromosome stability (By similarity).
FAT1	Plays an essential role for cellular polarization, directed cell migration and modulating cell-cell contact.
FAT3	May play a role in the interactions between neurites derived from specific subsets of neurons during development.
FBXW7	Substrate recognition component of an SCF (SKP1-CUL1-F-box protein) E3 ubiquitin-protein ligase complex which mediates the ubiquitination and subsequent proteasomal degradation of target proteins. Recognizes and binds phosphorylated sites/phosphodegrons within target proteins and thereafter bring them to the SCF complex for ubiquitination (PubMed:17434132). Identified substrates include cyclin-E (CCNE1 or CCNE2), JUN, MYC, NOTCH1 released notch intracellular domain (NICD), and probably PSEN1 (PubMed:11565034, PubMed:12354302, PubMed:11585921, PubMed:15103331, PubMed:14739463, PubMed:17558397, PubMed:17873522, PubMed:22608923). Acts as a negative regulator of JNK signaling by binding to phosphorylated JUN and promoting its ubiquitination and subsequent degradation (PubMed:14739463).
GATA2	Transcriptional activator which regulates endothelin-1 gene expression in endothelial cells. Binds to the consensus sequence 5-AGATAG-3
GLI1	Acts as a transcriptional activator (PubMed:19706761, PubMed:10806483, PubMed:19878745, PubMed:24311597, PubMed:24217340). Binds to the DNA consensus sequence 5'-GACCACCCA-3' (PubMed:2105456, PubMed:8378770, PubMed:24217340). May regulate the transcription of specific genes during normal development (PubMed:19706761). May play a role in craniofacial development and digital development, as well as development of the central nervous system and gastrointestinal tract. Mediates SHH signaling (PubMed:19706761). Plays a role in cell proliferation and differentiation via its role in SHH signaling (Probable). Isoform 2: Acts as a transcriptional activator, but activates a different set of genes than isoform 1. Activates expression of CD24, unlike isoform 1. Mediates SHH signaling. Promotes cancer cell migration.
GNAS	May inhibit the adenylyl cyclase-stimulating activity of guanine nucleotide-binding protein G(s) subunit alpha which is produced from the same locus in a different open reading frame. Guanine nucleotide-binding proteins (G proteins) are involved as modulators or transducers in various transmembrane signaling systems. The G(s) protein is involved in hormonal regulation of adenylate cyclase: it activates the cyclase in response to beta-adrenergic stimuli. XLas isoforms interact with the same set of receptors as Gnas isoforms (By similarity). Guanine nucleotide-binding proteins (G proteins) are involved as modulators or transducers in various transmembrane signaling systems. The G(s) protein is involved in hormonal regulation of adenylate cyclase: it activates the cyclase in response to beta-adrenergic stimuli. Stimulates the Ras signaling pathway via RAPGEF2.
IGSF10	Involved in the control of early migration of neurons expressing gonadotropin-releasing hormone (GNRH neurons) (By similarity). May be involved in the maintenance of osteochondroprogenitor cells pool (By similarity).
IL2RG	Common subunit for the receptors for a variety of interleukins.
JAK2	Non-receptor tyrosine kinase involved in various processes such as cell growth, development, differentiation or histone modifications. Mediates essential signaling events in both innate and adaptive immunity. In the cytoplasm, plays a pivotal role in signal transduction via its association with type I receptors such as growth hormone (GHR), prolactin (PRLR), leptin (LEPR), erythropoietin (EPOR), thrombopoietin (THPO); or type II receptors including IFN-alpha, IFN-beta, IFN-gamma and multiple interleukins. Following ligand-binding to cell surface receptors, phosphorylates specific tyrosine residues on the cytoplasmic tails of the receptor, creating docking sites for STATs proteins. Subsequently, phosphorylates the STATs proteins once they are recruited to the receptor. Phosphorylated STATs then form homodimer or heterodimers and translocate to the nucleus to activate gene transcription. For example, cell stimulation with erythropoietin (EPO) during erythropoiesis leads to JAK2 autophosphorylation, activation, and its association with erythropoietin receptor (EPOR) that becomes phosphorylated in its cytoplasmic domain. Then, STAT5 (STAT5A or STAT5B) is recruited, phosphorylated and activated by JAK2. Once activated, dimerized STAT5 translocates into the nucleus and promotes the transcription of several essential genes involved in the modulation of erythropoiesis. In addition, JAK2 mediates angiotensin-2-induced ARHGEF1 phosphorylation. Plays a role in cell cycle by phosphorylating CDKN1B. Cooperates with TEC through reciprocal phosphorylation to mediate cytokine-driven activation of FOS transcription. In the nucleus, plays a key role in chromatin by specifically mediating phosphorylation of Tyr-41 of histone H3 (H3Y41ph), a specific tag that promotes exclusion of CBX5 (HP1 alpha) from chromatin.
KDM5C	Histone demethylase that specifically demethylates Lys-4 of histone H3, thereby playing a central role in histone code. Does not demethylate histone H3 Lys-9, H3 Lys-27, H3 Lys-36, H3 Lys-79 or H4 Lys-20. Demethylates trimethylated and dimethylated but not monomethylated H3 Lys-4. Participates in transcriptional repression of neuronal genes by recruiting histone deacetylases and REST at neuron-restrictive silencer elements. Represses the CLOCK-ARNTL/BMAL1 heterodimer-mediated transcriptional activation of the core clock component PER2 (By similarity).
KMT2C	Histone methyltransferase. Methylates Lys-4 of histone H3. H3 Lys-4 methylation represents a specific tag for epigenetic transcriptional activation. Central component of the MLL2/3 complex, a coactivator complex of nuclear receptors, involved in transcriptional coactivation. KMT2C/MLL3 may be a catalytic subunit of this complex. May be involved in leukemogenesis and developmental disorder.
LAMA2	Binding to cells via a high affinity receptor, laminin is thought to mediate the attachment, migration and organization of cells into tissues during embryonic development by interacting with other extracellular matrix components.
MED12	Component of the Mediator complex, a coactivator involved in the regulated transcription of nearly all RNA polymerase II-dependent genes. Mediator functions as a bridge to convey information from gene-specific

Einsiedlerstrasse 23, 8834 Schindellegi, SWITZERLAND
E-mail: info@realtimeoncology.com **Web:** www.realtimeoncology.com

DRIVER ÉS TARGET GÉNEK LEÍRÁSA

DRIVER GÉNEK

Név	Leírás
	regulatory proteins to the basal RNA polymerase II transcription machinery. Mediator is recruited to promoters by direct interactions with regulatory proteins and serves as a scaffold for the assembly of a functional preinitiation complex with RNA polymerase II and the general transcription factors. This subunit may specifically regulate transcription of targets of the Wnt signaling pathway and SHH signaling pathway.
MED13	Component of the Mediator complex, a coactivator involved in the regulated transcription of nearly all RNA polymerase II-dependent genes. Mediator functions as a bridge to convey information from gene-specific regulatory proteins to the basal RNA polymerase II transcription machinery. Mediator is recruited to promoters by direct interactions with regulatory proteins and serves as a scaffold for the assembly of a functional preinitiation complex with RNA polymerase II and the general transcription factors.
MIER3	Transcriptional repressor.
MRE11	Component of the MRN complex, which plays a central role in double-strand break (DSB) repair, DNA recombination, maintenance of telomere integrity and meiosis. The complex possesses single-strand endonuclease activity and double-strand-specific 3-5 exonuclease activity, which are provided by MRE11A. RAD50 may be required to bind DNA ends and hold them in close proximity. This could facilitate searches for short or long regions of sequence homology in the recombining DNA templates, and may also stimulate the activity of DNA ligases and /or restrict the nuclease activity of MRE11A to prevent nucleolytic degradation past a given point. The complex may also be required for DNA damage signaling via activation of the ATM kinase. In telomeres the MRN complex may modulate t-loop formation
MST1R	Receptor tyrosine kinase that transduces signals from the extracellular matrix into the cytoplasm by binding to MST1 ligand. Regulates many physiological processes including cell survival, migration and differentiation. Ligand binding at the cell surface induces autophosphorylation of RON on its intracellular domain that provides docking sites for downstream signaling molecules. Following activation by ligand, interacts with the PI3-kinase subunit PIK3R1, PLCG1 or the adapter GAB1. Recruitment of these downstream effectors by RON leads to the activation of several signaling cascades including the RAS-ERK, PI3 kinase-AKT, or PLCgamma-PKC. RON signaling activates the wound healing response by promoting epithelial cell migration, proliferation as well as survival at the wound site. Plays also a role in the innate immune response by regulating the migration and phagocytic activity of macrophages. Alternatively, RON can also promote signals such as cell migration and proliferation in response to growth factors other than MST1 ligand.
OTOP1	Required for normal formation of otoconia in the inner ear. Inhibits P2Y purinoceptors. Modulates calcium homeostasis and influx of calcium in response to extracellular ATP (By similarity).
PAX5	May play an important role in B-cell differentiation as well as neural development and spermatogenesis. Involved in the regulation of the CD19 gene, a B-lymphoid-specific target gene
PIK3CA	Phosphoinositide-3-kinase (PI3K) that phosphorylates PtdIns (Phosphatidylinositol), PtdIns4P (Phosphatidylinositol 4-phosphate) and PtdIns(4,5)P2 (Phosphatidylinositol 4,5-bisphosphate) to generate phosphatidylinositol 3,4,5-trisphosphate (PIP3). PIP3 plays a key role by recruiting PH domain-containing proteins to the membrane, including AKT1 and PDPK1, activating signaling cascades involved in cell growth, survival, proliferation, motility and morphology. Participates in cellular signaling in response to various growth factors. Involved in the activation of AKT1 upon stimulation by receptor tyrosine kinases ligands such as EGF, insulin, IGF1, VEGFA and PDGF. Involved in signaling via insulin-receptor substrate (IRS) proteins. Essential in endothelial cell migration during vascular development through VEGFA signaling, possibly by regulating RhoA activity. Required for lymphatic vasculature development, possibly by binding to RAS and by activation by EGF and FGF2, but not by PDGF. Regulates invadopodia formation in breast cancer cells through the PDPK1-AKT1 pathway. Participates in cardiomyogenesis in embryonic stem cells through a AKT1 pathway. Participates in vasculogenesis in embryonic stem cells through PDK1 and protein kinase C pathway. Has also serine-protein kinase activity: phosphorylates PIK3R1 (p85alpha regulatory subunit), EIF4EBP1 and HRAS.
PIK3CB	Phosphoinositide-3-kinase (PI3K) that phosphorylates PtdIns (Phosphatidylinositol), PtdIns4P (Phosphatidylinositol 4-phosphate) and PtdIns(4,5)P2 (Phosphatidylinositol 4,5-bisphosphate) to generate phosphatidylinositol 3,4,5-trisphosphate (PIP3). PIP3 plays a key role by recruiting PH domain-containing proteins to the membrane, including AKT1 and PDPK1, activating signaling cascades involved in cell growth, survival, proliferation, motility and morphology. Involved in the activation of AKT1 upon stimulation by G-protein coupled receptors (GPCRs) ligands such as CXCL12, sphingosine 1-phosphate, and lysophosphatidic acid. May also act downstream receptor tyrosine kinases. Required in different signaling pathways for stable platelet adhesion and aggregation. Plays a role in platelet activation signaling triggered by GPCRs, alpha-IIb/beta-3 integrins (ITGA2B/ ITGB3) and ITAM (immunoreceptor tyrosine-based activation motif)-bearing receptors such as GP6. Regulates the strength of adhesion of ITGA2B/ ITGB3 activated receptors necessary for the cellular transmission of contractile forces. Required for platelet aggregation induced by F2 (thrombin) and thromboxane A2 (TXA2). Has a role in cell survival. May have a role in cell migration. Involved in the early stage of autophagosome formation. Modulates the intracellular level of PtdIns3P (Phosphatidylinositol 3-phosphate) and activates PIK3C3 kinase activity. May act as a scaffold, independently of its lipid kinase activity to positively regulate autophagy. May have a role in insulin signaling as scaffolding protein in which the lipid kinase activity is not required. May have a kinase-independent function in regulating cell proliferation and in clathrin-mediated endocytosis. Mediator of oncogenic signal in cell lines lacking PTEN. The lipid kinase activity is necessary for its role in oncogenic transformation. Required for the growth of ERBB2 and RAS driven tumors
PPP2R2A	The B regulatory subunit might modulate substrate selectivity and catalytic activity, and also might direct the localization of the catalytic enzyme to a particular subcellular compartment.
PREX2	Functions as a RAC1 guanine nucleotide exchange factor (GEF), activating Rac proteins by exchanging bound GDP for free GTP. Its activity is synergistically activated by phosphatidylinositol 3,4,5-trisphosphate and the beta gamma subunits of heterotrimeric G protein. Mediates the activation of RAC1 in a PI3K-dependent manner. May be an important mediator of Rac signaling, acting directly downstream of both G protein-coupled receptors and phosphoinositide 3-kinase.
PRF1	Plays a key role in secretory granule-dependent cell death, and in defense against virus-infected or neoplastic cells. Plays an important role in killing other cells that are recognized as non-self by the immune system, e.g. in

Einsiedlerstrasse 23, 8834 Schindellegi, SWITZERLAND
E-mail: info@realtimeoncology.com **Web:** www.realtimeoncology.com

DRIVER ÉS TARGET GÉNEK LEÍRÁSA

DRIVER GÉNEK

Név	Leírás
	transplant rejection or some forms of autoimmune disease. Can insert into the membrane of target cells in its calcium-bound form, oligomerize and form large pores. Promotes cytolysis and apoptosis of target cells by facilitating the uptake of cytotoxic granzymes.
PTEN	Tumor suppressor. Acts as a dual-specificity protein phosphatase, dephosphorylating tyrosine-, serine- and threonine-phosphorylated proteins. Also acts as a lipid phosphatase, removing the phosphate in the D3 position of the inositol ring from phosphatidylinositol 3,4,5-trisphosphate, phosphatidylinositol 3,4-diphosphate, phosphatidylinositol 3-phosphate and inositol 1,3,4,5-tetrakisphosphate with order of substrate preference in vitro PtdIns(3,4,5)P3 > PtdIns(3,4)P2 > PtdIns3P > Ins(1,3,4,5)P4. The lipid phosphatase activity is critical for its tumor suppressor function. Antagonizes the PI3K-AKT/PKB signaling pathway by dephosphorylating phosphoinositides and thereby modulating cell cycle progression and cell survival. The unphosphorylated form cooperates with AIP1 to suppress AKT1 activation. Dephosphorylates tyrosine-phosphorylated focal adhesion kinase and inhibits cell migration and integrin-mediated cell spreading and focal adhesion formation. Plays a role as a key modulator of the AKT-mTOR signaling pathway controlling the tempo of the process of newborn neurons integration during adult neurogenesis, including correct neuron positioning, dendritic development and synapse formation. May be a negative regulator of insulin signaling and glucose metabolism in adipose tissue. The nuclear monoubiquitinated form possesses greater apoptotic potential, whereas the cytoplasmic nonubiquitinated form induces less tumor suppressive ability. In motile cells, suppresses the formation of lateral pseudopods and thereby promotes cell polarization and directed movement Isoform alpha: Functional kinase, like isoform 1 it antagonizes the PI3K-AKT /PKB signaling pathway. Plays a role in mitochondrial energetic metabolism by promoting COX activity and ATP production, via collaboration with isoform 1 in increasing protein levels of PINK1
PTPN11	Acts downstream of various receptor and cytoplasmic protein tyrosine kinases to participate in the signal transduction from the cell surface to the nucleus. Dephosphorylates ROCK2 at Tyr-722 resulting in stimulatation of its RhoA binding activity.
RAD51D	Involved in the homologous recombination repair (HRR) pathway of double-stranded DNA breaks arising during DNA replication or induced by DNA-damaging agents. Bind to single-stranded DNA (ssDNA) and has DNA-dependent ATPase activity. Part of the Rad21 paralog protein complex BCDX2 which acts in the BRCA1-BRCA2-dependent HR pathway. Upon DNA damage, BCDX2 acts downstream of BRCA2 recruitment and upstream of RAD51 recruitment. BCDX2 binds predominantly to the intersection of the four duplex arms of the Holliday junction and to junction of replication forks. The BCDX2 complex was originally reported to bind single-stranded DNA, single-stranded gaps in duplex DNA and specifically to nicks in duplex DNA. Involved in telomere maintenance. The BCDX2 subcomplex XRCC2:RAD51D can stimulate Holliday junction resolution by BLM.
RPTOR	Involved in the control of the mammalian target of rapamycin complex 1 (mTORC1) activity which regulates cell growth and survival, and autophagy in response to nutrient and hormonal signals; functions as a scaffold for recruiting mTORC1 substrates. mTORC1 is activated in response to growth factors or amino acids. Growth factor-stimulated mTORC1 activation involves a AKT1-mediated phosphorylation of TSC1-TSC2, which leads to the activation of the RHEB GTPase that potently activates the protein kinase activity of mTORC1. Amino acid-signaling to mTORC1 requires its relocalization to the lysosomes mediated by the Ragulator complex and the Rag GTPases. Activated mTORC1 up-regulates protein synthesis by phosphorylating key regulators of mRNA translation and ribosome synthesis. mTORC1 phosphorylates EIF4EBP1 and releases it from inhibiting the elongation initiation factor 4E (eiF4E). mTORC1 phosphorylates and activates S6K1 at Thr-389, which then promotes protein synthesis by phosphorylating PDCD4 and targeting it for degradation. Involved in ciliogenesis.
SAMD9L	May be involved in endosome fusion. Mediates down-regulation of growth factor signaling via internalization of growth factor receptors.
SCN11A	This protein mediates the voltage-dependent sodium ion permeability of excitable membranes. Assuming opened or closed conformations in response to the voltage difference across the membrane, the protein forms a sodium-selective channel through which sodium ions may pass in accordance with their electrochemical gradient. It is a tetrodotoxin-resistant sodium channel isoform. Also involved, with the contribution of the receptor tyrosine kinase NTRK2, in rapid BDNF-evoked neuronal depolarization.
SEC16A	Defines endoplasmic reticulum exit sites (ERES) and is required for secretory cargo traffic from the endoplasmic reticulum to the Golgi apparatus. SAR1A-GTP-dependent assembly of SEC16A on the ER membrane forms an organized scaffold defining an ERES. Required for normal transitional endoplasmic reticulum (tER) organization.
SLC9A9	May act in electroneutral exchange of protons for Na+ across membranes. Involved in the effusion of Golgi luminal H+ in exchange for cytosolic cations. Involved in organelle ion homeostasis by contributing to the maintenance of the unique acidic pH values of the Golgi and post-Golgi compartments in the cell.
SLX4	Regulatory subunit that interacts with and increases the activity of different structure-specific endonucleases. Has several distinct roles in protecting genome stability by resolving diverse forms of deleterious DNA structures originating from replication and recombination intermediates and from DNA damage. Component of the SLX1-SLX4 structure-specific endonuclease that resolves DNA secondary structures generated during DNA repair and recombination. Has endonuclease activity towards branched DNA substrates, introducing single-strand cuts in duplex DNA close to junctions with ss-DNA. Has a preference for 5'-flap structures, and promotes symmetrical cleavage of static and migrating Holliday junctions (HJs). Resolves HJs by generating two pairs of ligatable, nicked duplex products. Interacts with the structure-specific ERCC4-ERCC1 endonuclease and promotes the cleavage of bubble structures. Interacts with the structure-specific MUS81-EME1 endonuclease and promotes the cleavage of 3'-flap and replication fork-like structures. SLX4 is required for recovery from alkylation-induced DNA damage and is involved in the resolution of DNA double-strand breaks.
SMAD2	Receptor-regulated SMAD (R-SMAD) that is an intracellular signal transducer and transcriptional modulator activated by TGF-beta (transforming growth factor) and activin type 1 receptor kinases. Binds the TRE element in the promoter region of many genes that are regulated by TGF-beta and, on formation of the SMAD2/SMAD4 complex, activates transcription. May act as a tumor suppressor in colorectal carcinoma. Positively regulates PDPK1 kinase activity by stimulating its dissociation from the 14-3-3 protein YWHAQ which acts as a negative regulator.
SMARCA4	Transcriptional coactivator cooperating with nuclear hormone receptors to potentiate transcriptional activation. Component of the CREST-BRG1 complex, a multiprotein complex that regulates promoter activation by

Einsiedlerstrasse 23, 8834 Schindellegi, SWITZERLAND
E-mail: info@realtimeoncology.com **Web:** www.realtimeoncology.com

DRIVER ÉS TARGET GÉNEK LEÍRÁSA

DRIVER GÉNEK

Név	Leírás
	orchestrating a calcium-dependent release of a repressor complex and a recruitment of an activator complex. In resting neurons, transcription of the c-FOS promoter is inhibited by BRG1-dependent recruitment of a phospho-RB1-HDAC repressor complex. Upon calcium influx, RB1 is dephosphorylated by calcineurin, which leads to release of the repressor complex. At the same time, there is increased recruitment of CREBBP to the promoter by a CREST-dependent mechanism, which leads to transcriptional activation. The CREST-BRG1 complex also binds to the NR2B promoter, and activity-dependent induction of NR2B expression involves a release of HDAC1 and recruitment of CREBBP. Belongs to the neural progenitors-specific chromatin remodeling complex (npBAF complex) and the neuron-specific chromatin remodeling complex (nBAF complex). During neural development a switch from a stem /progenitor to a post-mitotic chromatin remodeling mechanism occurs as neurons exit the cell cycle and become committed to their adult state. The transition from proliferating neural stem/progenitor cells to post-mitotic neurons requires a switch in subunit composition of the npBAF and nBAF complexes. As neural progenitors exit mitosis and differentiate into neurons, npBAF complexes which contain ACTL6A/BAF53A and PHF10/BAF45A, are exchanged for homologous alternative ACTL6B/BAF53B and DPF1/BAF45B or DPF3/BAF45C subunits in neuron-specific complexes (nBAF). The npBAF complex is essential for the self-renewal/proliferative capacity of the multipotent neural stem cells. The nBAF complex along with CREST plays a role regulating the activity of genes essential for dendrite growth. SMARCA4/BAF190A may promote neural stem cell self-renewal/proliferation by enhancing Notch-dependent proliferative signals, while concurrently making the neural stem cell insensitive to SHH-dependent differentiating cues (By similarity). Acts as a corepressor of ZEB1 to regulate E-cadherin transcription and is required for induction of epithelial-mesenchymal transition (EMT) by ZEB1.
SOX9	Plays an important role in the normal skeletal development. May regulate the expression of other genes involved in chondrogenesis by acting as a transcription factor for these genes
SYNE3	As a component of the LINC (LInker of Nucleoskeleton and Cytoskeleton) complex involved in the connection between the nuclear lamina and the cytoskeleton. The nucleocytoplasmic interactions established by the LINC complex play an important role in the transmission of mechanical forces across the nuclear envelope and in nuclear movement and positioning. Probable anchoring protein which tethers the nucleus to the cytoskeleton by binding PLEC which can associate with the intermediate filament system. Plays a role in the regulation of aortic epithelial cell morphology, and is required for flow-induced centrosome polarization and directional migration in aortic endothelial cells.
TAF1	Largest component and core scaffold of the TFIID basal transcription factor complex. Contains novel N- and C-terminal Ser/Thr kinase domains which can autophosphorylate or transphosphorylate other transcription factors. Phosphorylates TP53 on Thr-55 which leads to MDM2-mediated degradation of TP53. Phosphorylates GTF2A1 and GTF2F1 on Ser residues. Possesses DNA-binding activity. Essential for progression of the G1 phase of the cell cycle. Exhibits histone acetyltransferase activity towards histones H3 and H4.
TET2	Dioxygenase that catalyzes the conversion of the modified genomic base 5-methylcytosine (5mC) into 5-hydroxymethylcytosine (5hmC) and plays a key role in active DNA demethylation. Has a preference for 5-hydroxymethylcytosine in CpG motifs. Also mediates subsequent conversion of 5hmC into 5-formylcytosine (5fC), and conversion of 5fC to 5-carboxylcytosine (5caC). Conversion of 5mC into 5hmC, 5fC and 5caC probably constitutes the first step in cytosine demethylation. Methylation at the C5 position of cytosine bases is an epigenetic modification of the mammalian genome which plays an important role in transcriptional regulation. In addition to its role in DNA demethylation, also involved in the recruitment of the O-GlcNAc transferase OGT to CpG-rich transcription start sites of active genes, thereby promoting histone H2B GlcNAcylation by OGT.
TGFBR2	Transmembrane serine/threonine kinase forming with the TGF-beta type I serine/threonine kinase receptor, TGFBR1, the non-promiscuous receptor for the TGF-beta cytokines TGFB1, TGFB2 and TGFB3. Transduces the TGFB1, TGFB2 and TGFB3 signal from the cell surface to the cytoplasm and is thus regulating a plethora of physiological and pathological processes including cell cycle arrest in epithelial and hematopoietic cells, control of mesenchymal cell proliferation and differentiation, wound healing, extracellular matrix production, immunosuppression and carcinogenesis. The formation of the receptor complex composed of 2 TGFBR1 and 2 TGFBR2 molecules symmetrically bound to the cytokine dimer results in the phosphorylation and the activation of TGFRB1 by the constitutively active TGFBR2. Activated TGFBR1 phosphorylates SMAD2 which dissociates from the receptor and interacts with SMAD4. The SMAD2-SMAD4 complex is subsequently translocated to the nucleus where it modulates the transcription of the TGF-beta-regulated genes. This constitutes the canonical SMAD-dependent TGF-beta signaling cascade. Also involved in non-canonical, SMAD-independent TGF-beta signaling pathways.
TP53BP1	Double-strand break (DSB) repair protein involved in response to DNA damage, telomere dynamics and class-switch recombination (CSR) during antibody genesis (PubMed:12364621, PubMed:22553214, PubMed:23333306, PubMed:17190600, PubMed:21144835, PubMed:28241136). Plays a key role in the repair of double-strand DNA breaks (DSBs) in response to DNA damage by promoting non-homologous end joining (NHEJ)-mediated repair of DSBs and specifically counteracting the function of the homologous recombination (HR) repair protein BRCA1 (PubMed:22553214, PubMed:23727112, PubMed:23333306). In response to DSBs, phosphorylation by ATM promotes interaction with RIF1 and dissociation from NUDT16L1/TIRR, leading to recruitment to DSBs sites (PubMed:28241136). Recruited to DSBs sites by recognizing and binding histone H2A monoubiquitinated at 'Lys-15' (H2AK15Ub) and histone H4 dimethylated at 'Lys-20' (H4K20me2), two histone marks that are present at DSBs sites (PubMed:23760478, PubMed:28241136, PubMed:17190600). Required for immunoglobulin class-switch recombination (CSR) during antibody genesis, a process that involves the generation of DNA DSBs (PubMed:23345425). Participates to the repair and the orientation of the broken DNA ends during CSR (By similarity). In contrast, it is not required for classic NHEJ and V(D)J recombination (By similarity). Promotes NHEJ of dysfunctional telomeres via interaction with PAXIP1 (PubMed:23727112).
TRIO	Guanine nucleotide exchange factor (GEF) for RHOA and RAC1 GTPases (PubMed:8643598, PubMed:27418539). Involved in coordinating actin remodeling, which is necessary for cell migration and growth (PubMed:10341202). In developing hippocampal neurons, limits dendrite formation, without affecting the establishment of axon polarity. Once dendrites are formed, involved in the control of synaptic function by regulating the endocytosis of AMPA-selective glutamate receptors (AMPARs) at CA1 excitatory synapses (By similarity).
TSC2	In complex with TSC1, inhibits the nutrient-mediated or growth factor-stimulated phosphorylation of S6K1 and EIF4EBP1 by negatively regulating mTORC1 signaling. Acts as a GTPase-activating protein (GAP) for the small

Einsiedlerstrasse 23, 8834 Schindellegi, SWITZERLAND
E-mail: info@realtimeoncology.com **Web:** www.realtimeoncology.com

DRIVER ÉS TARGET GÉNEK LEÍRÁSA

DRIVER GÉNEK

Név	Leírás
	GTPase RHEB, a direct activator of the protein kinase activity of mTORC1. Implicated as a tumor suppressor. Involved in microtubule-mediated protein transport, but this seems to be due to unregulated mTOR signaling. Stimulates weakly the intrinsic GTPase activity of the Ras-related proteins RAP1A and RAB5 in vitro. Mutations in TSC2 lead to constitutive activation of RAP1A in tumors.
USP16	Specifically deubiquitinates 'Lys-120' of histone H2A (H2AK119Ub), a specific tag for epigenetic transcriptional repression, thereby acting as a coactivator. Deubiquitination of histone H2A is a prerequisite for subsequent phosphorylation at 'Ser-11' of histone H3 (H3S10ph), and is required for chromosome segregation when cells enter into mitosis. In resting B- and T-lymphocytes, phosphorylation by AURKB leads to enhance its activity, thereby maintaining transcription in resting lymphocytes. Regulates Hox gene expression via histone H2A deubiquitination. Prefers nucleosomal substrates. Does not deubiquitinate histone H2B.
WNK2	Serine/threonine kinase which plays an important role in the regulation of electrolyte homeostasis, cell signaling, survival, and proliferation. Acts as an activator and inhibitor of sodium-coupled chloride cotransporters and potassium-coupled chloride cotransporters respectively. Activates SLC12A2, SCNN1A, SCNN1B, SCNN1D and SGK1 and inhibits SLC12A5. Negatively regulates the EGF-induced activation of the ERK/MAPK-pathway and the downstream cell cycle progression. Affects MAPK3/MAPK1 activity by modulating the activity of MAP2K1 and this modulation depends on phosphorylation of MAP2K1 by PAK1. WNK2 acts by interfering with the activity of PAK1 by controlling the balance of the activity of upstream regulators of PAK1 activity, RHOA and RAC1, which display reciprocal activity.
ZMYM3	Plays a role in the regulation of cell morphology and cytoskeletal organization.
ZRSR2	Pre-mRNA-binding protein required for splicing of both U2- and U12-type introns. Selectively interacts with the 3-splice site of U2- and U12-type pre-mRNAs and promotes different steps in U2 and U12 intron splicing. Recruited to U12 pre-mRNAs in an ATP-dependent manner and is required for assembly of the prespliceosome, a precursor to other spliceosomal complexes. For U2-type introns, it is selectively and specifically required for the second step of splicing.

DRIVER ÉS TARGET GÉNEK LEÍRÁSA

TARGET GÉNEK

Név	Leírás
ABL1	Non-receptor tyrosine-protein kinase that plays a role in many key processes linked to cell growth and survival such as cytoskeleton remodeling in response to extracellular stimuli, cell motility and adhesion, receptor endocytosis, autophagy, DNA damage response and apoptosis. Coordinates actin remodeling through tyrosine phosphorylation of proteins controlling cytoskeleton dynamics like WASF3 (involved in branch formation); ANXA1 (involved in membrane anchoring); DBN1, DBNL, CTTN, RAPH1 and ENAH (involved in signaling); or MAPT and PXN (microtubule-binding proteins). Phosphorylation of WASF3 is critical for the stimulation of lamellipodia formation and cell migration. Involved in the regulation of cell adhesion and motility through phosphorylation of key regulators of these processes such as BCAR1, CRK, CRKL, DOK1, EFS or NEDD9. Phosphorylates multiple receptor tyrosine kinases and more particularly promotes endocytosis of EGFR, facilitates the formation of neuromuscular synapses through MUSK, inhibits PDGFRB-mediated chemotaxis and modulates the endocytosis of activated B-cell receptor complexes. Other substrates which are involved in endocytosis regulation are the caveolin (CAV1) and RIN1. Moreover, ABL1 regulates the CBL family of ubiquitin ligases that drive receptor down-regulation and actin remodeling. Phosphorylation of CBL leads to increased EGFR stability. Involved in late-stage autophagy by regulating positively the trafficking and function of lysosomal components. ABL1 targets to mitochondria in response to oxidative stress and thereby mediates mitochondrial dysfunction and cell death. ABL1 is also translocated in the nucleus where it has DNA-binding activity and is involved in DNA-damage response and apoptosis. Many substrates are known mediators of DNA repair: DDB1, DDB2, ERCC3, ERCC6, RAD9A, RAD51, RAD52 or WRN. Activates the proapoptotic pathway when the DNA damage is too severe to be repaired. Phosphorylates TP73, a primary regulator for this type of damage-induced apoptosis. Phosphorylates the caspase CASP9 on Tyr-153 and regulates its processing in the apoptotic response to DNA damage. Phosphorylates PSMA7 that leads to an inhibition of proteasomal activity and cell cycle transition blocks. ABL1 acts also as a regulator of multiple pathological signaling cascades during infection. Several known tyrosine-phosphorylated microbial proteins have been identified as ABL1 substrates. This is the case of A36R of Vaccinia virus, Tir (translocated intimin receptor) of pathogenic E.coli and possibly Citrobacter, CagA (cytotoxin-associated gene A) of H.pylori, or AnkA (ankyrin repeat-containing protein A) of A.phagocytophilum. Pathogens can highjack ABL1 kinase signaling to reorganize the host actin cytoskeleton for multiple purposes, like facilitating intracellular movement and host cell exit. Finally, functions as its own regulator through autocatalytic activity as well as through phosphorylation of its inhibitor, ABI1.
AKT1	AKT1 is one of 3 closely related serine/threonine-protein kinases (AKT1, AKT2 and AKT3) called the AKT kinase, and which regulate many processes including metabolism, proliferation, cell survival, growth and angiogenesis. This is mediated through serine and/or threonine phosphorylation of a range of downstream substrates. Over 100 substrate candidates have been reported so far, but for most of them, no isoform specificity has been reported. AKT is responsible of the regulation of glucose uptake by mediating insulin-induced translocation of the SLC2A4 /GLUT4 glucose transporter to the cell surface. Phosphorylation of PTPN1 at Ser-50 negatively modulates its phosphatase activity preventing dephosphorylation of the insulin receptor and the attenuation of insulin signaling. Phosphorylation of TBC1D4 triggers the binding of this effector to inhibitory 14-3-3 proteins, which is required for insulin-stimulated glucose transport. AKT regulates also the storage of glucose in the form of glycogen by phosphorylating GSK3A at Ser-21 and GSK3B at Ser-9, resulting in inhibition of its kinase activity. Phosphorylation of GSK3 isoforms by AKT is also thought to be one mechanism by which cell proliferation is driven. AKT regulates also cell survival via the phosphorylation of MAP3K5 (apoptosis signal-related kinase). Phosphorylation of Ser-83 decreases MAP3K5 kinase activity stimulated by oxidative stress and thereby prevents apoptosis. AKT mediates insulin-stimulated protein synthesis by phosphorylating TSC2 at Ser-939 and Thr-1462, thereby activating mTORC1 signaling and leading to both phosphorylation of 4E-BP1 and in activation of RPS6KB1. AKT is involved in the

Einsiedlerstrasse 23, 8834 Schindellegi, SWITZERLAND
E-mail: info@realtimeoncology.com **Web:** www.realtimeoncology.com

DRIVER ÉS TARGET GÉNEK LEÍRÁSA

TARGET GÉNEK

Név	Leírás
	phosphorylation of members of the FOXO factors (Forkhead family of transcription factors), leading to binding of 14-3-3 proteins and cytoplasmic localization. In particular, FOXO1 is phosphorylated at Thr-24, Ser-256 and Ser-319. FOXO3 and FOXO4 are phosphorylated on equivalent sites. AKT has an important role in the regulation of NF-kappa-B-dependent gene transcription and positively regulates the activity of CREB1 (cyclic AMP (cAMP)-response element binding protein). The phosphorylation of CREB1 induces the binding of accessory proteins that are necessary for the transcription of pro-survival genes such as BCL2 and MCL1. AKT phosphorylates Ser-454 on ATP citrate lyase (ACLY), thereby potentially regulating ACLY activity and fatty acid synthesis. Activates the 3B isoform of cyclic nucleotide phosphodiesterase (PDE3B) via phosphorylation of Ser-273, resulting in reduced cyclic AMP levels and inhibition of lipolysis. Phosphorylates PIKFYVE on Ser-318, which results in increased PI(3)P-5 activity. The Rho GTPase-activating protein DLC1 is another substrate and its phosphorylation is implicated in the regulation cell proliferation and cell growth. AKT plays a role as key modulator of the AKT-mTOR signaling pathway controlling the tempo of the process of newborn neurons integration during adult neurogenesis, including correct neuron positioning, dendritic development and synapse formation. Signals downstream of phosphatidylinositol 3-kinase (PI (3)K) to mediate the effects of various growth factors such as platelet-derived growth factor (PDGF), epidermal growth factor (EGF), insulin and insulin-like growth factor I (IGF-I). AKT mediates the antiapoptotic effects of IGF-I. Essential for the SPATA13-mediated regulation of cell migration and adhesion assembly and disassembly. May be involved in the regulation of the placental development. Phosphorylates STK4/MST1 at Thr-120 and Thr-387 leading to inhibition of its: kinase activity, nuclear translocation, autophosphorylation and ability to phosphorylate FOXO3. Phosphorylates STK3/MST2 at Thr-117 and Thr-384 leading to inhibition of its: cleavage, kinase activity, autophosphorylation at Thr-180, binding to RASSF1 and nuclear translocation. Phosphorylates SRPK2 and enhances its kinase activity towards SRSF2 and ACIN1 and promotes its nuclear translocation. Phosphorylates RAF1 at Ser-259 and negatively regulates its activity. Phosphorylat
AKT2	AKT2 is one of 3 closely related serine/threonine-protein kinases (AKT1, AKT2 and AKT3) called the AKT kinase, and which regulate many processes including metabolism, proliferation, cell survival, growth and angiogenesis. This is mediated through serine and/or threonine phosphorylation of a range of downstream substrates. Over 100 substrate candidates have been reported so far, but for most of them, no isoform specificity has been reported. AKT is responsible of the regulation of glucose uptake by mediating insulin-induced translocation of the SLC2A4 /GLUT4 glucose transporter to the cell surface. Phosphorylation of PTPN1 at Ser-50 negatively modulates its phosphatase activity preventing dephosphorylation of the insulin receptor and the attenuation of insulin signaling. Phosphorylation of TBC1D4 triggers the binding of this effector to inhibitory 14-3-3 proteins, which is required for insulin-stimulated glucose transport. AKT regulates also the storage of glucose in the form of glycogen by phosphorylating GSK3A at Ser-21 and GSK3B at Ser-9, resulting in inhibition of its kinase activity. Phosphorylation of GSK3 isoforms by AKT is also thought to be one mechanism by which cell proliferation is driven. AKT regulates also cell survival via the phosphorylation of MAP3K5 (apoptosis signal-related kinase). Phosphorylation of Ser-83 decreases MAP3K5 kinase activity stimulated by oxidative stress and thereby prevents apoptosis. AKT mediates insulin-stimulated protein synthesis by phosphorylating TSC2 at Ser-939 and Thr-1462, thereby activating mTORC1 signaling and leading to both phosphorylation of 4E-BP1 and in activation of RPS6KB1. AKT is involved in the phosphorylation of members of the FOXO factors (Forkhead family of transcription factors), leading to binding of 14-3-3 proteins and cytoplasmic localization. In particular, FOXO1 is phosphorylated at Thr-24, Ser-256 and Ser-319. FOXO3 and FOXO4 are phosphorylated on equivalent sites. AKT has an important role in the regulation of NF-kappa-B-dependent gene transcription and positively regulates the activity of CREB1 (cyclic AMP (cAMP)-response element binding protein). The phosphorylation of CREB1 induces the binding of accessory proteins that are necessary for the transcription of pro-survival genes such as BCL2 and MCL1. AKT phosphorylates Ser-454 on ATP citrate lyase (ACLY), thereby potentially regulating ACLY activity and fatty acid synthesis. Activates the 3B isoform of cyclic nucleotide phosphodiesterase (PDE3B) via phosphorylation of Ser-273, resulting in reduced cyclic AMP levels and inhibition of lipolysis. Phosphorylates PIKFYVE on Ser-318, which results in increased PI(3)P-5 activity. The Rho GTPase-activating protein DLC1 is another substrate and its phosphorylation is implicated in the regulation cell proliferation and cell growth. AKT plays a role as key modulator of the AKT-mTOR signaling pathway controlling the tempo of the process of newborn neurons integration during adult neurogenesis, including correct neuron positioning, dendritic development and synapse formation. Signals downstream of phosphatidylinositol 3-kinase (PI (3)K) to mediate the effects of various growth factors such as platelet-derived growth factor (PDGF), epidermal growth factor (EGF), insulin and insulin-like growth factor I (IGF-I). AKT mediates the antiapoptotic effects of IGF-I. Essential for the SPATA13-mediated regulation of cell migration and adhesion assembly and disassembly. May be involved in the regulation of the placental development One of the few specific substrates of AKT2 identified recently is PITX2. Phosphorylation of PITX2 impairs its association with the CCND1 mRNA-stabilizing complex thus shortening the half-life of CCND1. AKT2 seems also to be the principal isoform responsible of the regulation of glucose uptake. Phosphorylates C2CD5 on Ser-197 during insulin-stimulated adipocytes. AKT2 is also specifically involved in skeletal muscle differentiation, one of its substrates in this process being ANKRD2. Down-regulation by RNA interference reduces the expression of the pho
AKT3	AKT3 is one of 3 closely related serine/threonine-protein kinases (AKT1, AKT2 and AKT3) called the AKT kinase, and which regulate many processes including metabolism, proliferation, cell survival, growth and angiogenesis. This is mediated through serine and/or threonine phosphorylation of a range of downstream substrates. Over 100 substrate candidates have been reported so far, but for most of them, no isoform specificity has been reported. AKT3 is the least studied AKT isoform. It plays an important role in brain development and is crucial for the viability of malignant glioma cells. AKT3 isoform may also be the key molecule in up-regulation and down-regulation of MMP13 via IL13. Required for the coordination of mitochondrial biogenesis with growth factor-induced increases in cellular energy demands. Down-regulation by RNA interference reduces the expression of the phosphorylated form of BAD, resulting in the induction of caspase-dependent apoptosis.
ALK	Neuronal orphan receptor tyrosine kinase that is essentially and transiently expressed in specific regions of the central and peripheral nervous systems and plays an important role in the genesis and differentiation of the nervous system. Transduces signals from ligands at the cell surface, through specific activation of the mitogen-activated protein kinase (MAPK) pathway. Phosphorylates almost exclusively at the first tyrosine of the Y-x-x-x-Y-Y motif. Following activation by ligand, ALK induces tyrosine phosphorylation of CBL, FRS2, IRS1 and SHC1, as well as of the MAP kinases MAPK1/ERK2 and MAPK3/ERK1. Acts as a receptor for ligands pleiotrophin (PTN), a secreted growth factor, and midkine (MDK), a PTN-related factor, thus participating in PTN and MDK signal transduction. PTN-binding induces MAPK pathway activation, which is important for the anti-apoptotic signaling of PTN and

Einsiedlerstrasse 23, 8834 Schindellegi, SWITZERLAND
E-mail: info@realtimeoncology.com **Web:** www.realtimeoncology.com

DRIVER ÉS TARGET GÉNEK LEÍRÁSA

TARGET GÉNEK

Név	Leírás
	regulation of cell proliferation. MDK-binding induces phosphorylation of the ALK target insulin receptor substrate (IRS1), activates mitogen-activated protein kinases (MAPKs) and PI3-kinase, resulting also in cell proliferation induction. Drives NF-kappa-B activation, probably through IRS1 and the activation of the AKT serine/threonine kinase. Recruitment of IRS1 to activated ALK and the activation of NF-kappa-B are essential for the autocrine growth and survival signaling of MDK.
ARAF	Involved in the transduction of mitogenic signals from the cell membrane to the nucleus. May also regulate the TOR signaling cascade. Isoform 2: Serves as a positive regulator of myogenic differentiation by inducing cell cycle arrest, the expression of myogenin and other muscle-specific proteins, and myotube formation.
ATM	Serine/threonine protein kinase which activates checkpoint signaling upon double strand breaks (DSBs), apoptosis and genotoxic stresses such as ionizing ultraviolet A light (UVA), thereby acting as a DNA damage sensor. Recognizes the substrate consensus sequence [ST]-Q. Phosphorylates Ser-139 of histone variant H2AX/H2AFX at double strand breaks (DSBs), thereby regulating DNA damage response mechanism. Also plays a role in pre-B cell allelic exclusion, a process leading to expression of a single immunoglobulin heavy chain allele to enforce clonality and monospecific recognition by the B-cell antigen receptor (BCR) expressed on individual B-lymphocytes. After the introduction of DNA breaks by the RAG complex on one immunoglobulin allele, acts by mediating a repositioning of the second allele to pericentromeric heterochromatin, preventing accessibility to the RAG complex and recombination of the second allele. Also involved in signal transduction and cell cycle control. May function as a tumor suppressor. Necessary for activation of ABL1 and SAPK. Phosphorylates DYRK2, CHEK2, p53/TP53, FANCD2, NFKBIA, BRCA1, CTIP, nibrin (NBN), TERF1, RAD9 and DCLRE1C. May play a role in vesicle and/or protein transport. Could play a role in T-cell development, gonad and neurological function. Plays a role in replication-dependent histone mRNA degradation. Binds DNA ends. Phosphorylation of DYRK2 in nucleus in response to genotoxic stress prevents its MDM2-mediated ubiquitination and subsequent proteasome degradation. Phosphorylates ATF2 which stimulates its function in DNA damage response.
ATR	Serine/threonine protein kinase which activates checkpoint signaling upon genotoxic stresses such as ionizing radiation (IR), ultraviolet light (UV), or DNA replication stalling, thereby acting as a DNA damage sensor. Recognizes the substrate consensus sequence [ST]-Q. Phosphorylates BRCA1, CHEK1, MCM2, RAD17, RPA2, SMC1 and p53 /TP53, which collectively inhibit DNA replication and mitosis and promote DNA repair, recombination and apoptosis. Phosphorylates Ser-139 of histone variant H2AX/H2AFX at sites of DNA damage, thereby regulating DNA damage response mechanism. Required for FANCD2 ubiquitination. Critical for maintenance of fragile site stability and efficient regulation of centrosome duplication.
AURKA	Mitotic serine/threonine kinases that contributes to the regulation of cell cycle progression. Associates with the centrosome and the spindle microtubules during mitosis and plays a critical role in various mitotic events including the establishment of mitotic spindle, centrosome duplication, centrosome separation as well as maturation, chromosomal alignment, spindle assembly checkpoint, and cytokinesis. Required for initial activation of CDK1 at centrosomes. Phosphorylates numerous target proteins, including ARHGEF2, BORA, BRCA1, CDC25B, DLGP5, HDAC6, KIF2A, LATS2, NDEL1, PARD3, PPP1R2, PLK1, RASSF1, TACC3, p53/TP53 and TPX2. Regulates KIF2A tubulin depolymerase activity. Required for normal axon formation. Plays a role in microtubule remodeling during neurite extension. Important for microtubule formation and/or stabilization. Also acts as a key regulatory component of the p53/TP53 pathway, and particularly the checkpoint-response pathways critical for oncogenic transformation of cells, by phosphorylating and stabilizing p53/TP53. Phosphorylates its own inhibitors, the protein phosphatase type 1 (PP1) isoforms, to inhibit their activity. Necessary for proper cilia disassembly prior to mitosis.
AURKB	Serine/threonine-protein kinase component of the chromosomal passenger complex (CPC), a complex that acts as a key regulator of mitosis. The CPC complex has essential functions at the centromere in ensuring correct chromosome alignment and segregation and is required for chromatin-induced microtubule stabilization and spindle assembly. Involved in the bipolar attachment of spindle microtubules to kinetochores and is a key regulator for the onset of cytokinesis during mitosis. Required for central/midzone spindle assembly and cleavage furrow formation. Key component of the cytokinesis checkpoint, a process required to delay abscission to prevent both premature resolution of intercellular chromosome bridges and accumulation of DNA damage: phosphorylates CHMP4C, leading to retain abscission-competent VPS4 (VPS4A and/or VPS4B) at the midbody ring until abscission checkpoint signaling is terminated at late cytokinesis (PubMed:22422861, PubMed:24814515). AURKB phosphorylates the CPC complex subunits BIRC5/survivin, CDCA8/borealin and INCENP. Phosphorylation of INCENP leads to increased AURKB activity. Other known AURKB substrates involved in centromeric functions and mitosis are CENPA, DES/desmin, GPAF, KIF2C, NSUN2, RACGAP1, SEPT1, VIM/vimentin, GSG2/Haspin, and histone H3. A positive feedback loop involving GSG2 and AURKB contributes to localization of CPC to centromeres. Phosphorylation of VIM controls vimentin filament segregation in cytokinetic process, whereas histone H3 is phosphorylated at Ser-10 and Ser-28 during mitosis (H3S10ph and H3S28ph, respectively). A positive feedback between GSG2 and AURKB contributes to CPC localization. AURKB is also required for kinetochore localization of BUB1 and SGOL1. Phosphorylation of p53/TP53 negatively regulates its transcriptional activity. Key regulator of active promoters in resting B- and T-lymphocytes: acts by mediating phosphorylation of H3S28ph at active promoters in resting B-cells, inhibiting RNF2/RING1B-mediated ubiquitination of histone H2A and enhancing binding and activity of the USP16 deubiquitinase at transcribed genes.
BCL2	Suppresses apoptosis in a variety of cell systems including factor-dependent lymphohematopoietic and neural cells. Regulates cell death by controlling the mitochondrial membrane permeability. Appears to function in a feedback loop system with caspases. Inhibits caspase activity either by preventing the release of cytochrome c from the mitochondria and/or by binding to the apoptosis-activating factor (APAF-1).
BRD4	Chromatin reader protein that recognizes and binds acetylated histones and plays a key role in transmission of epigenetic memory across cell divisions and transcription regulation. Remains associated with acetylated chromatin throughout the entire cell cycle and provides epigenetic memory for postmitotic G1 gene transcription by preserving acetylated chromatin status and maintaining high-order chromatin structure. During interphase, plays a key role in regulating the transcription of signal-inducible genes by associating with the P-TEFb complex and recruiting it to promoters: BRD4 is required to form the transcriptionally active P-TEFb complex by displacing negative regulators such as HEXIM1 and 7SKsnRNA complex from P-TEFb, thereby transforming it into an active form that can then phosphorylate the C-terminal domain (CTD) of RNA polymerase II. Promotes phosphorylation of Ser-2 of the C-terminal domain (CTD) of RNA polymerase II. According to a report, directly acts as an atypical

Einsiedlerstrasse 23, 8834 Schindellegi, SWITZERLAND
E-mail: info@realtimeoncology.com **Web:** www.realtimeoncology.com

DRIVER ÉS TARGET GÉNEK LEÍRÁSA

TARGET GÉNEK

Név	Leírás
	protein kinase and mediates phosphorylation of Ser-2 of the C-terminal domain (CTD) of RNA polymerase II; these data however need additional evidences in vivo (PubMed:22509028). In addition to acetylated histones, also recognizes and binds acetylated RELA, leading to further recruitment of the P-TEFb complex and subsequent activation of NF-kappa-B. Also acts as a regulator of p53/TP53-mediated transcription: following phosphorylation by CK2, recruited to p53/TP53 specific target promoters. Isoform B: Acts as a chromatin insulator in the DNA damage response pathway. Inhibits DNA damage response signaling by recruiting the condensin-2 complex to acetylated histones, leading to chromatin structure remodeling, insulating the region from DNA damage response by limiting spreading of histone H2AFX/H2A.x phosphorylation
CDK1	Plays a key role in the control of the eukaryotic cell cycle by modulating the centrosome cycle as well as mitotic onset; promotes G2-M transition, and regulates G1 progress and G1-S transition via association with multiple interphase cyclins. Required in higher cells for entry into S-phase and mitosis. Phosphorylates PARVA/actopaxin, APC, AMPH, APC, BARD1, Bcl-xL/BCL2L1, BRCA2, CALD1, CASP8, CDC7, CDC20, CDC25A, CDC25C, CC2D1A, CSNK2 proteins/CKII, FZR1/CDH1, CDK7, CEBPB, CHAMP1, DMD/dystrophin, EEF1 proteins/EF-1, EZH2, KIF11/EG5, EGFR, FANCG, FOS, GFAP, GOLGA2/GM130, GRASP1, UBE2A/hHR6A, HIST1H1 proteins/histone H1, HMGA1, HIVEP3/KRC, LMNA, LMNB, LMNC, LBR, LATS1, MAP1B, MAP4, MARCKS, MCM2, MCM4, MKLP1, MYB, NEFH, NFIC, NPC/nuclear pore complex, PITPNM1/NIR2, NPM1, NCL, NUCKS1, NPM1/numatrin, ORC1, PRKAR2A, EEF1E1/p18, EIF3F/p47, p53/TP53, NONO/p54NRB, PAPOLA, PLEC/plectin, RB1, UL40/R2, RAB4A, RAP1GAP, RCC1, RPS6KB1 /S6K1, KHDRBS1/SAM68, ESPL1, SKI, BIRC5/survivin, STIP1, TEX14, beta-tubulins, MAPT/TAU, NEDD1, VIM/vimentin, TK1, FOXO1, RUNX1/AML1, SIRT2 and RUNX2. CDK1/CDC2-cyclin-B controls pronuclear union in interphase fertilized eggs. Essential for early stages of embryonic development. During G2 and early mitosis, CDC25A/B/C-mediated dephosphorylation activates CDK1/cyclin complexes which phosphorylate several substrates that trigger at least centrosome separation, Golgi dynamics, nuclear envelope breakdown and chromosome condensation. Once chromosomes are condensed and aligned at the metaphase plate, CDK1 activity is switched off by WEE1- and PKMYT1-mediated phosphorylation to allow sister chromatid separation, chromosome decondensation, reformation of the nuclear envelope and cytokinesis. Inactivated by PKR/EIF2AK2- and WEE1-mediated phosphorylation upon DNA damage to stop cell cycle and genome replication at the G2 checkpoint thus facilitating DNA repair. Reactivated after successful DNA repair through WIP1-dependent signaling leading to CDC25A/B/C-mediated dephosphorylation and restoring cell cycle progression. In proliferating cells, CDK1-mediated FOXO1 phosphorylation at the G2-M phase represses FOXO1 interaction with 14-3-3 proteins and thereby promotes FOXO1 nuclear accumulation and transcription factor activity, leading to cell death of postmitotic neurons. The phosphorylation of beta-tubulins regulates microtubule dynamics during mitosis. NEDD1 phosphorylation promotes PLK1-mediated NEDD1 phosphorylation and subsequent targeting of the gamma-tubulin ring complex (gTuRC) to the centrosome, an important step for spindle formation. In addition, CC2D1A phosphorylation regulates CC2D1A spindle pole localization and association with SCC1/RAD21 and centriole cohesion during mitosis. The phosphorylation of Bcl-xL/BCL2L1 after prolongated G2 arrest upon DNA damage triggers apoptosis. In contrast, CASP8 phosphorylation during mitosis prevents its activation by proteolysis and subsequent apoptosis. This phosphorylation occurs in cancer cell lines, as well as in primary breast tissues and lymphocytes. EZH2 phosphorylation promotes H3K27me3 maintenance and epigenetic gene silencing. CALD1 phosphorylation promotes Schwann cell migration during peripheral nerve regeneration.
CDK2	Serine/threonine-protein kinase involved in the control of the cell cycle; essential for meiosis, but dispensable for mitosis. Phosphorylates CTNNB1, USP37, p53/TP53, NPM1, CDK7, RB1, BRCA2, MYC, NPAT, EZH2. Interacts with cyclins A, B1, B3, D, or E. Triggers duplication of centrosomes and DNA. Acts at the G1-S transition to promote the E2F transcriptional program and the initiation of DNA synthesis, and modulates G2 progression; controls the timing of entry into mitosis/meiosis by controlling the subsequent activation of cyclin B/CDK1 by phosphorylation, and coordinates the activation of cyclin B/CDK1 at the centrosome and in the nucleus. Crucial role in orchestrating a fine balance between cellular proliferation, cell death, and DNA repair in human embryonic stem cells (hESCs). Activity of CDK2 is maximal during S phase and G2; activated by interaction with cyclin E during the early stages of DNA synthesis to permit G1-S transition, and subsequently activated by cyclin A2 (cyclin A1 in germ cells) during the late stages of DNA replication to drive the transition from S phase to mitosis, the G2 phase. EZH2 phosphorylation promotes H3K27me3 maintenance and epigenetic gene silencing. Phosphorylates CABLES1 (By similarity). Cyclin E /CDK2 prevents oxidative stress-mediated Ras-induced senescence by phosphorylating MYC. Involved in G1-S phase DNA damage checkpoint that prevents cells with damaged DNA from initiating mitosis; regulates homologous recombination-dependent repair by phosphorylating BRCA2, this phosphorylation is low in S phase when recombination is active, but increases as cells progress towards mitosis. In response to DNA damage, double-strand break repair by homologous recombination a reduction of CDK2-mediated BRCA2 phosphorylation. Phosphorylation of RB1 disturbs its interaction with E2F1. NPM1 phosphorylation by cyclin E/CDK2 promotes its dissociates from unduplicated centrosomes, thus initiating centrosome duplication. Cyclin E/CDK2-mediated phosphorylation of NPAT at G1-S transition and until prophase stimulates the NPAT-mediated activation of histone gene transcription during S phase. Required for vitamin D-mediated growth inhibition by being itself inactivated. Involved in the nitric oxide- (NO) mediated signaling in a nitrosylation/activation-dependent manner. USP37 is activated by phosphorylation and thus triggers G1-S transition. CTNNB1 phosphorylation regulates insulin internalization. Phosphorylates FOXP3 and negatively regulates its transcriptional activity and protein stability (By similarity).
CDK4	Ser/Thr-kinase component of cyclin D-CDK4 (DC) complexes that phosphorylate and inhibit members of the retinoblastoma (RB) protein family including RB1 and regulate the cell-cycle during G(1)/S transition. Phosphorylation of RB1 allows dissociation of the transcription factor E2F from the RB/E2F complexes and the subsequent transcription of E2F target genes which are responsible for the progression through the G(1) phase. Hypophosphorylates RB1 in early G(1) phase. Cyclin D-CDK4 complexes are major integrators of various mitogenic and antimitogenic signals. Also phosphorylates SMAD3 in a cell-cycle-dependent manner and represses its transcriptional activity. Component of the ternary complex, cyclin D/CDK4/CDKN1B, required for nuclear translocation and activity of the cyclin D-CDK4 complex.
CDK6	Serine/threonine-protein kinase involved in the control of the cell cycle and differentiation; promotes G1/S transition. Phosphorylates pRB/RB1 and NPM1. Interacts with D-type G1 cyclins during interphase at G1 to form a pRB /RB1 kinase and controls the entrance into the cell cycle. Involved in initiation and maintenance of cell cycle exit during cell differentiation; prevents cell proliferation and regulates negatively cell differentiation, but is required for the proliferation of specific cell types (e.g. erythroid and hematopoietic cells). Essential for cell proliferation within

Einsiedlerstrasse 23, 8834 Schindellegi, SWITZERLAND
E-mail: info@realtimeoncology.com **Web:** www.realtimeoncology.com

DRIVER ÉS TARGET GÉNEK LEÍRÁSA

TARGET GÉNEK

Név	Leírás
	the dentate gyrus of the hippocampus and the subventricular zone of the lateral ventricles. Required during thymocyte development. Promotes the production of newborn neurons, probably by modulating G1 length. Promotes, at least in astrocytes, changes in patterns of gene expression, changes in the actin cytoskeleton including loss of stress fibers, and enhanced motility during cell differentiation. Prevents myeloid differentiation by interfering with RUNX1 and reducing its transcription transactivation activity, but promotes proliferation of normal myeloid progenitors. Delays senescence. Promotes the proliferation of beta-cells in pancreatic islets of Langerhans. May play a role in the centrosome organization during the cell cycle phases (PubMed:23918663).
CHEK1	Serine/threonine-protein kinase which is required for checkpoint-mediated cell cycle arrest and activation of DNA repair in response to the presence of DNA damage or unreplicated DNA. May also negatively regulate cell cycle progression during unperturbed cell cycles. This regulation is achieved by a number of mechanisms that together help to preserve the integrity of the genome. Recognizes the substrate consensus sequence [R-X-X-S/T]. Binds to and phosphorylates CDC25A, CDC25B and CDC25C. Phosphorylation of CDC25A at Ser-178 and Thr-507 and phosphorylation of CDC25C at Ser-216 creates binding sites for 14-3-3 proteins which inhibit CDC25A and CDC25C. Phosphorylation of CDC25A at Ser-76, Ser-124, Ser-178, Ser-279 and Ser-293 promotes proteolysis of CDC25A. Phosphorylation of CDC25A at Ser-76 primes the protein for subsequent phosphorylation at Ser-79, Ser-82 and Ser-88 by NEK11, which is required for polyubiquitination and degradation of CDCD25A. Inhibition of CDC25 leads to increased inhibitory tyrosine phosphorylation of CDK-cyclin complexes and blocks cell cycle progression. Also phosphorylates NEK6. Binds to and phosphorylates RAD51 at Thr-309, which promotes the release of RAD51 from BRCA2 and enhances the association of RAD51 with chromatin, thereby promoting DNA repair by homologous recombination. Phosphorylates multiple sites within the C-terminus of TP53, which promotes activation of TP53 by acetylation and promotes cell cycle arrest and suppression of cellular proliferation. Also promotes repair of DNA cross-links through phosphorylation of FANCE. Binds to and phosphorylates TLK1 at Ser-743, which prevents the TLK1-dependent phosphorylation of the chromatin assembly factor ASF1A. This may enhance chromatin assembly both in the presence or absence of DNA damage. May also play a role in replication fork maintenance through regulation of PCNA. May regulate the transcription of genes that regulate cell-cycle progression through the phosphorylation of histones. Phosphorylates histone H3.1 (to form H3T11ph), which leads to epigenetic inhibition of a subset of genes. May also phosphorylate RB1 to promote its interaction with the E2F family of transcription factors and subsequent cell cycle arrest Isoform 2: Endogenous repressor of isoform 1, interacts with, and antagonizes CHK1 to promote the S to G2/M phase transition
CTLA4	Inhibitory receptor acting as a major negative regulator of T-cell responses. The affinity of CTLA4 for its natural B7 family ligands, CD80 and CD86, is considerably stronger than the affinity of their cognate stimulatory coreceptor CD28.
CTNNB1	Key downstream component of the canonical Wnt signaling pathway. In the absence of Wnt, forms a complex with AXIN1, AXIN2, APC, CSNK1A1 and GSK3B that promotes phosphorylation on N-terminal Ser and Thr residues and ubiquitination of CTNNB1 via BTRC and its subsequent degradation by the proteasome. In the presence of Wnt ligand, CTNNB1 is not ubiquitinated and accumulates in the nucleus, where it acts as a coactivator for transcription factors of the TCF/LEF family, leading to activate Wnt responsive genes. Involved in the regulation of cell adhesion. Acts as a negative regulator of centrosome cohesion. Involved in the CDK2/PTPN6/CTNNB1/CEACAM1 pathway of insulin internalization. Blocks anoikis of malignant kidney and intestinal epithelial cells and promotes their anchorage-independent growth by down-regulating DAPK2. Disrupts PML function and PML-NB formation by inhibiting RANBP2-mediated sumoylation of PML (PubMed:17524503, PubMed:18077326, PubMed:18086858, PubMed:18957423, PubMed:21262353, PubMed:22647378, PubMed:22699938, PubMed:22155184). Promotes neurogenesis by maintaining sympathetic neuroblasts within the cell cycle (By similarity).
DOT1L	Histone methyltransferase. Methylates Lys-79 of histone H3. Nucleosomes are preferred as substrate compared to free histones. Binds to DNA
ERBB4	Tyrosine-protein kinase that plays an essential role as cell surface receptor for neuregulins and EGF family members and regulates development of the heart, the central nervous system and the mammary gland, gene transcription, cell proliferation, differentiation, migration and apoptosis. Required for normal cardiac muscle differentiation during embryonic development, and for postnatal cardiomyocyte proliferation. Required for normal development of the embryonic central nervous system, especially for normal neural crest cell migration and normal axon guidance. Required for mammary gland differentiation, induction of milk proteins and lactation. Acts as cell-surface receptor for the neuregulins NRG1, NRG2, NRG3 and NRG4 and the EGF family members BTC, EREG and HBEGF. Ligand binding triggers receptor dimerization and autophosphorylation at specific tyrosine residues that then serve as binding sites for scaffold proteins and effectors. Ligand specificity and signaling is modulated by alternative splicing, proteolytic processing, and by the formation of heterodimers with other ERBB family members, thereby creating multiple combinations of intracellular phosphotyrosines that trigger ligand- and context-specific cellular responses. Mediates phosphorylation of SHC1 and activation of the MAP kinases MAPK1/ERK2 and MAPK3 /ERK1. Isoform JM-A CYT-1 and isoform JM-B CYT-1 phosphorylate PIK3R1, leading to the activation of phosphatidylinositol 3-kinase and AKT1 and protect cells against apoptosis. Isoform JM-A CYT-1 and isoform JM-B CYT-1 mediate reorganization of the actin cytoskeleton and promote cell migration in response to NRG1. Isoform JM-A CYT-2 and isoform JM-B CYT-2 lack the phosphotyrosine that mediates interaction with PIK3R1, and hence do not phosphorylate PIK3R1, do not protect cells against apoptosis, and do not promote reorganization of the actin cytoskeleton and cell migration. Proteolytic processing of isoform JM-A CYT-1 and isoform JM-A CYT-2 gives rise to the corresponding soluble intracellular domains (4ICD) that translocate to the nucleus, promote nuclear import of STAT5A, activation of STAT5A, mammary epithelium differentiation, cell proliferation and activation of gene expression. The ERBB4 soluble intracellular domains (4ICD) colocalize with STAT5A at the CSN2 promoter to regulate transcription of milk proteins during lactation. The ERBB4 soluble intracellular domains can also translocate to mitochondria and promote apoptosis.
ESR1	Nuclear hormone receptor. The steroid hormones and their receptors are involved in the regulation of eukaryotic gene expression and affect cellular proliferation and differentiation in target tissues. Ligand-dependent nuclear transactivation involves either direct homodimer binding to a palindromic estrogen response element (ERE) sequence or association with other DNA-binding transcription factors, such as AP-1/c-Jun, c-Fos, ATF-2, Sp1 and Sp3, to mediate ERE-independent signaling. Ligand binding induces a conformational change allowing subsequent or combinatorial association with multiprotein coactivator complexes through LXXLL motifs of their respective components. Mutual transrepression occurs between the estrogen receptor (ER) and NF-kappa-B in a cell-type

Einsiedlerstrasse 23, 8834 Schindellegi, SWITZERLAND
E-mail: info@realtimeoncology.com **Web:** www.realtimeoncology.com

DRIVER ÉS TARGET GÉNEK LEÍRÁSA

TARGET GÉNEK

Név	Leírás
	specific manner. Decreases NF-kappa-B DNA-binding activity and inhibits NF-kappa-B-mediated transcription from the IL6 promoter and displace RELA/p65 and associated coregulators from the promoter. Recruited to the NF-kappa-B response element of the CCL2 and IL8 promoters and can displace CREBBP. Present with NF-kappa-B components RELA/p65 and NFKB1/p50 on ERE sequences. Can also act synergistically with NF-kappa-B to activate transcription involving respective recruitment adjacent response elements; the function involves CREBBP. Can activate the transcriptional activity of TFF1. Also mediates membrane-initiated estrogen signaling involving various kinase cascades. Isoform 3 is involved in activation of NOS3 and endothelial nitric oxide production. Isoforms lacking one or several functional domains are thought to modulate transcriptional activity by competitive ligand or DNA binding and/or heterodimerization with the full length receptor. Essential for MTA1-mediated transcriptional regulation of BRCA1 and BCAS3. Isoform 3 can bind to ERE and inhibit isoform 1.
EZH2	Polycomb group (PcG) protein. Catalytic subunit of the PRC2/EED-EZH2 complex, which methylates Lys-9 (H3K9me) and Lys-27 (H3K27me) of histone H3, leading to transcriptional repression of the affected target gene. Able to mono-, di- and trimethylate Lys-27 of histone H3 to form H3K27me1, H3K27me2 and H3K27me3, respectively. Compared to EZH2-containing complexes, it is more abundant in embryonic stem cells and plays a major role in forming H3K27me3, which is required for embryonic stem cell identity and proper differentiation. The PRC2/EED-EZH2 complex may also serve as a recruiting platform for DNA methyltransferases, thereby linking two epigenetic repression systems. Genes repressed by the PRC2/EED-EZH2 complex include HOXC8, HOXA9, MYT1, CDKN2A and retinoic acid target genes. EZH2 can also methylate non-histone proteins such as the transcription factor GATA4 and the nuclear receptor RORA. Regulates the circadian clock via histone methylation at the promoter of the circadian genes. Essential for the CRY1/2-mediated repression of the transcriptional activation of PER1/2 by the CLOCK-ARNTL/BMAL1 heterodimer; involved in the di and trimethylation of Lys-27 of histone H3 on PER1/2 promoters which is necessary for the CRY1/2 proteins to inhibit transcription.
FGFR1	Tyrosine-protein kinase that acts as cell-surface receptor for fibroblast growth factors and plays an essential role in the regulation of embryonic development, cell proliferation, differentiation and migration. Required for normal mesoderm patterning and correct axial organization during embryonic development, normal skeletogenesis and normal development of the gonadotropin-releasing hormone (GnRH) neuronal system. Phosphorylates PLCG1, FRS2, GAB1 and SHB. Ligand binding leads to the activation of several signaling cascades. Activation of PLCG1 leads to the production of the cellular signaling molecules diacylglycerol and inositol 1,4,5-trisphosphate. Phosphorylation of FRS2 triggers recruitment of GRB2, GAB1, PIK3R1 and SOS1, and mediates activation of RAS, MAPK1/ERK2, MAPK3/ERK1 and the MAP kinase signaling pathway, as well as of the AKT1 signaling pathway. Promotes phosphorylation of SHC1, STAT1 and PTPN11/SHP2. In the nucleus, enhances RPS6KA1 and CREB1 activity and contributes to the regulation of transcription. FGFR1 signaling is down-regulated by IL17RD/SEF, and by FGFR1 ubiquitination, internalization and degradation.
GBF1	This gene encodes a member of the Sec7 domain family. The encoded protein is a guanine nucleotide exchange factor that regulates the recruitment of proteins to membranes by mediating GDP to GTP exchange. The encoded protein is localized to the Golgi apparatus and plays a role in vesicular trafficking by activating ADP ribosylation factor 1. The encoded protein has also been identified as an important host factor for viral replication. Multiple transcript variants have been observed for this gene.
HMGCR	HMG-CoA reductase is the rate-limiting enzyme for cholesterol synthesis and is regulated via a negative feedback mechanism mediated by sterols and non-sterol metabolites derived from mevalonate, the product of the reaction catalyzed by reductase. Normally in mammalian cells this enzyme is suppressed by cholesterol derived from the internalization and degradation of low density lipoprotein (LDL) via the LDL receptor. Competitive inhibitors of the reductase induce the expression of LDL receptors in the liver, which in turn increases the catabolism of plasma LDL and lowers the plasma concentration of cholesterol, an important determinant of atherosclerosis. Alternatively spliced transcript variants encoding different isoforms have been found for this gene.
IDO1	This gene encodes indoleamine 2,3-dioxygenase (IDO) - a heme enzyme that catalyzes the first and rate-limiting step in tryptophan catabolism to N-formyl-kynurenine. This enzyme acts on multiple tryptophan substrates including D-tryptophan, L-tryptophan, 5-hydroxy-tryptophan, tryptamine, and serotonin. This enzyme is thought to play a role in a variety of pathophysiological processes such as antimicrobial and antitumor defense, neuropathology, immunoregulation, and antioxidant activity. Through its expression in dendritic cells, monocytes, and macrophages this enzyme modulates T-cell behavior by its peri-cellular catabolization of the essential amino acid tryptophan.
JAK1	Tyrosine kinase of the non-receptor type, involved in the IFN-alpha/beta/gamma signal pathway. Kinase partner for the interleukin (IL)-2 receptor.
JAK2	Non-receptor tyrosine kinase involved in various processes such as cell growth, development, differentiation or histone modifications. Mediates essential signaling events in both innate and adaptive immunity. In the cytoplasm, plays a pivotal role in signal transduction via its association with type I receptors such as growth hormone (GHR), prolactin (PRLR), leptin (LEPR), erythropoietin (EPOR), thrombopoietin (THPO); or type II receptors including IFN-alpha, IFN-beta, IFN-gamma and multiple interleukins. Following ligand-binding to cell surface receptors, phosphorylates specific tyrosine residues on the cytoplasmic tails of the receptor, creating docking sites for STATs proteins. Subsequently, phosphorylates the STATs proteins once they are recruited to the receptor. Phosphorylated STATs then form homodimer or heterodimers and translocate to the nucleus to activate gene transcription. For example, cell stimulation with erythropoietin (EPO) during erythropoiesis leads to JAK2 autophosphorylation, activation, and its association with erythropoietin receptor (EPOR) that becomes phosphorylated in its cytoplasmic domain. Then, STAT5 (STAT5A or STAT5B) is recruited, phosphorylated and activated by JAK2. Once activated, dimerized STAT5 translocates into the nucleus and promotes the transcription of several essential genes involved in the modulation of erythropoiesis. In addition, JAK2 mediates angiotensin-2-induced ARHGEF1 phosphorylation. Plays a role in cell cycle by phosphorylating CDKN1B. Cooperates with TEC through reciprocal phosphorylation to mediate cytokine-driven activation of FOS transcription. In the nucleus, plays a key role in chromatin by specifically mediating phosphorylation of Tyr-41 of histone H3 (H3Y41ph), a specific tag that promotes exclusion of CBX5 (HP1 alpha) from chromatin.
JAK3	Non-receptor tyrosine kinase involved in various processes such as cell growth, development, or differentiation. Mediates essential signaling events in both innate and adaptive immunity and plays a crucial role in hematopoiesis during T-cells development. In the cytoplasm, plays a pivotal role in signal transduction via its association with type I receptors sharing the common subunit gamma such as IL2R, IL4R, IL7R, IL9R, IL15R and IL21R. Following ligand

Einsiedlerstrasse 23, 8834 Schindellegi, SWITZERLAND
E-mail: info@realtimeoncology.com **Web:** www.realtimeoncology.com

DRIVER ÉS TARGET GÉNEK LEÍRÁSA

TARGET GÉNEK

Név	Leírás
	binding to cell surface receptors, phosphorylates specific tyrosine residues on the cytoplasmic tails of the receptor, creating docking sites for STATs proteins. Subsequently, phosphorylates the STATs proteins once they are recruited to the receptor. Phosphorylated STATs then form homodimer or heterodimers and translocate to the nucleus to activate gene transcription. For example, upon IL2R activation by IL2, JAK1 and JAK3 molecules bind to IL2R beta (IL2RB) and gamma chain (IL2RG) subunits inducing the tyrosine phosphorylation of both receptor subunits on their cytoplasmic domain. Then, STAT5A AND STAT5B are recruited, phosphorylated and activated by JAK1 and JAK3. Once activated, dimerized STAT5 translocates to the nucleus and promotes the transcription of specific target genes in a cytokine-specific fashion.
KDM1A	This gene encodes a nuclear protein containing a SWIRM domain, a FAD-binding motif, and an amine oxidase domain. This protein is a component of several histone deacetylase complexes, though it silences genes by functioning as a histone demethylase. Alternative splicing results in multiple transcript variants. [provided by RefSeq, Apr 2009]
LAG3	Lymphocyte-activation protein 3 belongs to Ig superfamily and contains 4 extracellular Ig-like domains. The LAG3 gene contains 8 exons. The sequence data, exon/intron organization, and chromosomal localization all indicate a close relationship of LAG3 to CD4.
LYN	Non-receptor tyrosine-protein kinase that transmits signals from cell surface receptors and plays an important role in the regulation of innate and adaptive immune responses, hematopoiesis, responses to growth factors and cytokines, integrin signaling, but also responses to DNA damage and genotoxic agents. Functions primarily as negative regulator, but can also function as activator, depending on the context. Required for the initiation of the B-cell response, but also for its down-regulation and termination. Plays an important role in the regulation of B-cell differentiation, proliferation, survival and apoptosis, and is important for immune self-tolerance. Acts downstream of several immune receptors, including the B-cell receptor, CD79A, CD79B, CD5, CD19, CD22, FCER1, FCGR2, FCGR1A, TLR2 and TLR4. Plays a role in the inflammatory response to bacterial lipopolysaccharide. Mediates the responses to cytokines and growth factors in hematopoietic progenitors, platelets, erythrocytes, and in mature myeloid cells, such as dendritic cells, neutrophils and eosinophils. Acts downstream of EPOR, KIT, MPL, the chemokine receptor CXCR4, as well as the receptors for IL3, IL5 and CSF2. Plays an important role in integrin signaling. Regulates cell proliferation, survival, differentiation, migration, adhesion, degranulation, and cytokine release. Down-regulates signaling pathways by phosphorylation of immunoreceptor tyrosine-based inhibitory motifs (ITIM), that then serve as binding sites for phosphatases, such as PTPN6/SHP-1, PTPN11/SHP-2 and INPP5D /SHIP-1, that modulate signaling by dephosphorylation of kinases and their substrates. Phosphorylates LIME1 in response to CD22 activation. Phosphorylates BTK, CBL, CD5, CD19, CD72, CD79A, CD79B, CSF2RB, DOK1, HCLS1, LILRB3/PIR-B, MS4A2/FCER1B, PTK2B/PYK2, SYK and TEC. Promotes phosphorylation of SIRPA, PTPN6/SHP-1, PTPN11/SHP-2 and INPP5D/SHIP-1. Mediates phosphorylation of the BCR-ABL fusion protein. Required for rapid phosphorylation of FER in response to FCER1 activation. Mediates KIT phosphorylation. Acts as an effector of EPOR (erythropoietin receptor) in controlling KIT expression and may play a role in erythroid differentiation during the switch between proliferation and maturation. Depending on the context, activates or inhibits several signaling cascades. Regulates phosphatidylinositol 3-kinase activity and AKT1 activation. Regulates activation of the MAP kinase signaling cascade, including activation of MAP2K1/MEK1, MAPK1/ERK2, MAPK3/ERK1, MAPK8/JNK1 and MAPK9/JNK2. Mediates activation of STAT5A and/or STAT5B. Phosphorylates LPXN on Tyr-72. Kinase activity facilitates TLR4-TLR6 heterodimerization and signal initiation.
MCL1	Involved in the regulation of apoptosis versus cell survival, and in the maintenance of viability but not of proliferation. Mediates its effects by interactions with a number of other regulators of apoptosis. Isoform 1 inhibits apoptosis. Isoform 2 promotes apoptosis.
MET	Receptor tyrosine kinase that transduces signals from the extracellular matrix into the cytoplasm by binding to hepatocyte growth factor/HGF ligand. Regulates many physiological processes including proliferation, scattering, morphogenesis and survival. Ligand binding at the cell surface induces autophosphorylation of MET on its intracellular domain that provides docking sites for downstream signaling molecules. Following activation by ligand, interacts with the PI3-kinase subunit PIK3R1, PLCG1, SRC, GRB2, STAT3 or the adapter GAB1. Recruitment of these downstream effectors by MET leads to the activation of several signaling cascades including the RAS-ERK, PI3 kinase-AKT, or PLCgamma-PKC. The RAS-ERK activation is associated with the morphogenetic effects while PI3K /AKT coordinates prosurvival effects. During embryonic development, MET signaling plays a role in gastrulation, development and migration of muscles and neuronal precursors, angiogenesis and kidney formation. In adults, participates in wound healing as well as organ regeneration and tissue remodeling. Promotes also differentiation and proliferation of hematopoietic cells Acts as a receptor for Listeria internalin inlB, mediating entry of the pathogen into cells
MTOR	Serine/threonine protein kinase which is a central regulator of cellular metabolism, growth and survival in response to hormones, growth factors, nutrients, energy and stress signals. MTOR directly or indirectly regulates the phosphorylation of at least 800 proteins. Functions as part of 2 structurally and functionally distinct signaling complexes mTORC1 and mTORC2 (mTOR complex 1 and 2). Activated mTORC1 up-regulates protein synthesis by phosphorylating key regulators of mRNA translation and ribosome synthesis. This includes phosphorylation of EIF4EBP1 and release of its inhibition toward the elongation initiation factor 4E (eiF4E). Moreover, phosphorylates and activates RPS6KB1 and RPS6KB2 that promote protein synthesis by modulating the activity of their downstream targets including ribosomal protein S6, eukaryotic translation initiation factor EIF4B, and the inhibitor of translation initiation PDCD4. Stimulates the pyrimidine biosynthesis pathway, both by acute regulation through RPS6KB1-mediated phosphorylation of the biosynthetic enzyme CAD, and delayed regulation, through transcriptional enhancement of the pentose phosphate pathway which produces 5-phosphoribosyl-1-pyrophosphate (PRPP), an allosteric activator of CAD at a later step in synthesis, this function is dependent on the mTORC1 complex. Regulates ribosome synthesis by activating RNA polymerase III-dependent transcription through phosphorylation and inhibition of MAF1 an RNA polymerase III-repressor. In parallel to protein synthesis, also regulates lipid synthesis through SREBF1/SREBP1 and LPIN1. To maintain energy homeostasis mTORC1 may also regulate mitochondrial biogenesis through regulation of PPARGC1A. mTORC1 also negatively regulates autophagy through phosphorylation of ULK1. Under nutrient sufficiency, phosphorylates ULK1 at Ser-758, disrupting the interaction with AMPK and preventing activation of ULK1. Also prevents autophagy through phosphorylation of the autophagy inhibitor DAP. mTORC1 exerts a feedback control on upstream growth factor signaling that includes phosphorylation and activation of GRB10 a INSR-dependent signaling suppressor. Among other potential targets

Einsiedlerstrasse 23, 8834 Schindellegi, SWITZERLAND
E-mail: info@realtimeoncology.com **Web:** www.realtimeoncology.com

DRIVER ÉS TARGET GÉNEK LEÍRÁSA

TARGET GÉNEK

Név	Leírás
	mTORC1 may phosphorylate CLIP1 and regulate microtubules. As part of the mTORC2 complex MTOR may regulate other cellular processes including survival and organization of the cytoskeleton. Plays a critical role in the phosphorylation at Ser-473 of AKT1, a pro-survival effector of phosphoinositide 3-kinase, facilitating its activation by PDK1. mTORC2 may regulate the actin cytoskeleton, through phosphorylation of PRKCA, PXN and activation of the Rho-type guanine nucleotide exchange factors RHOA and RAC1A or RAC1B. mTORC2 also regulates the phosphorylation of SGK1 at Ser-422.
NOTCH1	Functions as a receptor for membrane-bound ligands Jagged1, Jagged2 and Delta1 to regulate cell-fate determination. Upon ligand activation through the released notch intracellular domain (NICD) it forms a transcriptional activator complex with RBPJ/RBPSUH and activates genes of the enhancer of split locus. Affects the implementation of differentiation, proliferation and apoptotic programs. Involved in angiogenesis; negatively regulates endothelial cell proliferation and migration and angiogenic sprouting. Involved in the maturation of both CD4+ and CD8+ cells in the thymus. Important for follicular differentiation and possibly cell fate selection within the follicle. During cerebellar development, functions as a receptor for neuronal DNER and is involved in the differentiation of Bergmann glia. Represses neuronal and myogenic differentiation. May play an essential role in postimplantation development, probably in some aspect of cell specification and/or differentiation. May be involved in mesoderm development, somite formation and neurogenesis. May enhance HIF1A function by sequestering HIF1AN away from HIF1A. Required for the THBS4 function in regulating protective astrogenesis from the subventricular zone (SVZ) niche after injury. Involved in determination of left/right symmetry by modulating the balance between motile and immotile (sensory) cilia at the left-right organiser (LRO).
NPY5R	The protein encoded by this gene is a receptor for neuropeptide Y and peptide YY. The encoded protein appears to be involved in regulating food intake, with defects in this gene being associated with eating disorders. Also, the encoded protein is involved in a pathway that protects neuroblastoma cells from chemotherapy-induced cell death, providing a possible therapeutic target against neuroblastoma. Three transcript variants encoding the same protein have been found for this gene.
NTRK1	Receptor tyrosine kinase involved in the development and the maturation of the central and peripheral nervous systems through regulation of proliferation, differentiation and survival of sympathetic and nervous neurons. High affinity receptor for NGF which is its primary ligand, it can also bind and be activated by NTF3/neurotrophin-3. However, NTF3 only supports axonal extension through NTRK1 but has no effect on neuron survival. Upon dimeric NGF ligand-binding, undergoes homodimerization, autophosphorylation and activation. Recruits, phosphorylates and/or activates several downstream effectors including SHC1, FRS2, SH2B1, SH2B2 and PLCG1 that regulate distinct overlapping signaling cascades driving cell survival and differentiation. Through SHC1 and FRS2 activates a GRB2-Ras-MAPK cascade that regulates cell differentiation and survival. Through PLCG1 controls NF-Kappa-B activation and the transcription of genes involved in cell survival. Through SHC1 and SH2B1 controls a Ras-PI3 kinase-AKT1 signaling cascade that is also regulating survival. In absence of ligand and activation, may promote cell death, making the survival of neurons dependent on trophic factors Isoform TrkA-III is resistant to NGF, constitutively activates AKT1 and NF-kappa-B and is unable to activate the Ras-MAPK signaling cascade. Antagonizes the anti-proliferative NGF-NTRK1 signaling that promotes neuronal precursors differentiation. Isoform TrkA-III promotes angiogenesis and has oncogenic activity when overexpressed
PARP1	Involved in the base excision repair (BER) pathway, by catalyzing the poly(ADP-ribosyl)ation of a limited number of acceptor proteins involved in chromatin architecture and in DNA metabolism. This modification follows DNA damages and appears as an obligatory step in a detection/signaling pathway leading to the reparation of DNA strand breaks. Mediates the poly(ADP-ribosyl)ation of APLF and CHFR. Positively regulates the transcription of MTUS1 and negatively regulates the transcription of MTUS2/TIP150. With EEF1A1 and TXK, forms a complex that acts as a T-helper 1 (Th1) cell-specific transcription factor and binds the promoter of IFN-gamma to directly regulate its transcription, and is thus involved importantly in Th1 cytokine production. Required for PARP9 and DTX3L recruitment to DNA damage sites. PARP1-dependent PARP9-DTX3L-mediated ubiquitination promotes the rapid and specific recruitment of 53BP1/TP53BP1, UIMC1/RAP80, and BRCA1 to DNA damage sites.
PD-1	Inhibitory cell surface receptor involved in the regulation of T-cell function during immunity and tolerance. Upon ligand binding, inhibits T-cell effector functions in an antigen-specific manner. Possible cell death inducer, in association with other factors.
PD-L1	Involved in the costimulatory signal, essential for T-cell proliferation and production of IL10 and IFNG, in an IL2-dependent and a PDCD1-independent manner. Interaction with PDCD1 inhibits T-cell proliferation and cytokine production.
PDGFRA	Tyrosine-protein kinase that acts as a cell-surface receptor for PDGFA, PDGFB and PDGFC and plays an essential role in the regulation of embryonic development, cell proliferation, survival and chemotaxis. Depending on the context, promotes or inhibits cell proliferation and cell migration. Plays an important role in the differentiation of bone marrow-derived mesenchymal stem cells. Required for normal skeleton development and cephalic closure during embryonic development. Required for normal development of the mucosa lining the gastrointestinal tract, and for recruitment of mesenchymal cells and normal development of intestinal villi. Plays a role in cell migration and chemotaxis in wound healing. Plays a role in platelet activation, secretion of agonists from platelet granules, and in thrombin-induced platelet aggregation. Binding of its cognate ligands - homodimeric PDGFA, homodimeric PDGFB, heterodimers formed by PDGFA and PDGFB or homodimeric PDGFC -leads to the activation of several signaling cascades; the response depends on the nature of the bound ligand and is modulated by the formation of heterodimers between PDGFRA and PDGFRB. Phosphorylates PIK3R1, PLCG1, and PTPN11. Activation of PLCG1 leads to the production of the cellular signaling molecules diacylglycerol and inositol 1,4,5-trisphosphate, mobilization of cytosolic Ca(2+) and the activation of protein kinase C. Phosphorylates PIK3R1, the regulatory subunit of phosphatidylinositol 3-kinase, and thereby mediates activation of the AKT1 signaling pathway. Mediates activation of HRAS and of the MAP kinases MAPK1/ERK2 and/or MAPK3/ERK1. Promotes activation of STAT family members STAT1, STAT3 and STAT5A and/or STAT5B. Receptor signaling is down-regulated by protein phosphatases that dephosphorylate the receptor and its down-stream effectors, and by rapid internalization of the activated receptor.
PDGFRB	Tyrosine-protein kinase that acts as cell-surface receptor for homodimeric PDGFB and PDGFD and for heterodimers formed by PDGFA and PDGFB, and plays an essential role in the regulation of embryonic development, cell proliferation, survival, differentiation, chemotaxis and migration. Plays an essential role in blood

Einsiedlerstrasse 23, 8834 Schindellegi, SWITZERLAND
E-mail: info@realtimeoncology.com **Web:** www.realtimeoncology.com

DRIVER ÉS TARGET GÉNEK LEÍRÁSA

TARGET GÉNEK

Név	Leírás
	vessel development by promoting proliferation, migration and recruitment of pericytes and smooth muscle cells to endothelial cells. Plays a role in the migration of vascular smooth muscle cells and the formation of neointima at vascular injury sites. Required for normal development of the cardiovascular system. Required for normal recruitment of pericytes (mesangial cells) in the kidney glomerulus, and for normal formation of a branched network of capillaries in kidney glomeruli. Promotes rearrangement of the actin cytoskeleton and the formation of membrane ruffles. Binding of its cognate ligands - homodimeric PDGFB, heterodimers formed by PDGFA and PDGFB or homodimeric PDGFD -leads to the activation of several signaling cascades; the response depends on the nature of the bound ligand and is modulated by the formation of heterodimers between PDGFRA and PDGFRB. Phosphorylates PLCG1, PIK3R1, PTPN11, RASA1/GAP, CBL, SHC1 and NCK1. Activation of PLCG1 leads to the production of the cellular signaling molecules diacylglycerol and inositol 1,4,5-trisphosphate, mobilization of cytosolic Ca(2+) and the activation of protein kinase C. Phosphorylation of PIK3R1, the regulatory subunit of phosphatidylinositol 3-kinase, leads to the activation of the AKT1 signaling pathway. Phosphorylation of SHC1, or of the C-terminus of PTPN11, creates a binding site for GRB2, resulting in the activation of HRAS, RAF1 and down-stream MAP kinases, including MAPK1/ERK2 and/or MAPK3/ERK1. Promotes phosphorylation and activation of SRC family kinases. Promotes phosphorylation of PDCD6IP/ALIX and STAM. Receptor signaling is down-regulated by protein phosphatases that dephosphorylate the receptor and its down-stream effectors, and by rapid internalization of the activated receptor.
PIK3CA	Phosphoinositide-3-kinase (PI3K) that phosphorylates PtdIns (Phosphatidylinositol), PtdIns4P (Phosphatidylinositol 4-phosphate) and PtdIns(4,5)P2 (Phosphatidylinositol 4,5-bisphosphate) to generate phosphatidylinositol 3,4,5-trisphosphate (PIP3). PIP3 plays a key role by recruiting PH domain-containing proteins to the membrane, including AKT1 and PDPK1, activating signaling cascades involved in cell growth, survival, proliferation, motility and morphology. Participates in cellular signaling in response to various growth factors. Involved in the activation of AKT1 upon stimulation by receptor tyrosine kinases ligands such as EGF, insulin, IGF1, VEGFA and PDGF. Involved in signaling via insulin-receptor substrate (IRS) proteins. Essential in endothelial cell migration during vascular development through VEGFA signaling, possibly by regulating RhoA activity. Required for lymphatic vasculature development, possibly by binding to RAS and by activation by EGF and FGF2, but not by PDGF. Regulates invadopodia formation in breast cancer cells through the PDPK1-AKT1 pathway. Participates in cardiomyogenesis in embryonic stem cells through a AKT1 pathway. Participates in vasculogenesis in embryonic stem cells through PDK1 and protein kinase C pathway. Has also serine-protein kinase activity: phosphorylates PIK3R1 (p85alpha regulatory subunit), EIF4EBP1 and HRAS.
PIK3CB	Phosphoinositide-3-kinase (PI3K) that phosphorylates PtdIns (Phosphatidylinositol), PtdIns4P (Phosphatidylinositol 4-phosphate) and PtdIns(4,5)P2 (Phosphatidylinositol 4,5-bisphosphate) to generate phosphatidylinositol 3,4,5-trisphosphate (PIP3). PIP3 plays a key role by recruiting PH domain-containing proteins to the membrane, including AKT1 and PDPK1, activating signaling cascades involved in cell growth, survival, proliferation, motility and morphology. Involved in the activation of AKT1 upon stimulation by G-protein coupled receptors (GPCRs) ligands such as CXCL12, sphingosine 1-phosphate, and lysophosphatidic acid. May also act downstream receptor tyrosine kinases. Required in different signaling pathways for stable platelet adhesion and aggregation. Plays a role in platelet activation signaling triggered by GPCRs, alpha-IIb/beta-3 integrins (ITGA2B/ ITGB3) and ITAM (immunoreceptor tyrosine-based activation motif)-bearing receptors such as GP6. Regulates the strength of adhesion of ITGA2B/ ITGB3 activated receptors necessary for the cellular transmission of contractile forces. Required for platelet aggregation induced by F2 (thrombin) and thromboxane A2 (TXA2). Has a role in cell survival. May have a role in cell migration. Involved in the early stage of autophagosome formation. Modulates the intracellular level of PtdIns3P (Phosphatidylinositol 3-phosphate) and activates PIK3C3 kinase activity. May act as a scaffold, independently of its lipid kinase activity to positively regulate autophagy. May have a role in insulin signaling as scaffolding protein in which the lipid kinase activity is not required. May have a kinase-independent function in regulating cell proliferation and in clathrin-mediated endocytosis. Mediator of oncogenic signal in cell lines lacking PTEN. The lipid kinase activity is necessary for its role in oncogenic transformation. Required for the growth of ERBB2 and RAS driven tumors
PIK3CG	Phosphoinositide-3-kinase (PI3K) that phosphorylates PtdIns(4,5)P2 (Phosphatidylinositol 4,5-bisphosphate) to generate phosphatidylinositol 3,4,5-trisphosphate (PIP3). PIP3 plays a key role by recruiting PH domain-containing proteins to the membrane, including AKT1 and PDPK1, activating signaling cascades involved in cell growth, survival, proliferation, motility and morphology. Links G-protein coupled receptor activation to PIP3 production. Involved in immune, inflammatory and allergic responses. Modulates leukocyte chemotaxis to inflammatory sites and in response to chemoattractant agents. May control leukocyte polarization and migration by regulating the spatial accumulation of PIP3 and by regulating the organization of F-actin formation and integrin-based adhesion at the leading edge. Controls motility of dendritic cells. Together with PIK3CD is involved in natural killer (NK) cell development and migration towards the sites of inflammation. Participates in T-lymphocyte migration. Regulates T-lymphocyte proliferation and cytokine production. Together with PIK3CD participates in T-lymphocyte development. Required for B-lymphocyte development and signaling. Together with PIK3CD participates in neutrophil respiratory burst. Together with PIK3CD is involved in neutrophil chemotaxis and extravasation. Together with PIK3CB promotes platelet aggregation and thrombosis. Regulates alpha-IIb/beta-3 integrins (ITGA2B/ ITGB3) adhesive function in platelets downstream of P2Y12 through a lipid kinase activity-independent mechanism. May have also a lipid kinase activity-dependent function in platelet aggregation. Involved in endothelial progenitor cell migration. Negative regulator of cardiac contractility. Modulates cardiac contractility by anchoring protein kinase A (PKA) and PDE3B activation, reducing cAMP levels. Regulates cardiac contractility also by promoting beta-adrenergic receptor internalization by binding to ADRBK1 and by non-muscle tropomyosin phosphorylation. Also has serine/threonine protein kinase activity: both lipid and protein kinase activities are required for beta-adrenergic receptor endocytosis. May also have a scaffolding role in modulating cardiac contractility. Contributes to cardiac hypertrophy under pathological stress. Through simultaneous binding of PDE3B to RAPGEF3 and PIK3R6 is assembled in a signaling complex in which the PI3K gamma complex is activated by RAPGEF3 and which is involved in angiogenesis.
PRKACA	Phosphorylates a large number of substrates in the cytoplasm and the nucleus. Regulates the abundance of compartmentalized pools of its regulatory subunits through phosphorylation of PJA2 which binds and ubiquitinates these subunits, leading to their subsequent proteolysis. Phosphorylates CDC25B, ABL1, NFKB1, CLDN3, PSMC5 /RPT6, PJA2, RYR2, RORA and VASP. RORA is activated by phosphorylation. Required for glucose-mediated adipogenic differentiation increase and osteogenic differentiation inhibition from osteoblasts. Involved in the

Einsiedlerstrasse 23, 8834 Schindellegi, SWITZERLAND
E-mail: info@realtimeoncology.com **Web:** www.realtimeoncology.com

DRIVER ÉS TARGET GÉNEK LEÍRÁSA

TARGET GÉNEK

Név	Leírás
	regulation of platelets in response to thrombin and collagen; maintains circulating platelets in a resting state by phosphorylating proteins in numerous platelet inhibitory pathways when in complex with NF-kappa-B (NFKB1 and NFKB2) and I-kappa-B-alpha (NFKBIA), but thrombin and collagen disrupt these complexes and free active PRKACA stimulates platelets and leads to platelet aggregation by phosphorylating VASP. Prevents the antiproliferative and anti-invasive effects of alpha-difluoromethylornithine in breast cancer cells when activated. RYR2 channel activity is potentiated by phosphorylation in presence of luminal Ca2+, leading to reduced amplitude and increased frequency of store overload-induced Ca2+ release (SOICR) characterized by an increased rate of Ca2+ release and propagation velocity of spontaneous Ca2+ waves, despite reduced wave amplitude and resting cytosolic Ca2+. PSMC5/RPT6 activation by phosphorylation stimulates proteasome. Negatively regulates tight junctions (TJs) in ovarian cancer cells via CLDN3 phosphorylation. NFKB1 phosphorylation promotes NF-kappa-B p50-p50 DNA binding. Involved in embryonic development by down-regulating the Hedgehog (Hh) signaling pathway that determines embryo pattern formation and morphogenesis. Prevents meiosis resumption in prophase-arrested oocytes via CDC25B inactivation by phosphorylation. May also regulate rapid eye movement (REM) sleep in the pedunculopontine tegmental (PPT). Phosphorylates APOBEC3G and AICDA. Isoform 2 phosphorylates and activates ABL1 in sperm flagellum to promote spermatozoa capacitation. Phosphorylates HSF1; this phosphorylation promotes HSF1 nuclear localization and transcriptional activity upon heat shock (PubMed:21085490).
RET	Receptor tyrosine-protein kinase involved in numerous cellular mechanisms including cell proliferation, neuronal navigation, cell migration, and cell differentiation upon binding with glial cell derived neurotrophic factor family ligands. Phosphorylates PTK2/FAK1. Regulates both cell death/survival balance and positional information. Required for the molecular mechanisms orchestration during intestine organogenesis; involved in the development of enteric nervous system and renal organogenesis during embryonic life, and promotes the formation of Peyers patch-like structures, a major component of the gut-associated lymphoid tissue. Modulates cell adhesion via its cleavage by caspase in sympathetic neurons and mediates cell migration in an integrin (e.g. ITGB1 and ITGB3)-dependent manner. Involved in the development of the neural crest. Active in the absence of ligand, triggering apoptosis through a mechanism that requires receptor intracellular caspase cleavage. Acts as a dependence receptor; in the presence of the ligand GDNF in somatotrophs (within pituitary), promotes survival and down regulates growth hormone (GH) production, but triggers apoptosis in absence of GDNF. Regulates nociceptor survival and size. Triggers the differentiation of rapidly adapting (RA) mechanoreceptors. Mediator of several diseases such as neuroendocrine cancers; these diseases are characterized by aberrant integrins-regulated cell migration.
ROS1	Orphan receptor tyrosine kinase (RTK) that plays a role in epithelial cell differentiation and regionalization of the proximal epididymal epithelium. May activate several downstream signaling pathways related to cell differentiation, proliferation, growth and survival including the PI3 kinase-mTOR signaling pathway. Mediates the phosphorylation of PTPN11, an activator of this pathway. May also phosphorylate and activate the transcription factor STAT3 to control anchorage-independent cell growth. Mediates the phosphorylation and the activation of VAV3, a guanine nucleotide exchange factor regulating cell morphology. May activate other downstream signaling proteins including AKT1, MAPK1, MAPK3, IRS1 and PLCG2.
SRC	Non-receptor protein tyrosine kinase which is activated following engagement of many different classes of cellular receptors including immune response receptors, integrins and other adhesion receptors, receptor protein tyrosine kinases, G protein-coupled receptors as well as cytokine receptors. Participates in signaling pathways that control a diverse spectrum of biological activities including gene transcription, immune response, cell adhesion, cell cycle progression, apoptosis, migration, and transformation. Due to functional redundancy between members of the SRC kinase family, identification of the specific role of each SRC kinase is very difficult. SRC appears to be one of the primary kinases activated following engagement of receptors and plays a role in the activation of other protein tyrosine kinase (PTK) families. Receptor clustering or dimerization leads to recruitment of SRC to the receptor complexes where it phosphorylates the tyrosine residues within the receptor cytoplasmic domains. Plays an important role in the regulation of cytoskeletal organization through phosphorylation of specific substrates such as AFAP1. Phosphorylation of AFAP1 allows the SRC SH2 domain to bind AFAP1 and to localize to actin filaments. Cytoskeletal reorganization is also controlled through the phosphorylation of cortactin (CTTN). When cells adhere via focal adhesions to the extracellular matrix, signals are transmitted by integrins into the cell resulting in tyrosine phosphorylation of a number of focal adhesion proteins, including PTK2/FAK1 and paxillin (PXN). In addition to phosphorylating focal adhesion proteins, SRC is also active at the sites of cell-cell contact adherens junctions and phosphorylates substrates such as beta-catenin (CTNNB1), delta-catenin (CTNND1), and plakoglobin (JUP). Another type of cell-cell junction, the gap junction, is also a target for SRC, which phosphorylates connexin-43 (GJA1). SRC is implicated in regulation of pre-mRNA-processing and phosphorylates RNA-binding proteins such as KHDRBS1. Also plays a role in PDGF-mediated tyrosine phosphorylation of both STAT1 and STAT3, leading to increased DNA binding activity of these transcription factors. Involved in the RAS pathway through phosphorylation of RASA1 and RASGRF1. Plays a role in EGF-mediated calcium-activated chloride channel activation. Required for epidermal growth factor receptor (EGFR) internalization through phosphorylation of clathrin heavy chain (CLTC and CLTCL1) at Tyr-1477. Involved in beta-arrestin (ARRB1 and ARRB2) desensitization through phosphorylation and activation of ADRBK1, leading to beta-arrestin phosphorylation and internalization. Has a critical role in the stimulation of the CDK20/MAPK3 mitogen-activated protein kinase cascade by epidermal growth factor. Might be involved not only in mediating the transduction of mitogenic signals at the level of the plasma membrane but also in controlling progression through the cell cycle via interaction with regulatory proteins in the nucleus. Plays an important role in osteoclastic bone resorption in conjunction with PTK2B/PYK2. Both the formation of a SRC-PTK2B/PYK2 complex and SRC kinase activity are necessary for this function. Recruited to activated integrins by PTK2B/PYK2, thereby phosphorylating CBL, which in turn induces the activation and recruitment of phosphatidylinositol 3-kinase to the cell membrane in a signaling pathway that is critical for osteoclast function. Promotes energy production in osteoclasts by activating mitochondrial cytochrome C oxidase. Phosphorylates DDR2 on tyrosine residues, thereby promoting its subsequent autophosphorylation. Phosphorylates RUNX3 and COX2 on tyrosine residues, TNK2 on Tyr-284 and CBL on Tyr-731. Enhances DDX58/RIG-I-elicited antiviral signaling. Phosphorylates PDPK1 at Tyr-9, Tyr-373 and Tyr-376. Phosphorylates BCAR1 at Tyr-128. Phosphorylates CBLC at multiple tyrosine residues, phosphorylation at Tyr-341 activates CBLC E3 activity.
TTK	Phosphorylates proteins on serine, threonine, and tyrosine. Probably associated with cell proliferation. Essential for chromosome alignment by enhancing AURKB activity (via direct CDCA8 phosphorylation) at the centromere, and for the mitotic checkpoint.

Einsiedlerstrasse 23, 8834 Schindellegi, SWITZERLAND
E-mail: info@realtimeoncology.com **Web:** www.realtimeoncology.com

Oncompass Report

A Realtime Oncology Molecular Treatment Calculator számításaival

AZONOSÍTÓ	431898
NÉV	Anonymous

DRIVER ÉS TARGET GÉNEK LEÍRÁSA

TARGET GÉNEK

Név	Leírás
WRN	Multifunctional enzyme that has both magnesium and ATP-dependent DNA-helicase activity and 3->5 exonuclease activity towards double-stranded DNA with a 5-overhang. Has no nuclease activity towards single-stranded DNA or blunt-ended double-stranded DNA. Binds preferentially to DNA substrates containing alternate secondary structures, such as replication forks and Holliday junctions. May play an important role in the dissociation of joint DNA molecules that can arise as products of homologous recombination, at stalled replication forks or during DNA repair. Alleviates stalling of DNA polymerases at the site of DNA lesions. Important for genomic integrity. Plays a role in the formation of DNA replication focal centers; stably associates with foci elements generating binding sites for RP-A (By similarity). Plays a role in double-strand break repair after gamma-irradiation.
YES1	Non-receptor protein tyrosine kinase that is involved in the regulation of cell growth and survival, apoptosis, cell-cell adhesion, cytoskeleton remodeling, and differentiation. Stimulation by receptor tyrosine kinases (RTKs) including EGRF, PDGFR, CSF1R and FGFR leads to recruitment of YES1 to the phosphorylated receptor, and activation and phosphorylation of downstream substrates. Upon EGFR activation, promotes the phosphorylation of PARD3 to favor epithelial tight junction assembly. Participates in the phosphorylation of specific junctional components such as CTNND1 by stimulating the FYN and FER tyrosine kinases at cell-cell contacts. Upon T-cell stimulation by CXCL12, phosphorylates collapsin response mediator protein 2/DPYSL2 and induces T-cell migration. Participates in CD95L/FASLG signaling pathway and mediates AKT-mediated cell migration. Plays a role in cell cycle progression by phosphorylating the cyclin-dependent kinase 4/CDK4 thus regulating the G1 phase. Also involved in G2/M progression and cytokinesis.

FÜGGELÉK

CÉLZOTT HATÓANYAGOK

FORGALOMBAN LÉVŐ GYÓGYSZEREK (75): ABEMACICLIB, ACALABRUTINIB, AFATINIB, ALECTINIB, ATEZOLIZUMAB, AVELUMAB, AXITINIB, BELINOSTAT, BEVACIZUMAB, BORTEZOMIB, BOSUTINIB, BRIGATINIB, CABOZANTINIB, CARFILZOMIB, CEDIRANIB, CERITINIB, CETUXIMAB, COBIMETINIB, COPANLISIB, CRIZOTINIB, DABRAFENIB, DARATUMUMAB, DASATINIB, DURVALUMAB, ELOTUZUMAB, ENASIDENIB, ERLOTINIB, EVEROLIMUS, GEFITINIB, IBRUTINIB, IDELALISIB, IMATINIB, INOTUZUMAB OZOGAMICIN, IPILIMUMAB, IXAZOMIB, LAPATINIB, LENALIDOMIDE, LENVATINIB, METFORMIN, MIDOSTAURIN, NECITUMUMAB, NERATINIB, NILOTINIB, NINTEDANIB, NIRAPARIB, NIVOLUMAB, OLAPARIB, OLARATUMAB, OSIMERTINIB, PALBOCICLIB, PANITUMUMAB, PANOBINOSTAT, PAZOPANIB, PEMBROLIZUMAB, PERTUZUMAB, POMALIDOMIDE, PONATINIB, RAMUCIRUMAB, REGORAFENIB, RIBOCICLIB, ROMIDEPSIN, RUCAPARIB, SORAFENIB, SUNITINIB, T-DM1, TEMSIROLIMUS, THALIDOMIDE, TRAMETINIB, TRASTUZUMAB, VANDETANIB, VEMURAFENIB, VISMODEGIB, VORINOSTAT, ZIV-AFLIBERCEPT

KLINIKAI VIZSGÁLATBAN ELÉRHETŐ HATÓANYAGOK (445): 17-AAG, 4SC-201, 4SC-202, 4SC-203, AAL881, AB-010, ABBV-221, ABT-414, ABT-494, ABT-700, ABT-767, ABT-806, ABTL0812, AC0010MA, AC-480, ACE-041, ACP-319, ACY-1215, ACY-241, ADU-623, AEB071, AEE788, AG-014699, AG-120, AG-881, AGI-5198, AKN-028, ALLITINIB, ALRN-6924, AMG208, AMG-232, AMG319, AMG337, AMG595, AMUVATINIB, ANLOTINIB, AP26113, AP32788, APRINOCARSEN, AR-42, ARGX-111, ARQ087, ARQ736, ARRY-380, ARRY382, ARX788, AS-703026, AS703988, ASP2215, ASP3026, ASP5878, ASP8273, AT13387, AT7519, AT9283, AUY922, AV-412, AVX901, AZ628, AZD0156, AZD1480, AZD2014, AZD2461, AZD3759, AZD4547, AZD5438, AZD6094, AZD6244, AZD6738, AZD-7762, AZD8055, AZD8186, AZD8330, AZD8835, B-701, BARICITINIB, BAY1000394, BAY1082439, BAY1163877, BAY1179470, BAY1187982, BAY1436032, BAY54-9085, BAY87-2243, BEZ235, BGB-283, BGB-290, BGJ398, BGT226, BI-2536, BI6727, BI847325, BI-847325, BI860585, BIIB021, BIIB028, BKM120, BLU-285, BMN673, BMS-599626, BMS-690514, BMS-777607, BMS-906024, BMS-911543, BMS-986115, BRIVANIB, BRONTICTUZUMAB, BYL719, CAL-263, CANERTINIB, CAPMATINIB, CC-223, CEP-32496, CEP-37440, CEP-9722, CG200745, CGM097, CH5424802, CHIAURANIB, CHIR-124, CHIR-265, CHR-2845, CHR-3996, CLR457, CM-082, CP-724714, CPI-1205, CRA-024781, CRENOLANIB, CT-707, CT-P6, CUCD-101, CUDC-101, CUDC-907, CXD101, CYC065, CYC116, DACOMITINIB, DANUSERTIB, DCC-2618, debio0932, debio1347, DECERNOTINIB, DEMCIZUMAB, DOVITINIB, DS-2248, DS-3032b, DS-6051b, DS-7423, DS-8201a, E6201, E7016, E7050, E7090, E7449, EDO-S101, EGF816, EMD1204831, EMD1214063, ENMD-2076, ENMD-981693, ENTRECTINIB, ENZASTAURIN, EPITINIB, EPZ-6438, ERTUMAXOMAB, EZN-2968, FAMITINIB, FEDRATINIB, FILGOTINIB, FLUZOPARIB, FLX925, FORETINIB, FPA008, FPA144, FRUQUINTINIB, FS102, GANDOTINIB, GC1118, GDC-0084, GDC-0425, GDC-0575, GDC-0623, GDC-0941, GDC-0980, GF109203X, GLESATINIB, GLPG-0555, GOLVATINIB, GS-9820, GSK1059615, GSK2126458, GSK2636771, GSK2816126, GSK-461364, HDM201, HEMAY022, HGS1036, HM61713, HMN-214, HMR1275, HS-10241, HSP990, ICOTINIB, ICRUCUMAB, IDH1R132H, IDH305, ILORASERTIB, IMC-CS4, IMGN289, IMU-131, INC280, INCB039110, INCB040093, INCB047986, INCB050465, INCB052793, INCB054828, INCB-47986, INIPARIB, INO-1001, IPI-145, IPI-493, IPI-504, IPI-549, ITF2357, JNJ-26481585, JNJ-26483327, JNJ-26854165, JNJ-38877605, JNJ-42756493, JNJ-61186372, KA2237, KAI-1678, KOS-1022, KTN0158, KU55933, KW-2478, LBT613, LDK378, LESTAURTINIB, LGX818, LINIFANIB, LOP628, LORLATINIB, LUCITANIB, LXS196, LY2606368, LY287445, LY-2874455, LY2875358, LY294002, LY3023414, LY3039478, LY3076226, LY3164530, M344, MASITINIB, MATUZUMAB, MC1568, ME-344, ME-401, MEDI4276, MEHD7945A, MEK162, MFGR1877S, MGAH22, MGCD0103, MGCD265, MI-773, MK0752, MK-1496, MK-1775, MK-2461, MK-7965, MK-8242, MK-8776, MLN0128, MLN1117, MM-111, MM-151, MM-302, MOMELOTINIB, MOTESANIB, MPC-3100, MPT0E028, MR1-1, MRX34, MSC2156119J, NIMESULIDE, NIMOTUZUMAB, NMS-1286937, NMS-E973, NMS-P937, NS-018, NS-398, NVP-BEP800, OBP-801, ODM-203, ON-01910, ONARTUZUMAB, ORANTINIB, OSI-027, OSI-930, P1446A-05, P276-00, P7170, PACRITINIB, PARECOXIB, PCI-34051, PD-0166285, PD0325901, PD184352, PD98059, PEFICITINIB, PEGDINETANIB, PELITINIB, PEPIDH1M, PEXIDARTINIB, PF-00337210, PF-02341066, PF-03084014, PF-03446962, PF-04217903, PF-04691502, PF-04965842, PF-06459988, PF-06463922, PF-06747775, PF-477736, PHA-793887, PHA-848125AC, PKI-166, PKI179, PKI-587, PLX-5622, PLX8394, PLX-9486, POZIOTINIB, PQR309, PRT062070, PU-H71, PWT143, PWT33597, PX-478, PX-866, PYROTINIB, QUIZARTINIB, R547, RAF265, RDEA119, REBASTINIB, RG1530, RGB-286638, RIDAFOROLIMUS, RILOTUMUMAB, RINDOPEPIMUT, Ro3280, RO4929097, RO4987655, RO5045337, RO5083945, RO5126766, RO5212054, RO5503781, RO6839921, ROCILETINIB, RP6530, RUBOXISTAURIN, RXDX-101, S-222611, S49076, SAIT301, SAPITINIB, SAR125844, SAR260301, SB939, SCH-900776, SEMAGACESTAT, SEMAXANIB, SF1126, SGX523, SHP-141, SIMOTINIB, SNDX-275, SNS-032, SNX-2112, SNX-5422 mesylate, SOLCITINIB, SOTRASTAURIN, STA-9090, SU-014813, SU-11274, SU9516, SULFATINIB, Sym004, TAK-165, TAK-285, TAK-733, TANDUTINIB, TAREXTUMAB, TAS-120, TASELISIB, TELATINIB, TEPOTINIB, TESEVATINIB, TEW-7197, TG02, TG100-115, TG100-801, TG101348, TGR-1202, TIVANTINIB, TIVOZANIB, TSA, TSR-011, TSU-68, U0126, UCN-01, VARLITINIB, VATALANIB, VELIPARIB, VER155008, VER-49009, VER-50589, VS-5584, VX-970, WP1066, WX-037, WX-554, X-396, X-82, XL019, XL147, XL-281, XL647, XL765, XL-820, XL888, XL-999, ZALUTUMUMAB, ZD4547, ZM336372, ZSTK474

A gének funkcionális leírása a UniProt (Universal Protein Resource) adatbázisból származik.

Oncompass Report

A Realtime Oncology Molecular Treatment Calculator számításaival

AZONOSÍTÓ	431898
NÉV	Anonymous

felhasználásával információt szolgáltat a tumorok és a molekuláris profil közti összefüggésekről. A szakirodalom teljességéért és azok tartalmáért sem az Oncompass Medicine, sem a Realtime Oncology nem vállal felelősséget. A feltüntetett gyógyszerek az adott tumortípusban lehetnek törzskönyvezettek és/vagy finanszírozottak, annak viszonylatában, hogy a riportot melyik országban használják.

Istvan Petak, MD, PhD

Molekuláris farmakológus, Igazgató

Einsiedlerstrasse 23, 8834 Schindellegi, SWITZERLAND
E-mail: info@realtimeoncology.com **Web:** www.realtimeoncology.com