ONCOMPASS™ REPORT

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Realtime Oncology
Molecular Treatment Calculator™

Oncompass Report

A Realtime Oncology Molecular Treatment Calculator számításaival

AZONOSÍTÓ	
NÉV	Anonymous

BETEG ADATAI

Oncompass™ ID:	Primer daganat lokalizációja: breast
Név:	Szövettani típus: invasive carcinoma NST
Születési dátum: 1959	Metasztázis lokalizációja: bone, lymph node

SZAKÉRTŐK

Molekuláris Farmakológus: Dr. Peták István
Genetikai Tanácsadó: Déri Júlia, MSc
Molekuláris Biológus: Várkondi Edit, PhD
Konzulens Orvos: Dr. Pajkos Gábor
Szakértő: Dr. Szuszán Marianna
Betegút Koordinátor: Czető Réka
Info-bionikus Mérnök: Tihanyi Dóra, MSc
Molekuláris Bionikus Mérnök: Dirner Anna, MSc

PATOLÓGIAI ÉS MOLEKULÁRIS DIAGNOSZTIKAI VIZSGÁLATOK

Mintaazonosító: XXX (szövettani minta)
Minta eredete: nyirokcsomó metasztázis
Tumorarány: 50%
Tumortípus: invazív ductális emlő carcinoma

Elvégzett vizsgálatok:
IHC - PD-L1 normál expresszió
MSI - MSS
TMB - magas: 6,44 mut/Mb
NGS - 591 gén

Korábbi molekuláris vizsgálatok eredménye:
IHC - ER, PR, HER2 normál expresszió
IHC - PD-L1 overexpresszió (>1%)

KORÁBBI KEZELÉSEK

Neoadjuváns kezelés: DOCETAXEL + DOXORUBICIN
1. vonal: PACLITAXEL + BEVACIZUMAB
2. vonal: CARBOPLATIN + DOCETAXEL

ÖSSZEFOGLALÁS

Az Oncompass vizsgálat a következő mintából történt:
Mintaazonosító: XXX (szövettani minta), Minta eredete: nyirokcsomó metasztázis. Tumorarány: 50%

Elvégzett vizsgálatok:
IHC - PDL1 (Normál expresszió)
MSI - MSS
TMB - HIGH
NGS - 591 gén

Korábbi molekuláris vizsgálatok eredménye:
IHC - ER (Normál expresszió), HER2 (Normál expresszió), PR (Normál expresszió)

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ÖSSZEFOGLALÁS

IHC - PDL1 (Overexpresszió >1%)

591 gén NGS szekvenálása 5103 genetikai variánst mutatott ki a mintában. A molekuláris profilba feltöltött 34 variáns bioinformatikai és funkcionális szűrések eredményeként került kiválasztásra. Ezek a variánsok szerepelnek a Realtime Oncology Calculatorban további funkcionális interpretáció és orvosi döntéstámogatás céljából.

Az MTC algoritmusa az aktuális evidencia adatbázis alapján **driverként** listázta a következő eltéréseket: TMB-H driver (AEL: 803,92, AF/TR: NA /50%), PDL1 protein overexpression driver (AEL: 475,62, AF/TR: NA/NA), BRCA1-K654fs*47 driver (AEL: 85,31, AF/TR: 31.72%/50%), KMT2C-C391* driver (AEL: 16,09, AF/TR: 7.24%/50%),
További driver gén ismeretlen variánsaként -**VUS, driver gén** jelöléssel -listázott alterációkra vonatkozólag nem szerepel információ az evidencia adatbázisban, de ismert, hogy a gén más mutációi hozzájárulhatnak a daganatképződéshez: TP53-M160_A161dup VUS, driver gén (AEL: 22,52, AF/TR: 23.66% /50%), KIT-E930Q VUS, driver gén (AEL: 14,13, AF/TR: 12.1%/50%), CUL3-R162fs*9 VUS, driver gén (AEL: 0,07, AF/TR: 8.62%/50%),

TMB HIGH: A vizsgált mintában a szekvencia analízis (NGS) során kapott 1 megabázisra vonatkozó mutációk száma **(TMB): 6,44.** Az adatbázisunkban lévő kalkulált TMB értékek (n=585) eloszlása alapján az eseteink 90%-ában kaptunk ennél alacsonyabb TMB értéket.
A magas TMB érték pozitív asszociációban áll a PD-1 és PD-L1 inhibitorokra adott válasszal különböző tumortípusokban.
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.
TMB-High tripla negatív emlődaganat
A PEMBROLIZUMAB az FDA által törzskönyvezett magas TMB értékű, előrehaladott vagy metasztatikus, szolid tumorral rendelkező, felnőtt és gyermek betegek számára.
Az ATEZOLIZUMAB törzskönyvezett PD-L1 pozitív, irrezekábilis, lokálisan előrehaladott vagy metasztatikus tripla negatív emlődaganat (triple negative breast cancer, TNBC) indikációban nab-paclitaxellel kombinációban.(IMpassion130 klinikai vizsgálat).

PD-L1 overexpresszált tripla negatív emlődaganat
TNBC indikációban törzskönyvezett immunterápia az ATEZOLIZUMAB és a PEMBROLIZUMAB (csak az FDA által).
A PEMBROLIZUMAB (PD-1 inhibitor) az FDA által törzskönyvezett kemoterápiával kombinációban PD-L1 pozitív (10%), előrehaladott TNBC betegek számára.

A kópiaszám-variáció (copy number variation, CNV) vizsgálat eredménye
Magasabb kópiaszámban vannak jelen, a z FGFR1, CCNE1, RHPN2, CEBPA (n=8), TACC1 (n=7), ZNF703, BRCA1 (n=5).
Az NGS vizsgálat által detektált kópiaszám-változásokat klinikai relevancia esetében FISH vizsgálattal is javasoljuk megvizsgálni. Az FGFR1 gén FISH vizsgálata folyamatban van.
FGFR1 amplifikáció emlődaganatban: FGFR1 amplifikáció esetén az FGFR1 gátló gyógyszerek lehetnek hatékonyak. Törzskönyvezett multi-tirozin kináz gátlószerek, amelyek többek között az FGFR jelpályát is gátolják a LENVATINIB, a NINTEDANIB, a PAZOPANIB, a REGORAFENIB és a PONATINIB, illetve kevésbé specifikusak a SORAFENIB és a SUNITINIB. FDA által urotheliális daganatok indikációjában elfogadott FGFR gátló hatóanyag az ERDAFITINIB.
CCNE1 amplifikáció: CCNE1 amplifikáció esetén a CDK-k és a WEE1 említhetők pozitív asszociációban, mint indirekt targetek.
Egy preklinikai vizsgálat során PARP+ATR inhibitorok kombinációja CCNE1 amplifikált, PARPi- és platina-rezisztes ovárium daganat xenograft modellekben teljes terápiás választ és tumor regressziót eredményezett.

BRCA1-K654fs*47: Ez a mutáció a ClinVar és a BRCA Exchance adatbázisok és a tudományos irodalom szerint patogén. Szerepel a COSMIC adatbázisban is. A leolvasási kereteltolódást okozó mutáció (frameshift mutation) a BRCA1 gén nonsense-mediated decay (NMD) rezisztens pozícióját érinti. A mutáns génről egy csonka fehérjeváltozat képződik, ezért feltételezhető, hogy funkcióvesztéssel jár. BRCA inaktiváció esetén a PARP inhibitorok említhetőek pozitív asszociációban. Ováriumdaganatokban írták le, hogy BRCA mutáció esetén a PD-1/PD-L1 gátló immunterápiától is emelkedett hatékonyság várható.
BRCA mutáció emlődaganatban
Csíravonalas BRCA mutáció esetén HER2 negatív emlődaganatos betegek részére törzskönyvezett PARP gátló gyógyszer az OLAPARIB és a TALAZOPARIB. Mindkét gyógyszer neoadjuváns/adjuváns/metasztatikus vonalban alkalmazott kemoterápia után adható.

Frameshift mutációk

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ÖSSZEFOGLALÁS

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

ÖSSZEGEZVE:

Molekuláris profil alapján-amennyiben klinikailag támogatható- szóba jöhet: **IMMUNTERÁPIA+PARP gátló (Atezolizumab+Olaparib/vagy Talazoparib),** TMB-high/6,44, PDL1 pozitivitas és BRCA1 mutáció miatt,off label+EMK. *Az FDA törzskönyvezte az atezolizumabot PD-L1 pozitív, irrezekábilis, lokálisan előrehaladott vagy metasztatikus tripla negatív emlődaganat indikációban nab-paclitaxellel kombinációban. Csíravonalas BRCA mutáció esetén HER2 negatív emlődaganatos betegek részére törzskönyvezett PARP gátló gyógyszer az OLAPARIB és a TALAZOPARIB. Mindkét gyógyszer neoadjuváns/adjuváns/metasztatikus vonalban alkalmazott kemoterápia után adható.*
BRCA1 mutáció germline vizsgálata javasolható (vérből), illetve genetikai tanácsadás. A kezelőorvos kérésére BRCA1 mutáció vizsgálatát vérből elvégezzük.

MOLEKULÁRIS CÉLPONT ELEMZÉS

MOLEKULÁRIS ALTERÁCIÓK

TMB-H driver (AEL: 803,92, AF/TR: NA/50%),
PDL1 protein overexpression driver (AEL: 475,62, AF/TR: NA/NA),
BRCA1-K654fs*47 driver (AEL: 85,31, AF/TR: 31.72%/50%),
TP53-M160_A161dup VUS, driver gén (AEL: 22,52, AF/TR: 23.66%/50%),
KMT2C-C391* driver (AEL: 16,09, AF/TR: 7.24%/50%),
KIT-E930Q VUS, driver gén (AEL: 14,13, AF/TR: 12.1%/50%),
NFE2L2-G589D VUS, driver gén (AEL: 1,18, AF/TR: 11.01%/50%),
GNAS-P459R driver (AEL: 0,85, AF/TR: 30.3%/50%),
KDM5C-S299R VUS, driver gén (AEL: 0,50, AF/TR: 55.89%/50%),
CUL3-R162fs*9 VUS, driver gén (AEL: 0,07, AF/TR: 8.62%/50%),
FOXA1-L148V VUS, driver gén (AEL: 0,04, AF/TR: 69.51%/50%),
TENT5C-E299K driver (AEL: 0,01, AF/TR: 45.34%/50%),
GAS6-V673fs*37 driver (AEL: 0,01, AF/TR: 3%/50%),
ZNF703-A514del ellentmondásos driver (AEL: 0,00, AF/TR: 4.27%/50%),
ZNF703-P307S ellentmondásos driver (AEL: 0,00, AF/TR: 9.4%/50%),
AKAP9-Q1373E ellentmondásos driver (AEL: 0,00, AF/TR: 11.97%/50%),
MAGI2-E867K ellentmondásos driver (AEL: 0,00, AF/TR: 12.5%/50%),
BRCA1-D430N ellentmondásos driver (AEL: 0,00, AF/TR: 38.74%/50%),
OTOP1-V69M ellentmondásos driver (AEL: 0,00, AF/TR: 23.08%/50%),
KLHL6-Q317L ellentmondásos driver (AEL: 0,00, AF/TR: 38.4%/50%),
SEC16A-T1001I ellentmondásos driver (AEL: 0,00, AF/TR: 58.21%/50%),
PCBP1-N84S ellentmondásos driver (AEL: 0,00, AF/TR: 42.56%/50%),
PIK3CG-Q1071E ismeretlen jelentőségű variáns (AEL: 0,00, AF/TR: 9.09%/50%),
OTOP1-L104M ismeretlen jelentőségű variáns (AEL: 0,00, AF/TR: 51.92%/50%),
AXL-P279Q ismeretlen jelentőségű variáns (AEL: 0,00, AF/TR: 30.69%/50%),
SPEG-R1621C ismeretlen jelentőségű variáns (AEL: 0,00, AF/TR: 33.09%/50%),
BUB1B-Q487H ismeretlen jelentőségű variáns (AEL: 0,00, AF/TR: 8.43%/50%),
AMPH-Q71fs*4 ismeretlen jelentőségű variáns (AEL: 0,00, AF/TR: 25.2%/50%),
FGF14-N242T ismeretlen jelentőségű variáns (AEL: 0,00, AF/TR: 25%/50%),
CCNE1-R101S ismeretlen jelentőségű variáns (AEL: 0,00, AF/TR: 7.24%/50%),
KMT2C-R380L nem driver (AEL: -3,65, AF/TR: 7.5%/50%),
KIT-M541L nem driver (AEL: -4,20, AF/TR: 49.94%/50%),
GNAT2-A5V nem driver (AEL: -5,00, AF/TR: 50.15%/50%),
WNK2-H758N nem driver (AEL: -5,00, AF/TR: 61.82%/50%),
EPHA5-A672T nem driver (AEL: -10,00, AF/TR: 99.53%/50%),
NOTCH1-R1279H nem driver (AEL: -16,57, AF/TR: 61.04%/50%)

INDIREKT CÉLPONT GÉNEK

CD274 vad típus (AEL: 1764,22),
- PDL1 protein overexpression driver (AEL: 475,62) ;
- BRCA1-K654fs*47 driver (AEL: 85,31) ;
- TMB-H driver (AEL: 803,92) ;
- BRCA1-D430N driver (AEL: 0,00)

PD-1 vad típus (AEL: 1440,84),
- BRCA1-K654fs*47 driver (AEL: 85,31) ;
- TMB-H driver (AEL: 803,92) ;
- PDL1 protein overexpression driver (AEL: 475,62) ;
- BRCA1-D430N driver (AEL: 0,00)

CTLA4 vad típus (AEL: 809,26),
- TMB-H driver (AEL: 803,92)

PARP1 vad típus (AEL: 165,38),
- BRCA1-K654fs*47 driver (AEL: 85,31) ;
- BRCA1-D430N driver (AEL: 0,00)

KIT vad típus (AEL: 121,53),
- KIT-E930Q driver (AEL: 14,13)

CHEK1 vad típus (AEL: 109,87),
- BRCA1-D430N driver (AEL: 0,00) ;
- BRCA1-K654fs*47 driver (AEL: 85,31) ;
- TP53-M160_A161dup driver (AEL: 22,52)

PARP2 vad típus (AEL: 85,41),
- BRCA1-K654fs*47 driver (AEL: 85,31) ;
- BRCA1-D430N driver (AEL: 0,00)

WEE1 vad típus (AEL: 26,32),
- TP53-M160_A161dup driver (AEL: 22,52)

ATR vad típus (AEL: 23,86),
- TP53-M160_A161dup driver (AEL: 22,52)

CDK4 vad típus (AEL: 23,50),
- TP53-M160_A161dup driver (AEL: 22,52)

RARG vad típus (AEL: 23,41),
- TP53-M160_A161dup driver (AEL: 22,52)

PLK1 vad típus (AEL: 23,00),
- TP53-M160_A161dup driver (AEL: 22,52)

PRKDC vad típus (AEL: 22,92),
- TP53-M160_A161dup driver (AEL: 22,52)

CDK1 vad típus (AEL: 22,85),
- TP53-M160_A161dup driver (AEL: 22,52)

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NÉV	Anonymous

MOLEKULÁRIS CÉLPONT ELEMZÉS

CDK9 vad típus (AEL: 22,85),
- TP53-M160_A161dup driver (AEL: 22,52)

CDK2 vad típus (AEL: 22,85),
- TP53-M160_A161dup driver (AEL: 22,52)

AURKB vad típus (AEL: 22,80),
- TP53-M160_A161dup driver (AEL: 22,52)

BRD4 vad típus (AEL: 18,23),
- KMT2C-C391* driver (AEL: 16,09)

JAK2 vad típus (AEL: 14,55),
- KIT-E930Q driver (AEL: 14,13)

glutaminase vad típus (AEL: 4,45),
- NFE2L2-G589D driver (AEL: 1,18)

PRKACA vad típus (AEL: 1,35),
- GNAS-P459R driver (AEL: 0,85)

ATM vad típus (AEL: 0,72)
- CUL3-R162fs*9 driver (AEL: 0,07)

DAGANAT MOLEKULÁRIS PROFILJÁVAL POZITÍV KAPCSOLATBAN ÁLLÓ HATÓANYAGOK

FORGALOMBAN LÉVŐ
4 listázott hatóanyag (összesen 95)

PEMBROLIZUMAB (esophagus - squamous cell carcinoma [FDA]; lung - non-small cell carcinoma [FDA+EMA]; bármely tumor - renal cell carcinoma [FDA+EMA]; head-neck - squamous cell carcinoma [FDA+EMA]; rectum - bármely szövettan [FDA+EMA]; breast - bármely szövettan [FDA]; bármely tumor - mediastinal B-cell lymphoma [FDA]; gastroesophageal junction - adenocarcinoma [FDA]; gastric - adenocarcinoma [FDA]; bármely tumor - malignant melanoma [FDA+EMA]; skin - squamous cell carcinoma [FDA]; cervix - bármely szövettan [FDA]; lung - adenocarcinoma [FDA+EMA]; skin - Merkel cell carcinoma (MCC) [FDA]; bármely tumor - urothelial carcinoma [FDA+EMA]; liver - hepatocellular carcinoma [FDA]; endometrium - bármely szövettan [FDA]; bármely tumor - endometrioid carcinoma [FDA]; colon - bármely szövettan [FDA+EMA]; bármely tumor - Hodgkin lymphoma [FDA+EMA]) (AEL: 10455,98)
- TMB-H driver (AEL: 803,92) ;
- PD-1 vad típus target (AEL: 1440,84) ;
- PD-L1 protein overexpression driver (AEL: 475,62) ;
- PD-L1 vad típus target (AEL: 1764,23)

ATEZOLIZUMAB (bármely tumor - malignant melanoma [FDA]; lung - small cell carcinoma [FDA+EMA]; lung - non-small cell carcinoma [FDA+EMA]; bármely tumor - urothelial carcinoma [FDA+EMA]; breast - bármely szövettan [FDA+EMA]; liver - hepatocellular carcinoma [FDA+EMA]) (AEL: 3641,80)
- PD-L1 vad típus target (AEL: 1764,23) ;
- PD-L1 protein overexpression driver (AEL: 475,62)

OLAPARIB (pancreas - bármely szövettan [FDA+EMA]; peritoneum - bármely szövettan [FDA+EMA]; prostate - bármely szövettan [FDA+EMA]; fallopian tube - bármely szövettan [FDA+EMA]; ovary - bármely szövettan [FDA+EMA]; breast - bármely szövettan [FDA+EMA]) (AEL: 766,00)
- PARP1 vad típus target (AEL: 165,38) ;
- BRCA1-D430N driver (AEL: 0,00) ;
- BRCA1-K654fs*47 driver (AEL: 85,31)

NIRAPARIB (ovary - epithelial carcinoma [FDA+EMA]; fallopian tube - bármely szövettan [FDA+EMA]; peritoneum - bármely szövettan [FDA+EMA]) (AEL: 402,97)
- BRCA1-K654fs*47 driver (AEL: 85,31) ;
- PARP1 vad típus target (AEL: 165,38) ;
- BRCA1-D430N driver (AEL: 0,00) ;
- PARP2 vad típus target (AEL: 85,41)

DAGANAT MOLEKULÁRIS PROFILJÁVAL NEGATÍV KAPCSOLATBAN ÁLLÓ HATÓANYAGOK

FORGALOMBAN LÉVŐ
10 listázott hatóanyag (összesen 13)

DOXORUBICIN (bone marrow - multiple myeloma [FDA]; blood vessel - kaposi sarcoma [FDA]; ovary - carcinoma [FDA]; breast - carcinoma [FDA]) (AEL: -47,76)
- TP53-M160_A161dup driver (AEL: -22,52) ;
- KMT2C-C391* driver (AEL: -16,09)

CRIZOTINIB (lung - non-small cell carcinoma [FDA+EMA]; bármely tumor - anaplastic large cell lymphoma [FDA]) (AEL: -44,26)
- TP53-M160_A161dup driver (AEL: -22,52) ;
- KIT-E930Q driver (AEL: -14,13)

CHOP (AEL: -39,53)
- TP53-M160_A161dup driver (AEL: -22,52)

CYTARABINE (AEL: -24,65)
- KMT2C-C391* driver (AEL: -16,09)

PACLITAXEL (AEL: -22,56)
- TP53-M160_A161dup driver (AEL: -22,52)

ETOPOSIDE (AEL: -22,56)
- TP53-M160_A161dup driver (AEL: -22,52)

BAZEDOXIFENE (AEL: -16,16)
- ESR1 vad típus target (AEL: -16,38)

GEFITINIB (lung - squamous cell carcinoma [FDA+EMA]; lung - adenocarcinoma [FDA+EMA]; lung - non-small cell carcinoma [FDA+EMA]) (AEL: -1,40)

MELPHALAN (AEL: -0,17)

AFATINIB (lung - non-small cell carcinoma [FDA+EMA]; lung - squamous cell carcinoma [FDA+EMA]; lung - adenocarcinoma [FDA+EMA]) (AEL: -0,14)

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DAGANAT MOLEKULÁRIS PROFILJÁVAL POZITÍV KAPCSOLATBAN ÁLLÓ HATÓANYAGOK	DAGANAT MOLEKULÁRIS PROFILJÁVAL NEGATÍV KAPCSOLATBAN ÁLLÓ HATÓANYAGOK
KLINIKAI FEJLESZTÉS ALATT *10 listázott hatóanyag (összesen 108)* TORIPALIMAB (AEL: 2056,45) • PD-L1 protein overexpression driver (AEL: 475,62) ; • PD-1 vad típus target (AEL: 1440,84) SINTILIMAB (AEL: 1956,45) • PD-1 vad típus target (AEL: 1440,84) ; • PD-L1 protein overexpression driver (AEL: 475,62) CS1001 (AEL: 1764,48) • PD-L1 vad típus target (AEL: 1764,23) BINTRAFUSP ALFA (AEL: 1764,22) • PD-L1 vad típus target (AEL: 1764,23) PACMILIMAB (AEL: 1764,22) • PD-L1 vad típus target (AEL: 1764,23) MDX-1105 (AEL: 1764,22) • PD-L1 vad típus target (AEL: 1764,23) camrelizumab (AEL: 1441,74) • PD-1 vad típus target (AEL: 1440,84) TISLELIZUMAB (AEL: 1441,32) • PD-1 vad típus target (AEL: 1440,84) GEPTANOLIMAB (AEL: 1441,04) • PD-1 vad típus target (AEL: 1440,84) ABBV-181 (AEL: 1440,84) • PD-1 vad típus target (AEL: 1440,84)	KLINIKAI FEJLESZTÉS ALATT *7 listázott hatóanyag (összesen 7)* R-CHOP (AEL: -63,80) • TP53-M160_A161dup driver (AEL: -22,52) PATUPILONE (AEL: -22,59) • TP53-M160_A161dup driver (AEL: -22,52) AZD9496 (AEL: -16,38) • ESR1 vad típus target (AEL: -16,38) SRN-927 (AEL: -16,38) • ESR1 vad típus target (AEL: -16,38) ELACESTRANT (AEL: -16,16) • ESR1 vad típus target (AEL: -16,38) BRILANESTRANT (AEL: -16,11) • ESR1 vad típus target (AEL: -16,38) FK866 (AEL: -1,82)

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)

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Oncompass Report

A Realtime Oncology Molecular Treatment Calculator számításaival

AZONOSÍTÓ	
NÉV	Anonymous

KLINIKAI VIZSGÁLATOK

Keresési Kritériumok

ÁLLAPOT: Not yet recruiting,Active recruiting

AZONOSÍTÓ **LEÍRÁS**

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

AKAP9-Q1373E, AMPH-Q71FS*4, AXL-P279Q, BRCA1-D430N, BRCA1-K654FS*47, BUB1B-Q487H, CCNE1-R101S, CUL3-R162FS*9, EPHA5-A672T, FGF14-N242T, FOXA1-L148V, GAS6-V673FS*37, GNAS-P459R, GNAT2-A5V, KDM5C-S299R, KIT-E930Q, KIT-M541L, KLHL6-Q317L, KMT2C-C391*, KMT2C-R380L, MAGI2-E867K, NFE2L2-G589D, NOTCH1-R1279H, OTOP1-L104M, OTOP1-V69M, PCBP1-N84S, PIK3CG-Q1071E, SEC16A-T1001I, SPEG-R1621C, TENT5C-E299K, TP53-M160_A161DUP, WNK2-H758N, ZNF703-A514DEL, ZNF703-P307S

VAD TÍPUSÚ GÉNEK

ABCB1, ABCC2, ABL1, ABL2, ABRAXAS1, ACVR1B, ACVRL1, ADGRB3, AGTRAP, AIP, AKT1, AKT2, AKT3, ALK, AMER1, APC, APEX1, AR, ARAF, ARFRP1, ARID1A, ARID1B, ARID2, ASXL1, ATM, ATP11B, ATP4A, ATP6V0D2, ATR, ATRX, AURKA, AURKB, AXIN1, AXIN2, B2M, BAP1, BARD1, BAX, BAZ2B, BCL2, BCL2L1, BCL2L2, BCL6, BCL9, BCOR, BCORL1, BCR, BIM, BIRC2, BIRC3, BLM, BMPR1A, BRAF, BRCA2, BRD4, BRIP1, BTG1, BTK, CARD11, CASP8, CASR, CBFB, CBL, CBLB, CBLC, CCDC178, CCDC6, CCND1, CCND2, CCND3, CD74, CD79A, CD79B, CDA, CDC27, CDC73, CDH1, CDK12, CDK4, CDK6, CDK8, CDKN1A, CDKN1B, CDKN1C, CDKN2A, CDKN2B, CDKN2C, CEBPA, CEP57, CHD1, CHD2, CHD4, CHD7, CHEK1, CHEK2, CHIC2, CIC, CIT, CREBBP, CRKL, CRLF2, CSF1R, CSMD3, CSNK2A1, CTCF, CTNNA1, CTNNB1, CUBN, CYLD, CYP19A1, CYP2A6, CYP2B6, CYP2C19, CYP2C9, CYP2D6, DAXX, DCC, DCUN1D1, DDB2, DDR1, DDR2, DDX11, DDX3X, DICER1, DIS3L2, DMD, DNMT3A, DOT1L, DPH3, DPYD, DSE, ECT2L, EED, EGFR, ELMO1, EML4, EMSY, EP300, EPCAM, EPHA2, EPHA3, EPHA7, EPHB1, ERBB2, ERBB3, ERBB4, ERCC1, ERCC2, ERCC3, ERCC4, ERCC5, ERG, ERRFI1, ESR1, ESR2, ESRP1, ETV6, EXOC2, EXT1, EXT2, EZH2, EZR, FANCA, FANCB, FANCC, FANCD2, FANCE, FANCF, FANCG, FANCI, FANCL, FANCM, FAS, FAT1, FAT3, FBXO11, FBXO32, FBXW7, FGF10, FGF19, FGF23, FGF3, FGF4, FGF5, FGF6, FGF9, FGFR1, FGFR2, FGFR3, FGFR4, FH, FLCN, FLT1, FLT3, FLT4, FN1, FOXL2, FOXO1, FOXP1, FRS2, FSTL5, FUBP1, FZD3, G6PD, GABRA6, GALNT17, GATA1, GATA2, GATA3, GATA4, GATA6, GEN1, GID4, GLI1, GNA11, GNA13, GNAI2, GNAQ, GOPC, GPC3, GPR78, GREM1, GRIN2A, GRM3, GRM8, GSK3B, GSTP1, GXYLT1, H3-3A, H3C2, HGF, HNF1A, HOXB13, HRAS, HSD3B1, HSP90AA1, HSPH1, IDH1, IDH2, IFITM1, IFITM3, IGF1R, IGF2, IGF2R, IGSF10, IKBKE, IKZF1, IKZF4, IL2RA, IL2RB, IL2RG, IL6, IL6ST, IL7R, INHBA, INPP4B, IRAK4, IRF2, IRF4, IRS2, ITCH, JAK1, JAK2, JAK3, JUN, KAT6A, KDM4B, KDM5A, KDM6A, KDR, KEAP1, KEL, KIAA1549, KIF5B, KLF6, KMT2A, KMT2D, KNSTRN, KRAS, KREMEN1, LAMA2, LCK, LMO1, LPAR2, LRP1B, LRRK2, LTK, LYN, LZTR1, MAGI3, MAGOH, MAP2K1, MAP2K2, MAP2K4, MAP3K1, MAP3K4, MAP4K3, MAP7, MAPK1, MAPK3, MAS1L, MAX, MCL1, MDM2, MDM4, MED12, MED13, MEF2B, MEN1, MET, MIER3, MITF, MLH1, MLLT3, MPL, MRE11, MSH2, MSH3, MSH6, MST1R, MTOR, MUC16, MUTYH, MYC, MYCL1, MYCN, MYD88, MYO18A, MYO1B, NBN, NCOA2, NCOR1, NEK2, NF1, NF2, NFKBIA, NIPA2, NKX2-1, NKX2-8, NKX3-1, NOTCH2, NOTCH3, NPM1, NRAS, NRCAM, NRG1, NRP2, NSD1, NT5C2, NTRK1, NTRK2, NTRK3, NUP93, OR5L1, PAK3, PALB2, PAX3, PAX5, PAX7, PBRM1, PCGF2, PD-L1, PDGFRA, PDGFRB, PDK1, PDL2, PDZRN3, PHF6, PHOX2B, PIK3C2B, PIK3CA, PIK3CB, PIK3CD, PIK3R1, PIK3R2, PLCG2, PLEKHS1, PMS1, PMS2, PNP, POLD1, POLE, POT1, PPARG, PPM1L, PPP2R1A, PPP2R2A, PRDM1, PREX2, PRF1, PRKAR1A, PRKCI, PRKDC, PRKN, PRPF40B, PRSS8, PSMB1, PSMB2, PSMB5, PSMD1, PSMD2, PTCH1, PTEN, PTGFR, PTPN11, PTPN12, PTPRD, QKI, RAC1, RAC2, RAD21, RAD50, RAD51, RAD51B, RAD51C, RAD51D, RAD54L, RAF1, RANBP2, RARA, RARB, RARG, RB1, RBM10, RECQL4, RECQL5, RET, RHBDF2, RHEB, RHOA, RICTOR, RIT1, RNF43, ROS1, RPS6KB1, RPTOR, RUNX1, RUNX1T1, RXRA, RXRB, RXRG, S1PR2, SAMD9L, SBDS, SCN11A, SDC4, SDHA, SDHAF2, SDHB, SDHC, SDHD, SEPT9, SETBP1, SETD2, SF1, SF3A1, SF3B1, SH2B3, SHH, SHOC2, SLC22A1, SLC22A2, SLC31A1, SLC34A2, SLC45A3, SLC7A8, SLC9A9, SLCO1B1, SLIT2, SLX4, SMAD2, SMAD3, SMAD4, SMARCA4, SMARCB1, SMARCE1, SMC1A, SMC3, SMO, SNCAIP, SOCS1, SOS1, SOX10, SOX2, SOX9, SPEN, SPOP, SPRED1, SPTA1, SRC, SRSF2, SSTR1, STAG2, STAT3, STAT4, STK11, SUFU, SUZ12, SYK, SYNE3, TACC3, TAF1, TAS2R38, TBX20, TBX3, TCERG1, TCF7L2, TERC, TERT, TET2, TFG, TGFBR2, THSD7B, TIAF1, TMEM127, TMPRSS2, TNFAIP3, TNFRSF14, TOP1, TOP2A, TP53BP1, TP63, TPM3, TPM4, TPMT, TRAF5, TRIO, TRRAP, TSC1, TSC2, TSHR, TYK2, U2AF1, U2AF2, UBR3, UGT1A1, USP16, USP25, VCL, VEGFA, VHL, WDCP, WEE1, WISP3, WRN, WT1, WWP1, XPA, XPC, XPO1, XRCC2, YAP1, YES1, ZBED4, ZBTB2, ZFHX3, ZIC3, ZMYM3, ZNF2, ZNF217, ZNF226, ZNF473, ZNF595, ZRSR2

FISH/CNA/IHC POZITÍV GÉNEK

PD-L1 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, ERBB2 PROTEIN NORMÁL, ESR1 PROTEIN NORMÁL, 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, PGR PROTEIN NORMÁL, RAF1 TRANSLOCATION ABSENCE, RARA TRANSLOCATION ABSENCE, RET TRANSLOCATION ABSENCE, ROS1 TRANSLOCATION ABSENCE, TACC1 TRANSLOCATION ABSENCE, TACC3 TRANSLOCATION ABSENCE

MOLEKULÁRIS BIOLÓGIAI INTERPRETÁCIÓ

Oncompass Report

A Realtime Oncology Molecular Treatment Calculator számításaival

AZONOSÍTÓ	
NÉV	Anonymous

RÉSZLETES MOLEKULÁRIS PROFIL

MOLEKULÁRIS ALTERÁCIÓK

TMB-H driver (AEL: 803,92, AF/TR: NA/50%),
PDL1 protein overexpression driver (AEL: 475,62, AF/TR: NA/NA),
BRCA1-K654fs*47 driver (AEL: 85,31, AF/TR: 31.72%/50%),
TP53-M160_A161dup VUS, driver gén (AEL: 22,52, AF/TR: 23.66%/50%),
KMT2C-C391* driver (AEL: 16,09, AF/TR: 7.24%/50%),
KIT-E930Q VUS, driver gén (AEL: 14,13, AF/TR: 12.1%/50%),
NFE2L2-G589D VUS, driver gén (AEL: 1,18, AF/TR: 11.01%/50%),
GNAS-P459R driver (AEL: 0,85, AF/TR: 30.3%/50%),
KDM5C-S299R VUS, driver gén (AEL: 0,50, AF/TR: 55.89%/50%),
CUL3-R162fs*9 VUS, driver gén (AEL: 0,07, AF/TR: 8.62%/50%),
FOXA1-L148V VUS, driver gén (AEL: 0,04, AF/TR: 69.51%/50%),
TENT5C-E299K driver (AEL: 0,01, AF/TR: 45.34%/50%),
GAS6-V673fs*37 driver (AEL: 0,01, AF/TR: 3%/50%),
ZNF703-A514del ellentmondásos driver (AEL: 0,00, AF/TR: 4.27%/50%),
ZNF703-P307S ellentmondásos driver (AEL: 0,00, AF/TR: 9.4%/50%),
AKAP9-Q1373E ellentmondásos driver (AEL: 0,00, AF/TR: 11.97%/50%),
MAGI2-E867K ellentmondásos driver (AEL: 0,00, AF/TR: 12.5%/50%),
BRCA1-D430N ellentmondásos driver (AEL: 0,00, AF/TR: 38.74%/50%),
OTOP1-V69M ellentmondásos driver (AEL: 0,00, AF/TR: 23.08%/50%),
KLHL6-Q317L ellentmondásos driver (AEL: 0,00, AF/TR: 38.4%/50%),
SEC16A-T1001I ellentmondásos driver (AEL: 0,00, AF/TR: 58.21%/50%),
PCBP1-N84S ellentmondásos driver (AEL: 0,00, AF/TR: 42.56%/50%),
PIK3CG-Q1071E ismeretlen jelentőségű variáns (AEL: 0,00, AF/TR: 9.09%/50%),
OTOP1-L104M ismeretlen jelentőségű variáns (AEL: 0,00, AF/TR: 51.92%/50%),
AXL-P279Q ismeretlen jelentőségű variáns (AEL: 0,00, AF/TR: 30.69%/50%),
SPEG-R1621C ismeretlen jelentőségű variáns (AEL: 0,00, AF/TR: 33.09%/50%),
BUB1B-Q487H ismeretlen jelentőségű variáns (AEL: 0,00, AF/TR: 8.43%/50%),
AMPH-Q71fs*4 ismeretlen jelentőségű variáns (AEL: 0,00, AF/TR: 25.2%/50%),
FGF14-N242T ismeretlen jelentőségű variáns (AEL: 0,00, AF/TR: 25%/50%),
CCNE1-R101S ismeretlen jelentőségű variáns (AEL: 0,00, AF/TR: 7.24%/50%),
KMT2C-R380L nem driver (AEL: -3,65, AF/TR: 7.5%/50%),
KIT-M541L nem driver (AEL: -4,20, AF/TR: 49.94%/50%),
GNAT2-A5V nem driver (AEL: -5,00, AF/TR: 50.15%/50%),
WNK2-H758N nem driver (AEL: -5,00, AF/TR: 61.82%/50%),
EPHA5-A672T nem driver (AEL: -10,00, AF/TR: 99.53%/50%),
NOTCH1-R1279H nem driver (AEL: -16,57, AF/TR: 61.04%/50%)

INDIREKT CÉLPONT GÉNEK

CD274 vad típus (AEL: 1764,22),
- PDL1 protein overexpression driver (AEL: 475,62) ;
- BRCA1-K654fs*47 driver (AEL: 85,31) ;
- TMB-H driver (AEL: 803,92) ;
- BRCA1-D430N driver (AEL: 0,00)

PD-1 vad típus (AEL: 1440,84),
- BRCA1-K654fs*47 driver (AEL: 85,31) ;
- TMB-H driver (AEL: 803,92) ;
- PDL1 protein overexpression driver (AEL: 475,62) ;
- BRCA1-D430N driver (AEL: 0,00)

CTLA4 vad típus (AEL: 809,26),
- TMB-H driver (AEL: 803,92)

PARP1 vad típus (AEL: 165,38),
- BRCA1-K654fs*47 driver (AEL: 85,31) ;
- BRCA1-D430N driver (AEL: 0,00)

KIT vad típus (AEL: 121,53),
- KIT-E930Q driver (AEL: 14,13)

CHEK1 vad típus (AEL: 109,87),
- BRCA1-D430N driver (AEL: 0,00) ;
- BRCA1-K654fs*47 driver (AEL: 85,31) ;
- TP53-M160_A161dup driver (AEL: 22,52)

PARP2 vad típus (AEL: 85,41),
- BRCA1-K654fs*47 driver (AEL: 85,31) ;
- BRCA1-D430N driver (AEL: 0,00)

WEE1 vad típus (AEL: 26,32),
- TP53-M160_A161dup driver (AEL: 22,52)

ATR vad típus (AEL: 23,86),
- TP53-M160_A161dup driver (AEL: 22,52)

CDK4 vad típus (AEL: 23,50),
- TP53-M160_A161dup driver (AEL: 22,52)

RARG vad típus (AEL: 23,41),
- TP53-M160_A161dup driver (AEL: 22,52)

PLK1 vad típus (AEL: 23,00),
- TP53-M160_A161dup driver (AEL: 22,52)

PRKDC vad típus (AEL: 22,92),
- TP53-M160_A161dup driver (AEL: 22,52)

CDK1 vad típus (AEL: 22,85),
- TP53-M160_A161dup driver (AEL: 22,52)

CDK9 vad típus (AEL: 22,85),
- TP53-M160_A161dup driver (AEL: 22,52)

CDK2 vad típus (AEL: 22,85),
- TP53-M160_A161dup driver (AEL: 22,52)

AURKB vad típus (AEL: 22,80),
- TP53-M160_A161dup driver (AEL: 22,52)

BRD4 vad típus (AEL: 18,23),
- KMT2C-C391* driver (AEL: 16,09)

JAK2 vad típus (AEL: 14,55),
- KIT-E930Q driver (AEL: 14,13)

glutaminase vad típus (AEL: 4,45),
- NFE2L2-G589D driver (AEL: 1,18)

PRKACA vad típus (AEL: 1,35),
- GNAS-P459R driver (AEL: 0,85)

ATM vad típus (AEL: 0,72)
- CUL3-R162fs*9 driver (AEL: 0,07)

MOLEKULÁRIS BIOLÓGIAI INTERPRETÁCIÓ

A tumor mutational burden (TMB) vizsgálat eredménye

A vizsgált mintában a szekvencia analízis (NGS) során kapott 1 megabázisra vonatkozó mutációk száma (TMB): 6,44. Az adatbázisunkban lévő kalkulált TMB értékek (n=585) eloszlása alapján az eseteink 90%-ában kaptunk ennél alacsonyabb TMB értéket.

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%. 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

TMB-High tripla negatív emlődaganat

A PEMBROLIZUMAB az FDA által törzskönyvezett magas TMB értékű, előrehaladott vagy metasztatikus, szolid tumorral rendelkező, felnőtt és gyermek betegek számára.

Az ATEZOLIZUMAB törzskönyvezett PD-L1 pozitív, irrezekábilis, lokálisan előrehaladott vagy metasztatikus tripla negatív emlődaganat (triple negative breast cancer, TNBC) indikációban nab-paclitaxellel kombinációban. Az IMpassion130 klinikai vizsgálat eredményei szerint az első vonalas nab-paclitaxel-hez adott atezolizumab kezelés a teljes betegpopuláción és a PD-L1 pozitív alcsoportban is szignifikánsan növelte a progressziómentes túlélést (progression-free survival, PFS). Teljes betegpopuláción a medián PFS az atezolizumab plusz nab-paclitaxel kombinációs karban 7,2 hónapnak, míg a placebo plusz nab-paclitaxel karban 5,5 hónapnak adódott (1). Ebben a tanulmányban nem vizsgálták a TMB sátuszt.

TNBC betegek között a neoadjuváns kemoterápiához adott durvalumab (PD-L1 gátló) 53%-ra emelte a teljes válaszadási arányt, a placebo + kemoterápia karban 44% volt ez az érték. A TMB-H betegcsoportban a betegek 58%-ánál figyeltek meg teljes patológiai válaszadást, míg a TMB-L (low) csoportban ez az érték 38% volt (2).

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MOLEKULÁRIS BIOLÓGIAI INTERPRETÁCIÓ

Egy fázis Ib klinikai vizsgálatban előrehaladott, TNBC betegeket kezeltek első vonalban ipatasertib, atezolizumab és kemoterápia kombinációjával. A vizsgálat előzetes eredményei szerint a betegek 73%-ánál értek el teljes vagy részleges választ, biomarker státusztól függetlenül (3).

Fázis II vizsgálatban magas TMB értékkel előrehaladott emlődaganatos betegek vettek részt. A válaszadási arány 21% volt, a medián PFS 10,6 hét, a medián teljes túlélés (overall survival, OS) 31,6 hét (4).

Referenciák:

(1) Schmid P et al., Atezolizumab and Nab-Paclitaxel in Advanced Triple-Negative Breast Cancer. N Engl J Med. 2018 Nov 29;379(22):2108-2121. Epub 2018 Oct 20. PubMed PMID: 30345906

(2) Sibylle Loibl et al., Exome analysis of oncogenic pathways and tumor mutational burden (TMB) in triple-negative breast cancer (TNBC): Results of the translational biomarker program of the neoadjuvant double-blind placebo controlled GeparNuevo trial. J Clin Oncol 37, 2019 (suppl; abstr 509)

(3) firstwordpharma.com/node/1632490

(4) Alva AS 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.

PD-L1 overexpresszió

A PD-L1 overexpresszió több tumortípusban összefüggést mutat a PD-1 és PD-L1 gátló immunterápiák hatékonyságával (1, 2).
Forgalomban lévő PD-1 vagy PD-L1 gátló hatóanyagok a NIVOLUMAB, PEMBROLIZUMAB, AVELUMAB, DURVALUMAB, ATEZOLIZUMAB és a CEMIPLIMAB.

Referenciák:

(1) Patel SP, Kurzrock R. PD-L1 Expression as a Predictive Biomarker in Cancer Immunotherapy. Mol Cancer Ther. 2015 Apr;14(4):847-56. doi: 10.1158/1535-7163.MCT-14-0983. Epub 2015 Feb 18. Review. PubMed PMID: 25695955.

(2) Herbst RS et al., Predictive correlates of response to the anti-PD-L1 antibody MPDL3280A in cancer patients. Nature. 2014 Nov 27;515(7528): 563-7. doi: 10.1038/nature14011. PubMed PMID: 25428504

PD-L1 overexpresszált tripla negatív emlődaganat

A PD-L1 overexpresszió több tumortípusban összefüggést mutat a PD-1 és PD-L1 gátló immunterápiák hatékonyságával (1, 2).
Egy tanulmányban tripla negatív emlődaganatos (triple negative breast cancer, TNBC) betegek 19%-ában (20/105) mutattak ki >5% feletti PD-L1 expressziót (3). TNBC betegek körében intenzíven kutatott terület az immunterápiák alkalmazása (4).
TNBC indikációban törzskönyvezett immunterápia az ATEZOLIZUMAB és a PEMBROLIZUMAB (csak az FDA által).

Az ATEZOLIZUMAB (PD-L1 inhibitor) nab-paclitaxellel (nanorészecske albumin-kötött paclitaxel) kombinációban törzskönyvezett PD-L1 pozitív, irreszekábilis, lokálisan előrehaladott vagy metasztatikus TNBC betegek számára. Az IMpassion130 klinikai vizsgálat eredményei szerint a PD-L1 pozitív betegeknél a medián progressziómentes túlélés (progression-free survival, PFS) az atezolizumab plusz nab-paclitaxel kombinációs karban 7,5 hónapnak, míg a placebo plusz nab-paclitaxel karban 5,0 hónapnak adódott. A PD-L1 pozitív alcsoportban atezolizumab plusz nab-paclitaxel karban az esetek 59%-ában, míg a placebo plusz nab-paclitaxel karban az esetek 47%-ában értek el teljes vagy részleges választ. A teljes betegcsoporton a medián PFS és 7,2 hónap és 5,5 hónap, a medián teljes túlélés (overall survival; OS) 21,0 és 18,7 hónap, az objektív válaszadási ráta (objective response rate; ORR) 56% és 45,9% volt az atezolizumab és a placebo karban (5, 6).
Az IMpassion031 fázis III vizsgálat előzetes eredményei alapján az atezolizumab kombinálva nab-paclitaxellel majd doxorubicin+cyclophosphamide kemoterápiával (A-kemo) kedvezőbb patológiai teljes választ eredményezett a placebo és nab-paclitaxel majd kemoterápia (P-kemo) kombinációhoz képest előzetesen nem kezelt, korai stádiumú TNBC betegek körében, PD-L1 státusztól függetlenül (7).
Az IMpassion131 fázis III vizsgálat előzetes eredményei alapján az atezolizumab és paclitaxel kombináció nem eredményezett szignifikáns PFS és OS előnyt a placebo+paclitaxel terápiához képest elsővonalas kezelésként TNBC betegek számára (8).
Egy fázis I vizsgálatban (NCT01375842) metasztatikus TNBC betegek (n=112) részesültek atezolizumab terápiában. Az 1 éves OS ráta 45% volt a magas PD-L1 expressziójú tumor-infiltráló immunsejtekkel rendelkező betegek esetén és 37% a PD-L1-et alacsony szinten vagy nem expresszáló betegek között. A válaszadási ráta rendre 13% és 5% volt (9).
Egy fázis Ib klinikai vizsgálatban előrehaladott, TNBC betegeket kezeltek első vonalban ipatasertib, atezolizumab és kemoterápia kombinációjával. A vizsgálat előzetes eredményei szerint a betegek 73%-ánál értek el teljes vagy részleges választ, biomarker státusztól függetlenül (10).

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MOLEKULÁRIS BIOLÓGIAI INTERPRETÁCIÓ

Egy fázis Ib vizsgálatban (JAVELIN, NCT01772004), az avelumab (PD-L1 gátló) kezelés hatékonyságát tanulmányozták PD-L1 státusz alapján nem előszelektált, többszörösen előkezelt, metasztatikus emlődaganatos betegek (n=168) között. Az ORR a teljes csoportban 3,0% volt, a TNBC betegek (n=58) alcsoportjában 5,2%. Az ORR pozitív trendet mutatott a tumor asszociált immunsejtek PD-L1 expressziójával, TNBC betegek esetén 22,2% és 2,6% volt PD-L1 pozitív és negatív esetben (11).

A PEMBROLIZUMAB (PD-1 inhibitor) az FDA által törzskönyvezett kemoterápiával kombinációban PD-L1 pozitív (10%), előrehaladott TNBC betegek számára. A törzskönyv alapjául a fázis III KEYNOTE-355 vizsgálat szolgált, melyben a pembrolizumab vagy placebó és kemoterápia kombinációt hasonlították össze. A 10%-nál magasabb PD-L1 expresszióval rendelkező TNBC betegek alcsoportjában a medián PFS 9,7 hónap volt a pembrolizumab karban (n=220) és 5,6 hónap a placebo karban (n=103). PD-L1 státusztól függetlenül a medián PFS 7,5 hónap volt a pembrolizumab-karban (n=566), és 5,6 hónap a placebo-karban (n=281) (12).
Egy fázis II vizsgálatban (KEYNOTE-086, NCT02447003) a pembrolizumab (PD-1 inhibitor) hatékonyságát tanulmányozták előzetesen kezelt metasztatikus TNBC betegek között (kohort A). Az ORR 5,5% körüli értékű volt PD-L1 expressziótól függetlenül. A medián PFS 2,0 hónap, a medián OS 9,0 hónap volt, a 6-hónapos PFS és OS ráta rendre 14,9% és 69,1% volt (13).

Referenciák:

(1) Patel SP, Kurzrock R. PD-L1 Expression as a Predictive Biomarker in Cancer Immunotherapy. Mol Cancer Ther. 2015 Apr;14(4):847-56. Epub 2015 Feb 18. Review. PubMed PMID: 25695955

(2) Herbst RS et al., Predictive correlates of response to the anti-PD-L1 antibody MPDL3280A in cancer patients. Nature. 2014 Nov 27;515(7528): 563-7. PubMed PMID: 25428504

(3) Mittendorf EA et al., PD-L1 expression in triple-negative breast cancer. Cancer Immunol Res. 2014 Apr;2(4):361-70. PubMed PMID: 24764583

(4) Stagg J, Allard B. Immunotherapeutic approaches in triple-negative breast cancer: latest research and clinical prospects. Ther Adv Med Oncol. 2013 May;5(3):169-81. PubMed PMID: 23634195

(5) Schmid P et al., Atezolizumab and Nab-Paclitaxel in Advanced Triple-Negative Breast Cancer. N Engl J Med. 2018 Nov 29;379(22):2108-2121. Epub 2018 Oct 20. PubMed PMID: 30345906

(6) Emens LA et al., IMpassion130: Final OS analysis from the pivotal phase III study of atezolizumab + nab-paclitaxel vs placebo + nab-paclitaxel in previously untreated locally advanced or metastatic triple-negative breast cancer. Annals of Oncology. 2020;31(suppl_4):S1142-S1215. doi: 10.1016/annonc/annonc325.

(7) Mittendorf EA et al., 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:S0140-6736(20)31953-X. PMID: 32966830

(8) Miles DW et al., Primary results from IMpassion131, a double-blind placebo-controlled randomised phase III trial of first-line paclitaxel (PAC) ± atezolizumab (atezo) for unresectable locally advanced/metastatic triple-negative breast cancer (mTNBC). Annals of Oncology. 2020;31(suppl_4): S1142-S1215. doi: 10.1016/annonc/annonc325.

(9) Schmid P et al., Atezolizumab in metastatic TNBC (mTNBC): Long-term clinical outcomes and biomarker analyses [abstract]. In: Proceedings of the American Association for Cancer Research Annual Meeting 2017; 2017 Apr 1-5; Washington, DC. Philadelphia (PA): AACR; Cancer Res 2017; 77(13 Suppl):2986. doi:10.1158/1538-7445.AM2017-2986.

(10) Schmid P et al., Abstract CT049: Phase Ib study evaluating a triplet combination of ipatasertib (IPAT), atezolizumab (atezo), and paclitaxel (PAC) or nab-PAC as first-line (1L) therapy for locally advanced/metastatic triple-negative breast cancer (TNBC). 2019.

(11) Dirix LY et al., Avelumab, an anti-PD-L1 antibody, in patients with locally advanced or metastatic breast cancer: a phase 1b JAVELIN Solid Tumor study. Breast Cancer Res Treat. 2018 Feb;167(3):671-686. doi: 10.1007/s10549-017-4537-5. Epub 2017 Oct 23. PMID: 29063313

(12) Cortes J et al., Pembrolizumab plus chemotherapy versus placebo plus chemotherapy for previously untreated locally recurrent inoperable or metastatic triple-negative breast cancer (KEYNOTE-355): a randomised, placebo-controlled, double-blind, phase 3 clinical trial. Lancet. 2020 Dec 5;396(10265):1817-1828. PMID: 33278935

(13) Adams S et al., Pembrolizumab monotherapy for previously treated metastatic triple-negative breast cancer: cohort A of the phase II KEYNOTE-086 study. Ann Oncol. 2019 Mar 1;30(3):397-404. doi: 10.1093/annonc/mdy517. PMID: 30475950

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.
Az eredmény alapján feltételezhető kópiaszám-növekedést okozó genetikai eltérés jelenléte. Daganatképződéssel összefüggésbe hozható gének, melyek feltehetően magasabb kópiaszámban vannak jelen, a z FGFR1, CCNE1, RHPN2, CEBPA (n=8), TACC1 (n=7), ZNF703, BRCA1 (n=5).

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Az NGS vizsgálat által detektált kópiaszám-változásokat klinikai relevancia esetében FISH vizsgálattal is javasoljuk megvizsgálni. A kizárólag NGS-sel detektált kópiaszám-változások rutinszerűen nem szerepelnek a molekuláris profilban listázott azon variánsok között, amelyeket a digitális terápiatervezés figyelembe vesz. Az FGFR1 gén FISH vizsgálata folyamatban van.

FGFR1 amplifikáció emlődaganatban

Az FGFR1 amplifikáció ismert onkogenikus genetikai elváltozás emlőrákban. Egy tanulmányban a 880 vizsgált emlőtumor 8,7%-a mutatott FGFR1 amplifikációt. Az ösztrogénreceptor pozitív betegek között az FGFR1 amplifikáció rosszabb prognózissal korrelált (1).
Egy meta-analízis eredménye szerint az FGFR1 amplifikáció rövidebb betegségmentes túléléssel is korrelál (2).
FGFR1 amplifikáció esetén az FGFR1 gátló gyógyszerek lehetnek hatékonyak (3). Törzskönyvezett multi-tirozin kináz gátlószerek, amelyek többek között az FGFR jelpályát is gátolják a LENVATINIB, a NINTEDANIB, a PAZOPANIB, a REGORAFENIB és a PONATINIB, illetve kevésbé specifikusak a SORAFENIB és a SUNITINIB. FDA által urotheliális daganatok indikációjában elfogadott FGFR gátló hatóanyag az ERDAFITINIB.

Egy fázis I/IIa vizsgálatban 12 FGF aberrációval rendelkező előrehaladott emlőrákos beteg részesült LUCITANIB (fejlesztés alatt álló FGFR gátló hatóanyag) kezelésben. 6 beteg mutatott részleges tumorválaszt, és 6 betegnél írtak le stabil betegséget a kezelés hatására. A medián progressziómentes túlélés 40,4 hét volt (4). Egy fázis II vizsgálatban 178 metasztatikus emlődaganatos beteg részesült lucitanib kezelésben. A teljes válaszadási arány 3% volt, és nem írtak le különbséget a kezelés hatékonyságában az FGF aberrációk alapján (5). Egy másik lucitanibet tesztelő fázis II vizsgálatban (NCT02053636) 76 HR pozitív, HER2 negatív metasztatikus emlő carcinomás beteget vizsgáltak. A klinikai előny (azaz a teljes és részleges válaszadás, illetve a 24 hétnél hosszabb stabil betegség összesített aránya) 41% volt az FGFR1 amplifikált betegek esetén. A teljes válaszadási arány az FGFR1 erősen amplifikált páciensek esetében 25%, míg a gyengén amplifikált betegeknél 8% volt (6).

A DOVITINIB, fejlesztés alatt álló FGFR gátló hatóanyag, fázis II vizsgálatban 25%-os válaszadási arányt eredményezett FGFR1 amplifikált HR+ emlőrákos betegek körében, míg FGFR negatív HR+ emlőrákos betegek között a válaszadási arány 3% volt (7).

FGFR1 amplifikációt hordozó, emlőtumorból származó preklinikai modellekkel végzett kísérletekben specifikus FGFR1 gátlószerek (a ponatinib, illetve a klinikai fejlesztés alatt álló brivanib) aktivitást mutattak (8, 9). Kevésbé specifikus, az FGFR több típusát blokkoló tirozin kináz inhibitorok csökkentették az olyan emlő eredetű sejtvonalak osztódását, amelyekben a FGFR jelpálya aktiválódott, és ugyanezek a szerek hatástalanok voltak az aktiválódott jelátviteli útvonal jelenléte nélkül (9, 10).

Referenciák:

(1) Elbauomy ES et al., FGFR1 amplification in breast carcinomas: a chromogenic in situ hybridisation analysis. Breast Cancer Res. 2007;9(2):R23. PubMed PMID: 17397528

(2) Chang J et al., Prognostic Value of FGFR Gene Amplification in Patients with Different Types of Cancer: A Systematic Review and Meta-Analysis. PLOS ONE. 2014 Aug 29;9(8):e105524. PubMed PMID: 25171497

(3) Brady N et al., The FGF/FGFR axis as a therapeutic target in breast cancer. Expert Rev Endocrinol Metab. 2013 Jul;8(4):391–402. PubMed PMID: 25400686

(4) Soria J-C et al., Phase I/IIa study evaluating the safety, efficacy, pharmacokinetics, and pharmacodynamics of lucitanib in advanced solid tumors. Ann Oncol. 2014 Nov 1;25(11):2244–51. PubMed PMID: 25193991

(5) Mayer IA et al., A phase 2 open-label study of lucitanib in patients (pts) with FGF aberrant metastatic breast cancer (MBC). Cancer Res. 2017 Feb 15;77(4 Supplement):P6-11-03-P6-11-03.

(6) Hui R et al., Lucitanib for the Treatment of HR+/HER2- Metastatic Breast Cancer: Results from the Multicohort Phase II FINESSE Study. Clin Cancer Res. 2020 Jan 15;26(2):354-363. Epub 2019 Oct 16. PMID: 31619444

(7) André F et al., Targeting FGFR with Dovitinib (TKI258): Preclinical and Clinical Data in Breast Cancer. Clin Cancer Res. 2013 Jul 1;19(13):3693–702. PubMed PMID: 23658459

(8) Medina RL et al., Phase I trial of the combination of the multikinase inhibitor nintedanib plus letrozole: A window of opportunity trial in adjuvant hormone-receptor positive breast cancer (HRPBC). JCO. 2016 May 20;34(15_suppl):TPS615-TPS615.

(9) Gozgit JM et al., Ponatinib (AP24534), a Multitargeted Pan-FGFR Inhibitor with Activity in Multiple FGFR-Amplified or Mutated Cancer Models, Mol Cancer Ther. 2012;11(3):690-9 PubMed PMID: 22238366

(10) Shiang CY et al., Amplification of fibroblast growth factor receptor-1 in breast cancer and the effects of brivanib alaninate, Breast Cancer Res Treat. 2010;123(3):747-55 PubMed PMID: 20024612

CCNE1 amplifikáció

A CCNE1 által kódolt cyclin E1, a G1-S fázistranzíciót irányítja a ciklin-dependens kináz 2 (CDK2) fehérjével komplexet képezve, és fontos szerepet játszik a sejtciklus szabályozás, DNS replikáció és kromoszóma szegregáció folyamatában (1).

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MOLEKULÁRIS BIOLÓGIAI INTERPRETÁCIÓ

A tudományos irodalom alapján a CCNE1 kópiaszám-növekedés és overexpresszió rossz prognózissal asszociált különböző daganattípusokban, különösen tripla-negatív emlőtumorok (TNBC) esetén (1-3). A CCNE1 amplifikáció TP53-mutáns gyomordaganatban májáttéttel asszociált egy tanulmány szerint (4).

CCNE1 amplifikáció esetén a CDK-k és a WEE1 említhetők pozitív asszociációban, mint indirekt targetek (5).

A CDK2 és pan-CDK gátlók ugyan ígéretesnek tűntek preklinikai kísérletekben CCNE1 amplifikáció esetén, azonban nem jutottak túl fázis II vizsgálatokon monoterápiaként az off-target gátlás okozta mellékhatások miatt. Jelenleg a CDK2 inhibitorokat PI3K inhibitorokkal vagy kemoterápiával kombinációban tanulmányozzák (5).

Egy tanulmányban a ciklin-E1 overexpressziója növelte a WEE1 aktivitást, CDK2-függő módon aktiválta a DNS replikációs stressz útvonalakat, és érzékenyítette a TNBC-s sejtvonalakat az adavosertib WEE1 inhibitorra (3).

Megnövekedett CCNE1 kópiaszámú ovarium tumoros sejtvonalak proliferációját gátolta, migrációját, kolóniaformáló képességét csökkentette DINACICLIB és az SDHA inhibitor 3NPA kombinációja egy preklinikai vizsgálat során (6).

Egy preklinikai vizsgálat során PARP+ATR inhibitorok kombinációja CCNE1 amplifikált, PARPi- és platina-rezisztes ovárium daganat xenograft modellekben teljes terápiás választ és tumor regressziót eredményezett (7).

Referenciák:

(1) Zhao H et al., Prognostic Values of CCNE1 Amplification and Overexpression in Cancer Patients: A Systematic Review and Meta-analysis. J Cancer. 2018 Jun 14;9(13):2397-2407. PMID: 30026836

(2) Zhao ZM et al., CCNE1 amplification is associated with poor prognosis in patients with triple negative breast cancer. BMC Cancer. 2019 Jan 21; 19(1):96. PMID: 30665374

(3) Chen X et al., Cyclin E Overexpression Sensitizes Triple-Negative Breast Cancer to Wee1 Kinase Inhibition. Clin Cancer Res. 2018 Dec 15;24 (24):6594-6610. Epub 2018 Sep 4. PMID: 30181387

(4) Kim B et al., CCNE1 amplification is associated with liver metastasis in gastric carcinoma. Pathol Res Pract. 2019 Aug;215(8):152434. Epub 2019 May 4. PMID: 31178228

(5) Gorski JW et al., CCNE1 Amplification as a Predictive Biomarker of Chemotherapy Resistance in Epithelial Ovarian Cancer. Diagnostics (Basel). 2020 May 5;10(5):279. PMID: 32380689

(6) Guo T et al., Inhibition of succinate dehydrogenase sensitizes cyclin E-driven ovarian cancer to CDK inhibition. Biofactors. 2016;42(2):171-178. PMID: 26826064

(7) Kim H et al., Combining PARP with ATR inhibition overcomes PARP inhibitor and platinum resistance in ovarian cancer models. Nat Commun. 2020 Jul 24;11(1):3726. PMID: 32709856

TACC1 kópiaszám-nyerés

A TACC1 fehérjéről egérmodellekben kimutatták, hogy onkogenikus tulajdonságaival hozzájárulhat az emlődaganatok kialakulásához (1). Prosztatadaganatokban a TACC1 gén expressziós szintje az androgén-független stádiummal asszociált (2).

Referenciák:

(1) Cully M et al., Transforming acidic coiled coil 1 promotes transformation and mammary tumorigenesis. *Cancer Res. 2005 Nov 15; 65(22):10363-70.*

(2) Devilard E et al., FGFR1 and WT1 are markers of human prostate cancer progression. BMC Cancer 6, 272 (2006) doi:10.1186/1471-2407-6-272

ZNF703 kópiaszám-nyerés

A ZNF703 proto-onkogén emelkedett kópiaszáma overexpresszióval és rosszabb klinikai kimenetellel asszociál (1, 2). A ZNF703 overexpresszió jellemző luminal B típusú (hormon receptor pozitív) emlő daganatokban. Overexpressziója esetén az AKT/mTOR útvonal aktivációja és az ERalfa csökkent működése figyelhető meg (3, 4). Feltehetően hozzájárulhat tamoxifen hormonkezeléssel szemben való rezisztencia kialakulásához (3). mTOR gátló hatóanyag alkalmazása növelte a ZNF703 overexpresszáló sejtek érzékenységét tamoxifennel szemben (3). Preklinikai vizsgálatban az AKT inhibitor MK2206 és a PI3K inhibitor LY294002 egyaránt csökkentette a ZNF703 overexpresszáló sejtek proliferációját (4).

Referenciák:

(1) Holland DG et al,. ZNF703 is a common Luminal B breast cancer oncogene that differentially regulates luminal and basal progenitors in human mammary epithelium. EMBO Mol Med. 2011 Mar;3(3):167-80. doi: 10.1002/emmm.201100122. Epub 2011 Feb 18. PMID: 21337521

(2) Sircoulomb F et al., ZNF703 gene amplification at 8p12 specifies luminal B breast cancer. EMBO Mol Med. 2011 Mar;3(3):153-66. doi: 10.1002 /emmm.201100121. Epub 2011 Feb 15. PMID: 21328542

(3) Zhang X et al., Luminal breast cancer cell lines overexpressing ZNF703 are resistant to tamoxifen through activation of Akt/mTOR signaling. PLoS One. 2013 Aug 26;8(8):e72053. doi: 10.1371/journal.pone.0072053. eCollection 2013. PMID: 23991038

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(4) Wang H et al., Elevated Expression of Zinc Finger Protein 703 Promotes Cell Proliferation and Metastasis through PI3K/AKT/GSK-3 Signalling in Oral Squamous Cell Carcinoma. Cell Physiol Biochem. 2017;44(3):920-934. doi: 10.1159/000485360. Epub 2017 Nov 24. PMID: 29176314

Az újgenerációs szekvenálás (NGS) eredménye

591 gén NGS szekvenálása 5103 genetikai variánst mutatott ki a mintában. A molekuláris profilba feltöltött 34 variáns bioinformatikai és funkcionális szűrések eredményeként került kiválasztásra. Ezek a variánsok szerepelnek a Realtime Oncology Calculatorban további funkcionális interpretáció és orvosi döntéstámogatás céljából.

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).

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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.

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.

BRCA1-K654fs*47

Ez a mutáció a ClinVar és a BRCA Exchance adatbázisok és a tudományos irodalom (1) szerint patogén. Szerepel a COSMIC adatbázisban is. A leolvasási kereteltolódást okozó mutáció (frameshift mutation) a BRCA1 gén nonsense-mediated decay (NMD) rezisztens pozícióját érinti, ezért nagy valószínűséggel az NMD folyamat nem vezet a mutáns mRNS lebomlásához (1). A mutáns génről egy csonka fehérjeváltozat képződik, ezért feltételezhető, hogy funkcióvesztéssel jár.

Referenciák:

(1) Li J, et al, Bajalica-Lagercrantz S, Dunning AM, Decker B, Allen J, Luccarini C, Pooley K, Simard J, Dorling L, Easton DF, Teo SH, Hall P, Borg Å, Grönberg H, Czene K. Prevalence of BRCA1 and BRCA2 pathogenic variants in a large, unselected breast cancer cohort. Int J Cancer. 2019 03 01;144(5):1195-1204. doi: 10.1002/ijc.31841. Epub 2018 Mar 09. PubMed PMID: 30175445.

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

BRCA mutáns gén - célpontok

BRCA inaktiváció esetén a PARP inhibitorok említhetőek pozitív asszociációban (1, 2). Forgalomban lévő PARP gátló gyógyszerek az OLAPARIB, RUCAPARIB, NIRAPARIB és a TALAZOPARIB.
Egy meta-analízis szerint BRCA mutáns szolid daganatos betegek között az olaparib kezelés szignifikáns túlélési előnyt jelentett (3).
Ovárium daganatokban írták le, hogy BRCA mutáció esetén a PD-1/PD-L1 gátló immunterápiától is emelkedett hatékonyság várható (4, 5).
Emlő- és pancreas daganatokban leírták már, hogy a BRCA mutáns tumorok jól reagálnak platina-alapú terápiára (6-8).

Referenciák:

(1) Farmer H et al.,Targeting the DNA repair defect in BRCA mutant cells as a therapeutic strategy. Nature. 2005 Apr 14;434(7035):917-21. PubMed PMID: 15829967

(2) Livraghi L, Garber JE. PARP inhibitors in the management of breast cancer: current data and future prospects. BMC Med. 2015 Aug 13;13:188. Review. PubMed PMID: 26268938

(3) Guo XX et al., The efficacy and safety of olaparib in the treatment of cancers: a meta-analysis of randomized controlled trials. Cancer Manag Res. 2018 Aug 10;10:2553-2562. eCollection 2018. PubMed PMID: 30127642

(4) Strickland KC et al., Association and prognostic significance of BRCA1/2-mutation status with neoantigen load, number of tumor-infiltrating lymphocytes and expression of PD-1/PD-L1 in high grade serous ovarian cancer. Oncotarget. 2016 Mar 22;7(12):13587-98. PubMed PMID: 26871470

(5) Matsuo K et al., Nivolumab use for BRCA gene mutation carriers with recurrent epithelial ovarian cancer: A case series. Gynecol Oncol Rep. 2018 Jun 20;25:98-101. eCollection 2018 Aug. PubMed PMID: 29998185

(6) Byrski T et al., Cisplatin chemotherapy in the treatment of BRCA1-positive metastatic breast cancer (MBC). Journal of Clinical Oncology, 2009, 27.15_suppl: 1099-1099.

(7) Golan T et al., Overall survival and clinical characteristics of pancreatic cancer in BRCA mutation carriers. Br J Cancer. 2014 Sep 9;111(6):1132-8. Epub 2014 Jul 29. PubMed PMID: 25072261

(8) Byrski T et al., Pathologic complete response rates in young women with BRCA1-positive breast cancers after neoadjuvant chemotherapy. J Clin Oncol. 2010 Jan 20;28(3):375-9. Epub 2009 Dec 14. PubMed PMID: 20008645

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BRCA mutáció emlődaganatban

Csíravonalas BRCA mutáció esetén HER2 negatív emlődaganatos betegek részére törzskönyvezett PARP gátló gyógyszer az OLAPARIB és a TALAZOPARIB. Mindkét gyógyszer neoadjuváns/adjuváns/metasztatikus vonalban alkalmazott kemoterápia után adható. Hormonreceptor pozitív betegeknél az előzetes hormonkezelés is szükséges.

Fázis III vizsgálatban HER2 negatív, deleterious vagy likely deleterious csíravonalas BRCA mutációt hordozó emlődaganatos betegeket kezeltek olaparibbal, vagy az orvos választása szerinti hatóanyaggal (treatment of physician's choice, PCT). Az objektív válaszadási arány (objective response rate, ORR) 59,9% volt az olaparib kezelésben részesülő csoportnál és 28,8% az egyéb kezelést kapó betegek körében. A medián progresszió mentes túlélés (progression-free survival, PFS) rendre 7,0 és 4,2 hónap volt az olaparibot és az egyéb kezelés kapó betegek csoportjában. Az olaparib kezelés hormonreceptor pozitív és negatív betegek körében is hatékonyabbnak bizonyult a standard kezelésnél (1).

Fázis III vizsgálatban a talazoparib monoterápia 8,6 hónapos PFS-t eredményezett BRCA mutáns előrehaladott emlőrákos betegek között, míg standard kemoterápia kezelés esetén a medián PFS 5,6 hónap volt. Az ORR 62,6% volt a talazoparib karon, 27,2% a kemoterápia karon (2).

Egy fázis III klinikai vizsgálatban HER2-negatív, csíravonalas BRCA1/2 mutációkat hordozó, előrehaladott emlődaganatos betegek talazoparib kezelést, vagy a kezelőorvos által választott kemoterápiát (PCT) kaptak. A talazoparib esetében statisztikailag szignifikáns becsült általános javulást tapasztaltak a kiindulási állapothoz képest a globális egészségi állapotban / életminőségben (GHS / QoL), szemben a PCT statisztikailag szignifikáns romlásával (3,0 és -5,4). A talazoparib hatására statisztikailag szignifikánsan nagyobb késést figyeltek meg a GHS / QoL végleges klinikailag jelentős romlásáig a PCT-hez viszonyítva (medián 24,3, illetve 6,3 hónap) (3).

Egy fázis II-es klinikai vizsgálatban BRCA1/2 mutációkat hordozó, előrehaladott emlődaganatos betegek talazoparib kezelést kaptak. Az ORR a BRCA1 (1-es csoport), illetve BRCA2 (2-es csoport) mutációkat hordozó betegeknél 23%-nak, valamint 33%-nak adódott. Tripla-negatív emlődaganatos és hormon-receptor pozitív betegek esetén az ORR 26% és 29% volt. A medián PFS és OS az 1-es csoportban 4 és 12,7 hónap, a 2-es csoportban 5,6 és 14,7 hónap volt (4).

Egy fázis I-es klinikai vizsgálatban 14 emlő-, és 12 ováriumdaganatos, csíravonalas BRCA1/2 mutációkat hordozó beteg talazoparib kezelést kapott. Az emlődaganatos betegeknél az ORR 50%-nak adódott. Egy betegnél teljes válaszadást, 6-nál részleges válaszadást, 5-nél pedig stabil betegséget figyeltek meg. A klinikai hasznosulási arány 86%-os volt, a medián PFS 34,6 hétnek adódott. Az ováriumdaganatos betegeknél az ORR 42%, a klinikai hasznosulási arány pedig 67%-os volt. Egy betegnél komplett választ, 6-nál részleges választ, 5-nél stabil betegséget figyeltek meg. A medián PFS 36,4 hétnek bizonyult (5).

Egy fázis I-es klinikai vizsgálatban 19 emlődaganatos, csíravonalas BRCA1/2 mutációkat hordozó beteg neoadjuváns talazoparib kezelést kapott. 10 betegnél RCB-0-t (RCB-0 = CR), 2-nél RCB-I-et, 5-nél RCB-II-t és 3-nál RCB-III-mat figyeltek meg. Az RCB-0/CR arány 53%, az RCB-0/I/CR arány 63% volt (6).

Fázis II vizsgálatban molekulárisan nem szelektált tripla negatív emlődaganatos betegek között a niraparib (PARP gátló) és a pembrolizumab (PD-1 gátló) kombinációja 21%-os válaszadási arányt és 49%-os betegség kontroll arányt eredményezett. A BRCA mutáns alcsoportban a válaszadási arány 47%, a betegség kontroll arány 80%, a medián progressziómentes túlélés 8,3 hónap volt. A BRCA vad típusú alcsoportban a válaszadási arány 11%, a betegség kontroll arány 33%, a medián progressziómentes túlélés 2,1 hónap volt (7).

Referenciák:

(1) Robson M et al., Olaparib for Metastatic Breast Cancer in Patients with a Germline BRCA Mutation. N Engl J Med. 2017 Aug 10;377(6):523-533. Epub 2017 Jun 4. Erratum in: N Engl J Med. 2017 Oct 26;377(17):1700. PMID: 28578601

(2) Drew Y et al., Phase 2 multicentre trial investigating intermittent and continuous dosing schedules of the poly(ADP-ribose) polymerase inhibitor rucaparib in germline BRCA mutation carriers with advanced ovarian and breast cancer. Br J Cancer. 2016 Mar 29;114(7):723-30. PMID: 27002934

(3) Ettl J et al., Quality of life with talazoparib versus physician's choice of chemotherapy in patients with advanced breast cancer and germline BRCA1/2 mutation: patient-reported outcomes from the EMBRACA phase III trial. Ann Oncol. 2018 Sep 1;29(9):1939-1947. PubMed PMID: 30124753

(4) Turner NC et al., A Phase II Study of Talazoparib after Platinum or Cytotoxic Nonplatinum Regimens in Patients with Advanced Breast Cancer and Germline BRCA1/2 Mutations (ABRAZO). Clin Cancer Res. 2019 May 1;25(9):2717-2724. Epub 2018 Dec 18. PubMed PMID: 30563931

(5) de Bono J et al., Phase I, Dose-Escalation, Two-Part Trial of the PARP Inhibitor Talazoparib in Patients with Advanced Germline BRCA1/2 Mutations and Selected Sporadic Cancers. Cancer Discov. 2017 Jun;7(6):620-629. Epub 2017 Feb 27. PubMed PMID: 28242752

(6) Litton JK et al., Neoadjuvant Talazoparib for Patients With Operable Breast Cancer With a Germline BRCA Pathogenic Variant. J Clin Oncol. 2019 Aug 28:JCO1901304. [Epub ahead of print] PubMed PMID: 31461380

(7) Vinayak S, Tet al. Open-Label Clinical Trial of Niraparib Combined With Pembrolizumab for Treatment of Advanced or Metastatic Triple-Negative Breast Cancer. JAMA Oncol. 2019 Jun 13;5(8):1132–40. doi: 10.1001/jamaoncol.2019.1029. Epub ahead of print. PMID: 31194225.

Frameshift mutációk

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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

KMT2C-C391*

A variánst több, mint 100 alkalommal szerepel a COSMIC adatbázisban. Az NCBI ClinVar mutációs adatbázisban nem található bejegyzés az alteráció pathogenitására vonatkozóan. Az alteráció az egyik PHD-ujj régióban található. A korai STOP kodon megjelenését eredményező mutáció (nonsense mutation) következtében egy jelentősen rövidebb fehérjeváltozatot kódoló KMT2C variáns jön létre, amelyről hiányoznak a FYR és a SET domének is. Ezért a mutáció valószínűleg a szubsztrátfelismerés hibájához vezet, és ezáltal a KMT2C metiltranszferáz funkciójának elvesztését eredményezi (1, 2). A LOVD adatbázisban azonban benignus, vélhetően benignus besorolással szerepel.

Referenciák:

(1) Yang B et al. Comprehensive analysis of age-related somatic mutation profiles in Chinese young lung adenocarcinoma patients. Cancer Med. 2019 04;8(4):1350-1358. doi: 10.1002/cam4.1839. Epub 2019 Nov 01. PubMed PMID: 30821106.

(2) Cho SJ et al. KMT2C Mutations in Diffuse-Type Gastric Adenocarcinoma Promote Epithelial-to-Mesenchymal Transition. Clin Cancer Res. 2018 Dec 15;24(24):6556-6569. doi: 10.1158/1078-0432.CCR-17-1679. Epub 2018 Aug 14. PubMed PMID: 30108106.

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MOLEKULÁRIS BIOLÓGIAI INTERPRETÁCIÓ

KMT2C mutáns gén - célpontok

A tumorszupresszor funkciójú hiszton metiltranszferáz KMT2C/MLL3 fehérje (1) funkcióvesztő mutációiról több daganattípusban leírták már, hogy hozzájárulhatnak a daganatképződéshez (2-4). MLL3 hiányos leukémia sejtek ellenállóak voltak hagyományos kemoterápiával szemben, de érzékenynek mutatkoztak a BET gátló JQ1 hatóanyagra (1).

Referenciák:

(1) Chen C et al. MLL3 is a haploinsufficient 7q tumor suppressor in acute myeloid leukemia. Cancer Cell. 2014 May 12;25(5):652-65. Epub 2014 May 1. PMID: 24794707

(2) Weirich S et al. Somatic cancer mutations in the MLL3-SET domain alter the catalytic properties of the enzyme. Clin Epigenetics. 2015 Mar 28; 7(1):36. PMID: 25829971

(3) Guo C et al. KMT2D maintains neoplastic cell proliferation and global histone H3 lysine 4 monomethylation. Oncotarget. 2013 Nov;4(11):2144-53. PMID: 24240169

(4) Fujimoto A et al. Whole-genome sequencing of liver cancers identifies etiological influences on mutation patterns and recurrent mutations in chromatin regulators. Nat Genet. 2012 May 27;44(7):760-4. PMID: 22634756

ZNF703-P307S

Ez a variáns alacsony frekvenciával szerepel a COSMIC adatbázisban (n<5). A tudományos irodalomban nem érhető el adat a funkcionális jelentőségéről.

GNAS-P459R

Ez a variáns alacsony frekvenciával szerepel a COSMIC adatbázisban (n<15). A SNPeffect adatbázis szerint a mutáció GNAS hiperfunkció megbetegedést (GNASHYP) okoz.

GNAS mutáns gén - célpontok

A GNAS egy proto-onkogén (1), de bizonyos tumortípusokban tumorszupresszor szerepét is leírták (2). Egy kontroll nélküli GNAS mutáns xenograft modellen végzett kísérlet alapján a GNAS génben detektált funkcióvesztő driver mutációval kapcsolatban említhető indirekt target a PKA (PKACA) (1), melynek inhibitorai jelenleg klinikai fejlesztés alatt állnak.

Referenciák:

(1) Ritterhouse LL, et al. Mod Pathol. 2017 Dec;30(12):1720-1727. doi: 10.1038/modpathol.2017.88. Epub 2017 Aug 4. PMID: 28776576.

(2) He X, et al. The G protein subunit Gs is a tumor suppressor in Sonic hedgehog-driven medulloblastoma. Nat Med. 2014 Sep;20(9):1035-42. doi: 10.1038/nm.3666. Epub 2014 Aug 24. PMID: 25150496; PMCID: PMC4334261.

(3) Dana Jean Steffen et al., GNAS-PKA Oncosignaling Network in Colorectal Cancer, April 2017The FASEB Journalvol. 31 no. 1 Supplementlb527

CUL3-R162fs*9

A leolvasási kereteltolódást okozó mutáció (frameshift mutation) következtében egy jelentősen rövidebb fehérjeváltozatot kódoló CUL3 variáns jön létre, így a funkcióvesztés nagymértékben valószínűsíthető.

CUL3 mutáns gén - célpontok

A CUL3 gén egy ubiquitin ligázt kódol. Funkcióvesztése TP53 mutáns sejtekben daganatképződéshez vezet. A TP53 és CUL3 együttes funkcióvesztése érzékenyít ATM gátló hatóanyagokra (1).

Referenciák:

(1) Drainas AP, et al. Genome-wide Screens Implicate Loss of Cullin Ring Ligase 3 in Persistent Proliferation and Genome Instability in TP53-Deficient Cells. Cell Rep. 2020 Apr 07;31(1):107465. doi: 10.1016/j.celrep.2020.03.029. PubMed PMID: 32268084.

ZNF703-A514del

A mutáció szerepel a COSMIC adatbázisban, azonban funkcionális jelentőségéről nem található adat a szakirodalomban.

TENT5C-E299K

Ez a variáns alacsony frekvenciával szerepel a COSMIC adatbázisban (n<15). A tudományos irodalomban nem érhető el adat a funkcionális jelentőségéről.

GAS6-V673fs*37

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MOLEKULÁRIS BIOLÓGIAI INTERPRETÁCIÓ

Ez az alteráció szerepel a COSMIC adatbázisban.. A leolvasási kereteltolódást okozó mutáció (frameshift mutation) következtében egy jelentősen rövidebb fehérjeváltozatot kódoló GAS6 variáns jön létre, így a funkcióvesztés nagymértékben valószínűsíthető.

KIT-M541L

A mutáció megtalálható a COSMIC adatbázisban. A szakirodalomban (1, 2), a ClinVar adatbázisban és az SNPEffect adatbázisban tumorigenikus hatás nélküli polimorfizmusként írják le, azonban összefüggésbe hozták gyermekkori mastocytosissal (3). Sejtvonalas evidenciák alapján az imatinib KIT-inhibitorra a vad típushoz képest nagyjából kétszeres, növekedett érzékenységet mutat (3). Öt krónikus eozinofil leukémiás beteget bevonó tanulmányban alacsony dózisú (100 mg/nap) imatinib kezelés mellett teljes remissziót tapasztaltak mind az 5 beteg esetében (a medián követési idő 74 hónap volt). A tanulmányba bevont betegek közül négy páciens KIT-M541L variánst hordozott, de egy esetben sem detektáltak olyan genetikai elváltozást, amely érzékenységet mutatna imatinib kezelés esetén (BCR/ABL1, FIP1L1/PDGFR, illetve JAK2 mutáció) (4).

Referenciák:

(1) Grabellus F et al. The prevalence of the c-kit exon 10 variant, M541L, in aggressive fibromatosis does not differ from the general population. J Clin Pathol. 2011 Nov;64(11):1021-4. PubMed PMID: 21757432

(2) Krüger S et al. The c-kit (CD117) sequence variation M541L, but not N564K, is frequent in the general population, and is not associated with CML in Caucasians. Leukemia. 2006;20(2):354-5; discussion 356-7. PubMed PMID: 16307017

(3) Foster R et al. Association of paediatric mastocytosis with a polymorphism resulting in an amino acid substitution (M541L) in the transmembrane domain of c-KIT. Br J Dermatol. 2008 Nov;159(5):1160-9. PubMed PMID: 18795925

(4) Alessandra Iurlo et al. Identification of kitM541L somatic mutation in chronic eosinophilic leukemia, not otherwise specified and its implication in low-dose imatinib response. Oncotarget. 2014 Jul; 5(13): 4665–4670. PubMed PMID: 25015329

Molekuláris profiltól függetlenül törzskönyvezett hatóanyagok emlődaganat indikációban

Az angiogenezis gátló hatóanyag BEVACIZUMAB törzskönyvezett emlő tumor indikációban.

Egy vizsgálat során 722 metasztatikus emlődaganatos betegben hasonlították össze a bevacizumab + paclitaxel kezelés és a paclitaxel monoterápia hatását (1). Egy másik vizsgálatban 1237 beteg esetében végeztek összehasonlítást a különböző kemoterápiás kezelésekkel (például capecitabine) kombinációban kapott bevacizumab illetve placebo hatása között (2). A vizsgálatok eredménye azt mutatta, hogy a bevacizumab adása növelte a progressziómentes túlélést (progression-free survival, PFS). A bevacizumab + paclitaxel kombináció esetében a PFS mediánja 11,4 hónap volt, szemben az önálló paclitaxel kezeléssel, ahol 5,8 hónapot mértek. A bevacizumabot capecitabine terápiával kombinálva a 8,6 hónapra nőtt a medián PFS a capecitabine + placebo kontroll csoportban megfigyelt 5,7 hónaphoz képest (2).

Referenciák:

(1) Miller K et al., Paclitaxel plus bevacizumab versus paclitaxel alone for metastatic breast cancer. N Engl J Med. 2007 Dec 27;357(26):2666-76. PubMed PMID: 18160686

(2) Robert NJ et al., RIBBON-1: randomized, double-blind, placebo-controlled, phase III trial of chemotherapy with or without bevacizumab for first-line treatment of human epidermal growth factor receptor 2-negative, locally recurrent or metastatic breast cancer. J Clin Oncol. 2011 Apr 1; 29(10):1252-60. Epub 2011 Mar 7. PubMed PMID: 21383283

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HATÓANYAG NEVE	REFERENCIA
PEMBROLIZUMAB	Robert C, Ribas A, Schachter J, Arance A, Grob JJ, Mortier L, Daud A, Carlino MS, McNeil CM, Lotem M, Larkin JMG, Lorigan P, Neyns B, Blank CU, Petrella TM, Hamid O, Su SC, Krepler C, Ibrahim N, Long GV. Pembrolizumab versus ipilimumab in advanced melanoma (KEYNOTE-006): post-hoc 5-year results from an open-label, multicentre, randomised, controlled, phase 3 study. Lancet Oncol. 2019 09;20(9):1239-1251. doi: 10.1016/S1470-2045(19)30388-2. Epub 2019 Jul 22. PubMed PMID: 31345627. 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. 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. 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 Fuchs CS, Doi T, Jang RW, Muro K, Satoh T, Machado M, Sun W, Jalal SI, Shah MA, Metges JP, Garrido M, Golan T, Mandala M, Wainberg ZA, Catenacci DV, Ohtsu A, Shitara K, Geva R, Bleeker J, Ko AH, Ku G, Philip P, Enzinger PC, Bang YJ, Levitan D, Wang J, Rosales M, Dalal RP, Yoon HH. Safety and Efficacy of Pembrolizumab Monotherapy in Patients With Previously Treated Advanced Gastric and Gastroesophageal Junction Cancer: Phase 2 Clinical KEYNOTE-059 Trial. JAMA Oncol. 2018 May 10;4(5):e180013. doi: 10.1001/jamaoncol.2018.0013. Epub 2018 May 10. PubMed PMID: 29543932; PubMed Central PMCID: PMC5885175.
ATEZOLIZUMAB	Rosenberg JE, Hoffman-Censits J, Powles T, van der Heijden MS, Balar AV, Necchi A, Dawson N, O'Donnell PH, Balmanoukian A, Loriot Y, Srinivas S, Retz MM, Grivas P, Joseph RW, Galsky MD, Fleming MT, Petrylak DP, Perez-Gracia JL, Burris HA, Castellano D, Canil C, Bellmunt J, Bajorin D, Nickles D, Bourgon R, Frampton GM, Cui N, Mariathasan S, Abidoye O, Fine GD, Dreicer R. Atezolizumab in patients with locally advanced and metastatic urothelial carcinoma who have progressed following treatment with platinum-based chemotherapy: a single-arm, multicentre, phase 2 trial. Lancet. 2016 May 7;387(10031):1909-20. doi: 10.1016/S0140-6736(16)00561-4. Epub 2016 Mar 4. PubMed PMID: 26952546; PubMed Central PMCID: PMC5480242. 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. Schmid P, Adams S, Rugo HS, Schneeweiss A, Barrios CH, Iwata H, Diéras V, Hegg R, Im SA, Shaw Wright G, Henschel V, Molinero L, Chui SY, Funke R, Husain A, Winer EP, Loi S, Emens LA, . Atezolizumab and Nab-Paclitaxel in Advanced Triple-Negative Breast Cancer. N Engl J Med. 2018 11 29;379(22):2108-2121. doi: 10.1056/NEJMoa1809615. Epub 2018 Sep 20. PubMed PMID: 30345906. 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. 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, 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.

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HATÓANYAG NEVE	REFERENCIA
AVELUMAB	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. 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. 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. Aguiar PN Jr, De Mello RA, Hall P, Tadokoro H, Lima Lopes G. PD-L1 expression as a predictive biomarker in advanced non-small-cell lung cancer: updated survival data. Immunotherapy. 2017 May;9(6):499-506. doi: 10.2217/imt-2016-0150. PubMed PMID: 28472902. Dirix LY, Takacs I, Jerusalem G, Nikolinakos P, Arkenau HT, Forero-Torres A, Boccia R, Lippman ME, Somer R, Smakal M, Emens LA, Hrinczenko B, Edenfield W, Gurtler J, von Heydebreck A, Grote HJ, Chin K, Hamilton EP. Avelumab, an anti-PD-L1 antibody, in patients with locally advanced or metastatic breast cancer: a phase 1b JAVELIN Solid Tumor study. Breast Cancer Res Treat. 2017 Oct 23. doi: 10.1007/s10549-017-4537-5. [Epub ahead of print] PubMed PMID: 29063313.
NIVOLUMAB	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. Zimmer L, Livingstone E, Hassel JC, Fluck M, Eigentler T, Loquai C, Haferkamp S, Gutzmer R, Meier F, Mohr P, Hauschild A, Schilling B, Menzer C, Kieker F, Dippel E, Rösch A, Simon JC, Conrad B, Körner S, Windemuth-Kieselbach C, Schwarz L, Garbe C, Becker JC, Schadendorf D, . Adjuvant nivolumab plus ipilimumab or nivolumab monotherapy versus placebo in patients with resected stage IV melanoma with no evidence of disease (IMMUNED): a randomised, double-blind, placebo-controlled, phase 2 trial. Lancet. 2020 05 16;395(10236):1558-1568. doi: 10.1016/S0140-6736(20)30417-7. PubMed PMID: 32416781. 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. http://ascopubs.org/doi/abs/10.1200/JCO.2017.35.4_suppl.2 Hamanishi J, Mandai M, Ikeda T, Minami M, Kawaguchi A, Murayama T, Kanai M, Mori Y, Matsumoto S, Chikuma S, Matsumura N, Abiko K, Baba T, Yamaguchi K, Ueda A, Hosoe Y, Morita S, Yokode M, Shimizu A, Honjo T, Konishi I. Safety and Antitumor Activity of Anti-PD-1 Antibody, Nivolumab, in Patients With Platinum-Resistant Ovarian Cancer. J Clin Oncol. 2015 Dec 1;33(34):4015-22. doi: 10.1200/JCO.2015.62.3397. Epub 2015 Sep 8. PubMed PMID: 26351349.
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 Aguiar PN Jr, De Mello RA, Hall P, Tadokoro H, Lima Lopes G. PD-L1 expression as a predictive biomarker in advanced non-small-cell lung cancer: updated survival data. Immunotherapy. 2017 May;9(6):499-506. doi: 10.2217/imt-2016-0150. PubMed PMID: 28472902. 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. Paz-Ares L, Spira A, Raben D, Planchard D, Cho BC, Özgüroğlu M, Daniel D, Villegas A, Vicente D, Hui R, Murakami S, Spigel D, Senan S, Langer CJ, Perez BA, Boothman AM, Broadhurst H, Wadsworth C, Dennis PA, Antonia SJ, Faivre-Finn C. Outcomes with durvalumab by tumour PD-L1 expression in unresectable, stage III non-small-cell lung cancer in the PACIFIC trial. Ann Oncol. 2020 Mar 21. pii: S0923-7534(20)36374-2. doi: 10.1016/j.annonc.2020.03.287. [Epub ahead of print] PubMed PMID: 32209338.

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HATÓANYAG NEVE	REFERENCIA
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. Tang B, Yan X, Sheng X, Si L, Cui C, Kong Y, Mao L, Lian B, Bai X, Wang X, Li S, Zhou L, Yu J, Dai J, Wang K, Hu J, Dong L, Song H, Wu H, Feng H, Yao S, Chi Z, Guo J. Safety and clinical activity with an anti-PD-1 antibody JS001 in advanced melanoma or urologic cancer patients. J Hematol Oncol. 2019 01 14;12(1):7. doi: 10.1186/s13045-018-0693-2. Epub 2019 Feb 14. PubMed PMID: 30642373; PubMed Central PMCID: PMC6332582.
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. Jianming Xu, Yi Li, Qingxia Fan, Yongqian Shu, Zhijun Wu, Tongjian Cui, Kangsheng Gu, Min Tao, Xiuwen Wang, Chengxu Cui, Nong Xu, Juxiang Xiao, Quanli Gao, Yunpeng Liu, Tao Zhang, Hui Zhou, Yan Wang, Linxinyu Xu, Zhuo Ma, Yanqi Wang. Sintilimab in patients with advanced esophageal squamous cell carcinoma refractory to previous chemotherapy: A randomized, open-label phase II trial (ORIENT-2). DOI: 10.1200/JCO.2020.38.15_suppl. 4511 Journal of Clinical Oncology 38, no. 15_suppl (May 20, 2020) 4511-4511.
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.
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.
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
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.
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
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.

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HATÓANYAG NEVE	REFERENCIA
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
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. Anantha RW, Simhadri S, Foo TK, Miao S, Liu J, Shen Z, Ganesan S, Xia B. Functional and mutational landscapes of BRCA1 for homology-directed repair and therapy resistance. Elife. 2017 Apr 11;6. pii: e21350. doi: 10.7554/eLife.21350. PubMed PMID: 28398198; PubMed Central PMCID: PMC5432210. 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. 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. 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.
TIRAGOLUMAB	Delvys Rodriguez-Abreu, Melissa Lynne Johnson, Maen A. Hussein, Manuel Cobo, Anjan Jayantilal Patel, Nevena Milica Secen, Ki Hyeong Lee, Bartomeu Massuti, Sandrine Hiret, James Chih-Hsin Yang, Fabrice Barlesi, Dae Ho Lee, Luis G. Paz-Ares, Robert Wenchen Hsieh, Karen Miller, Namrata Patil, Patrick Twomey, Amy V. Kapp, Raymond Meng, Byoung Chul Cho. Primary analysis of a randomized, double-blind, phase II study of the anti-TIGIT antibody tiragolumab (tira) plus atezolizumab (atezo) versus placebo plus atezo as first-line (1L) treatment in patients with PD-L1-selected NSCLC (CITYSCAPE). J Clin Oncol 38: 2020 (suppl; abstr 9503). doi: 10.1200/JCO.2020.38.15_suppl.9503.

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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.
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. http://www.ascopost.com/News/58335 Litton JK, Rugo HS, Ettl J, Hurvitz SA, Gonçalves A, Lee KH, Fehrenbacher L, Yerushalmi R, Mina LA, Martin M, Roché H, Im YH, Quek RGW, Markova D, Tudor IC, Hannah AL, Eiermann W, Blum JL. Talazoparib in Patients with Advanced Breast Cancer and a Germline BRCA Mutation. N Engl J Med. 2018 Aug 23;379(8):753-763. doi: 10.1056/NEJMoa1802905. Epub 2018 Aug 15. PubMed PMID: 30110579.
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. Diéras V, Han HS, Kaufman B, Wildiers H, Friedlander M, Ayoub JP, Puhalla SL, Bondarenko I, Campone M, Jakobsen EH, Jalving M, Oprean C, Palácová M, Park YH, Shparyk Y, Yañez E, Khandelwal N, Kundu MG, Dudley M, Ratajczak CK, Maag D, Arun BK. Veliparib with carboplatin and paclitaxel in BRCA-mutated advanced breast cancer (BROCADE3): a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet Oncol. 2020 Aug 27;:. doi: 10.1016/S1470-2045(20)30447-2. Epub 2020 Oct 27. PubMed PMID: 32861273.
2X-121	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 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. McGonigle S, Chen Z, Wu J, Ackermann K, Tendyke K, Moniz G, et al. Abstract 4688: E7449: A novel PARP inhibitor enhances the efficacy of radiotherapy and chemotherapy and has potent single agent anticancer activity in BRCA-deficient tumors. Cancer Res. 2012 Apr 15;72(8 Supplement):4688–4688.

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HATÓANYAG NEVE	REFERENCIA
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. 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. Drew Y, Ledermann J, Hall G, Rea D, Glasspool R, Highley M, Jayson G, Sludden J, Murray J, Jamieson D, Halford S, Acton G, Backholer Z, Mangano R, Boddy A, Curtin N, Plummer R. Phase 2 multicentre trial investigating intermittent and continuous dosing schedules of the poly(ADP-ribose) polymerase inhibitor rucaparib in germline BRCA mutation carriers with advanced ovarian and breast cancer. Br J Cancer. 2016 Mar 29;114(7):723-30. doi: 10.1038/bjc.2016.41. Epub 2016 Mar 22. Erratum in: Br J Cancer. 2016 Jun 14;114(12):e21. PubMed PMID: 27002934; PubMed Central PMCID: PMC4882768. Moore DC, Ringley JT, Patel J. Rucaparib: A Poly(ADP-Ribose) Polymerase Inhibitor for BRCA-Mutated Relapsed Ovarian Cancer. J Pharm Pract. 2017 Jan 1:897190017743131. doi: 10.1177/0897190017743131. [Epub ahead of print] PubMed PMID: 29166829. Abida W, Patnaik A, Campbell D, Shapiro J, Bryce AH, McDermott R, Sautois B, Vogelzang NJ, Bambury RM, Voog E, Zhang J, Piulats JM, Ryan CJ, Merseburger AS, Daugaard G, Heidenreich A, Fizazi K, Higano CS, Krieger LE, Sternberg CN, Watkins SP, Despain D, Simmons AD, Loehr A, Dowson M, Golsorkhi T, Chowdhury S, . Rucaparib in Men With Metastatic Castration-Resistant Prostate Cancer Harboring a BRCA1 or BRCA2 Gene Alteration. J Clin Oncol. 2020 Aug 14;:JCO2001035. doi: 10.1200/JCO.20.01035. Epub 2020 Oct 14. PubMed PMID: 32795228.
IMATINIB	Nakamura T, Mitomi H, Onozato W, Sato T, Ikeda A, Naito M, Ogura N, Kamata H, Ooki A, Watanabe M. Laparoscopic resection of a gastrointestinal stromal tumor of the rectum after treatment with imatinib mesylate: report of a case. Surg Today. 2012 Nov;42(11):1096-9. PubMed PMID: 22294424. 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. 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. Yun J, Lee J, Jang J, Lee EJ, Jang KT, Kim JH, Kim KM. KIT amplification and gene mutations in acral/mucosal melanoma in Korea. APMIS. 2011 Jun;119(6):330-5. doi: 10.1111/j.1600-0463.2011.02737.x. Epub 2011 Mar 24. PubMed PMID: 21569090. Kurtz JE, Asmane I, Voegeli AC, Neuville A, Dufresne A, Litique V, Chevreau C, Bergerat JP. A V530I Mutation in c-KIT Exon 10 Is Associated to Imatinib Response in Extraabdominal Aggressive Fibromatosis. Sarcoma. 2010;2010:458156. doi: 10.1155/2010/458156. Epub 2010 Mar 17. PubMed PMID: 20339585; PubMed Central PMCID: PMC2841250.
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.
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.
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

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HATÓANYAG NEVE	REFERENCIA
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. 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. 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. S. Bozzarelli L. Rimassa L. Giordano S. Sala M.C. Tronconi M. Baretti N. Personeni T. Pressiani A. Santoro. Regorafenib in patients with refractory metastatic pancreatic cancer. An open-label phase II study (RESOUND). Annals of Oncology, Volume 27, Issue suppl_6, 1 October 2016, 692P, https://doi.org/10.1093/annonc/mdw371.84
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.
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.
NILOTINIB	Cho JH, Kim KM, Kwon M, Kim JH, Lee J. Nilotinib in patients with metastatic melanoma harboring KIT gene aberration. Invest New Drugs. 2012 Oct;30(5):2008-14. doi: 10.1007/s10637-011-9763-9. Epub 2011 Nov 9. PubMed PMID: 22068222. 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. Hsueh YS, Lin CL, Chiang NJ, Yen CC, Li CF, Shan YS, Ko CH, Shih NY, Wang LM, Chen TS, Chen LT. Selecting tyrosine kinase inhibitors for gastrointestinal stromal tumor with secondary KIT activation-loop domain mutations. PLoS One. 2013 Jun 20;8(6):e65762. doi: 10.1371/journal.pone.0065762. Print 2013. PubMed PMID: 23840364; PubMed Central PMCID: PMC3688691. Hochhaus A, Baccarani M, Giles FJ, le Coutre PD, Müller MC, Reiter A, Santanastasio H, Leung M, Novick S, Kantarjian HM. Nilotinib in patients with systemic mastocytosis: analysis of the phase 2, open-label, single-arm nilotinib registration study. J Cancer Res Clin Oncol. 2015 Nov;141(11):2047-60. doi: 10.1007/s00432-015-1988-0. Epub 2015 May 23. PubMed PMID: 26002753; PubMed Central PMCID: PMC4768228. Sawaki A, Nishida T, Doi T, Yamada Y, Komatsu Y, Kanda T, Kakeji Y, Onozawa Y, Yamasaki M, Ohtsu A. Phase 2 study of nilotinib as third-line therapy for patients with gastrointestinal stromal tumor. Cancer. 2011 Oct 15;117(20):4633-41. doi: 10.1002/cncr.26120. Epub 2011 Mar 31. PubMed PMID: 21456006.
SORAFENIB	Schöffski P, Dumez H, Clement P, Hoeben A, Prenen H, Wolter P, Joniau S, Roskams T, Van Poppel H. Emerging role of tyrosine kinase inhibitors in the treatment of advanced renal cell cancer: a review. Ann Oncol. 2006 Aug;17(8):1185-96. Epub 2006 Jan 17. Review. PubMed PMID: 16418310. 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. 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. Hsueh YS, Lin CL, Chiang NJ, Yen CC, Li CF, Shan YS, Ko CH, Shih NY, Wang LM, Chen TS, Chen LT. Selecting tyrosine kinase inhibitors for gastrointestinal stromal tumor with secondary KIT activation-loop domain mutations. PLoS One. 2013 Jun 20;8(6):e65762. doi: 10.1371/journal.pone.0065762. Print 2013. PubMed PMID: 23840364; PubMed Central PMCID: PMC3688691. 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.

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HATÓANYAG NEVE	REFERENCIA
CARBOPLATIN	Tweddle DA, Malcolm AJ, Bown N, Pearson AD, Lunec J. Evidence for the development of p53 mutations after cytotoxic therapy in a neuroblastoma cell line. Cancer Res. 2001 Jan 1;61(1):8-13. PubMed PMID: 11196202. 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. Drost R, Bouwman P, Rottenberg S, Boon U, Schut E, Klarenbeek S, Klijn C, van der Heijden I, van der Gulden H, Wientjens E, Pieterse M, Catteau A, Green P, Solomon E, Morris JR, Jonkers J. BRCA1 RING function is essential for tumor suppression but dispensable for therapy resistance. Cancer Cell. 2011 Dec 13;20(6):797-809. doi: 10.1016/j.ccr.2011.11.014. PubMed PMID: 22172724. A Tutt, et al. TNT: A Randomized Phase III Trial of Carboplatin compared with Docetaxel for Patients with Metastatic or Recurrent Locally Advanced Triple Negative or BRCA 1/2 Breast Cancer. 2014 Golan T, Kanji ZS, Epelbaum R, Devaud N, Dagan E, Holter S, Aderka D, Paluch-Shimon S, Kaufman B, Gershoni-Baruch R, Hedley D, Moore MJ, Friedman E, Gallinger S. Overall survival and clinical characteristics of pancreatic cancer in BRCA mutation carriers. Br J Cancer. 2014 Sep 9;111(6):1132-8. doi: 10.1038/bjc.2014.418. Epub 2014 Jul 29. PubMed PMID: 25072261; PubMed Central PMCID: PMC4453851.
DASATINIB	Takeuchi Y, Fujino Y, Watanabe M, Nakagawa T, Ohno K, Sasaki N, Sugano S, Tsujimoto H. Aberrant autophosphorylation of c-Kit receptor in canine mast cell tumor cell lines. Vet Immunol Immunopathol. 2010 Oct 15; 137(3-4):208-16. doi: 10.1016/j.vetimm.2010.05.009. Epub 2010 May 31. PubMed PMID: 20591500. Schittenhelm MM, Shiraga S, Schroeder A, Corbin AS, Griffith D, Lee FY, Bokemeyer C, Deininger MW, Druker BJ, Heinrich MC. Dasatinib (BMS-354825), a dual SRC/ABL kinase inhibitor, inhibits the kinase activity of wild-type, juxtamembrane, and activation loop mutant KIT isoforms associated with human malignancies. Cancer Res. 2006 Jan 1;66(1):473-81. PubMed PMID: 16397263. Verstovsek S, Tefferi A, Cortes J, O'Brien S, Garcia-Manero G, Pardanani A, Akin C, Faderl S, Manshouri T, Thomas D, Kantarjian H. Phase II study of dasatinib in Philadelphia chromosome-negative acute and chronic myeloid diseases, including systemic mastocytosis. Clin Cancer Res. 2008 Jun 15;14(12):3906-15. doi: 10.1158/1078-0432.CCR-08-0366. PubMed PMID: 18559612. Hsueh YS, Lin CL, Chiang NJ, Yen CC, Li CF, Shan YS, Ko CH, Shih NY, Wang LM, Chen TS, Chen LT. Selecting tyrosine kinase inhibitors for gastrointestinal stromal tumor with secondary KIT activation-loop domain mutations. PLoS One. 2013 Jun 20;8(6):e65762. doi: 10.1371/journal.pone.0065762. Print 2013. PubMed PMID: 23840364; PubMed Central PMCID: PMC3688691. Meng D, Carvajal RD. KIT as an Oncogenic Driver in Melanoma: An Update on Clinical Development. Am J Clin Dermatol. 2019 Jun;20(3):315-323. doi: 10.1007/s40257-018-0414-1. PubMed PMID: 30707374.
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. 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. Smith BD, Kaufman MD, Lu WP, Gupta A, Leary CB, Wise SC, Rutkoski TJ, Ahn YM, Al-Ani G, Bulfer SL, Caldwell TM, Chun L, Ensinger CL, Hood MM, McKinley A, Patt WC, Ruiz-Soto R, Su Y, Telikepalli H, Town A, Turner BA, Vogeti L, Vogeti S, Yates K, Janku F, Abdul Razak AR, Rosen O, Heinrich MC, Flynn DL. Ripretinib (DCC-2618) Is a Switch Control Kinase Inhibitor of a Broad Spectrum of Oncogenic and Drug-Resistant KIT and PDGFRA Variants. Cancer Cell. 2019 May 13;35(5):738-751.e9. doi: 10.1016/j.ccell.2019.04.006. PubMed PMID: 31085175.
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.

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HATÓANYAG NEVE	REFERENCIA
BEVACIZUMAB	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. Lou E, Sumrall AL, Turner S, Peters KB, Desjardins A, Vredenburgh JJ, McLendon RE, Herndon JE 2nd, McSherry F, Norfleet J, Friedman HS, Reardon DA. Bevacizumab therapy for adults with recurrent/progressive meningioma: a retrospective series. J Neurooncol. 2012 Aug;109(1):63-70. doi: 10.1007/s11060-012-0861-0. Epub 2012 Apr 26. PubMed PMID: 22535433; PubMed Central PMCID: PMC3404217.
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. 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.
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. 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
MIDOSTAURIN	Saishin Y, Saishin Y, Takahashi K, Seo MS, Melia M, Campochiaro PA. The kinase inhibitor PKC412 suppresses epiretinal membrane formation and retinal detachment in mice with proliferative retinopathies. Invest Ophthalmol Vis Sci. 2003 Aug;44(8):3656-62. PubMed PMID: 12882820. 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.
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.
AKN-028	Eriksson A, Hermanson M, Wickström M, Lindhagen E, Ekholm C, Jenmalm Jensen A, Löthgren A, Lehmann F, Larsson R, Parrow V, Höglund M. The novel tyrosine kinase inhibitor AKN-028 has significant antileukemic activity in cell lines and primary cultures of acute myeloid leukemia. Blood Cancer J. 2012 Aug 3;2:e81. doi: 10.1038/bcj. 2012.28. PubMed PMID: 22864397; PubMed Central PMCID: PMC3432483.
MASITINIB	Humbert M, Castéran N, Letard S, Hanssens K, Iovanna J, Finetti P, Bertucci F, Bader T, Mansfield CD, Moussy A, Hermine O, Dubreuil P. Masitinib combined with standard gemcitabine chemotherapy: in vitro and in vivo studies in human pancreatic tumour cell lines and ectopic mouse model. PLoS One. 2010 Mar 4;5(3):e9430. doi: 10.1371 /journal.pone.0009430. PubMed PMID: 20209107; PubMed Central PMCID: PMC2832006.

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E-mail: info@realtimeoncology.com **Web:** www.realtimeoncology.com

HATÓANYAG NEVE	REFERENCIA
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.
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.
MOTESANIB DIPHOSPHATE	Caenepeel S, Renshaw-Gegg L, Baher A, Bush TL, Baron W, Juan T, Manoukian R, Tasker AS, Polverino A, Hughes PE. Motesanib inhibits Kit mutations associated with gastrointestinal stromal tumors. J Exp Clin Cancer Res. 2010 Jul 15;29:96. doi: 10.1186/1756-9966-29-96. PubMed PMID: 20633291; PubMed Central PMCID: PMC2912835. Grabellus F, Ebeling P, Worm K, Sheu SY, Antoch G, Frilling A, Schmid KW. Double resistance to imatinib and AMG 706 caused by multiple acquired KIT exon 17 mutations in a gastrointestinal stromal tumour. Gut. 2007 Jul;56(7):1025-6. PubMed PMID: 17566038; PubMed Central PMCID: PMC1994367.
CISPLATIN	Brachova P, Thiel KW, Leslie KK. The consequence of oncomorphic TP53 mutations in ovarian cancer. Int J Mol Sci. 2013 Sep 23;14(9):19257-75. doi: 10.3390/ijms140919257. Review. PubMed PMID: 24065105; PubMed Central PMCID: PMC3794832. Brachova P, Mueting SR, Carlson MJ, Goodheart MJ, Button AM, Mott SL, Dai D, Thiel KW, Devor EJ, Leslie KK. TP53 oncomorphic mutations predict resistance to platinum- and taxane-based standard chemotherapy in patients diagnosed with advanced serous ovarian carcinoma. Int J Oncol. 2015 Feb;46(2):607-18. doi: 10.3892/ijo.2014.2747. PubMed PMID: 25385265; PubMed Central PMCID: PMC4277253. Chang FL, Lai MD. Various forms of mutant p53 confer sensitivity to cisplatin and doxorubicin in bladder cancer cells. J Urol. 2001 Jul;166(1):304-10. PubMed PMID: 11435891. Li J, Yang L, Gaur S, Zhang K, Wu X, Yuan YC, Li H, Hu S, Weng Y, Yen Y. Mutants TP53 p.R273H and p.R273C but not p.R273G enhance cancer cell malignancy. Hum Mutat. 2014 May;35(5):575-84. doi: 10.1002/humu.22528. PubMed PMID: 24677579. Blandino G, Levine AJ, Oren M. Mutant p53 gain of function: differential effects of different p53 mutants on resistance of cultured cells to chemotherapy. Oncogene. 1999 Jan 14;18(2):477-85. PubMed PMID: 9927204.
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.

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HATÓANYAG NEVE	REFERENCIA
RONICICLIB	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. 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.
OXALIPLATIN	Golan T, Kanji ZS, Epelbaum R, Devaud N, Dagan E, Holter S, Aderka D, Paluch-Shimon S, Kaufman B, Gershoni-Baruch R, Hedley D, Moore MJ, Friedman E, Gallinger S. Overall survival and clinical characteristics of pancreatic cancer in BRCA mutation carriers. Br J Cancer. 2014 Sep 9;111(6):1132-8. doi: 10.1038/bjc.2014.418. Epub 2014 Jul 29. PubMed PMID: 25072261; PubMed Central PMCID: PMC4453851.
ZOTIRACICLIB	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.
PAZOPANIB	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. Glade Bender JL, Lee A, Reid JM, Baruchel S, Roberts T, Voss SD, Wu B, Ahern CH, Ingle AM, Harris P, Weigel BJ, Blaney SM. Phase I pharmacokinetic and pharmacodynamic study of pazopanib in children with soft tissue sarcoma and other refractory solid tumors: a children's oncology group phase I consortium report. J Clin Oncol. 2013 Aug 20;31(24):3034-43. doi: 10.1200/JCO.2012.47.0914. Epub 2013 Jul 15. PubMed PMID: 23857966; PubMed Central PMCID: PMC3739862. Grande E, Capdevila J, Castellano D, Teulé A, Durán I, Fuster J, Sevilla I, Escudero P, Sastre J, García-Donas J, Casanovas O, Earl J, Ortega L, Apellaniz-Ruiz M, Rodriguez-Antona C, Alonso-Gordoa T, Díez JJ, Carrato A, García-Carbonero R. Pazopanib in pretreated advanced neuroendocrine tumors: a phase II, open-label trial of the Spanish Task Force Group for Neuroendocrine Tumors (GETNE). Ann Oncol. 2015 Sep;26(9):1987-93. doi: 10.1093/annonc/mdv252. Epub 2015 Jun 10. PubMed PMID: 26063633. 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. du Bois A, Floquet A, Kim JW, Rau J, del Campo JM, Friedlander M, Pignata S, Fujiwara K, Vergote I, Colombo N, Mirza MR, Monk BJ, Kimmig R, Ray-Coquard I, Zang R, Diaz-Padilla I, Baumann KH, Mouret-Reynier MA, Kim JH, Kurzeder C, Lesoin A, Vasey P, Marth C, Canzler U, Scambia G, Shimada M, Calvert P, Pujade-Lauraine E, Kim BG, Herzog TJ, Mitrica I, Schade-Brittinger C, Wang Q, Crescenzo R, Harter P. Incorporation of pazopanib in maintenance therapy of ovarian cancer. J Clin Oncol. 2014 Oct 20;32(30):3374-82. doi: 10.1200/JCO.2014.55.7348. Epub 2014 Sep 15. PubMed PMID: 25225436.
SUNITINIB	Schmitt JM, Sommers SR, Fisher W, Ansari R, Robin E, Koneru K, McClean J, Liu Z, Tong Y, Hanna N. Sunitinib plus paclitaxel in patients with advanced esophageal cancer: a phase II study from the Hoosier Oncology Group. J Thorac Oncol. 2012 Apr;7(4):760-3. doi: 10.1097/JTO.0b013e31824abc7c. PubMed PMID: 22425927. Decoster L, Vande Broek I, Neyns B, Majois F, Baurain JF, Rottey S, Rorive A, Anckaert E, De Mey J, De Brakeleer S, De Grève J. Biomarker Analysis in a Phase II Study of Sunitinib in Patients with Advanced Melanoma. Anticancer Res. 2015 Dec;35(12):6893-9. PubMed PMID: 26637913. 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. Rossi V, Donini M, Sergio P, Passalacqua R, Rossi G, Buti S. When a thymic carcinoma "becomes" a GIST. Lung Cancer. 2013 Apr;80(1):106-8. doi: 10.1016/j.lungcan.2013.01.003. Epub 2013 Feb 1. PubMed PMID: 23375402. Prenen H, Cools J, Mentens N, Folens C, Sciot R, Schöffski P, Van Oosterom A, Marynen P, Debiec-Rychter M. Efficacy of the kinase inhibitor SU11248 against gastrointestinal stromal tumor mutants refractory to imatinib mesylate. Clin Cancer Res. 2006 Apr 15;12(8):2622-7. PubMed PMID: 16638875.
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.
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.

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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.
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.
ADAVOSERTIB	Caldwell JT, Edwards H, Buck SA, Ge Y, Taub JW. Targeting the wee1 kinase for treatment of pediatric Down syndrome acute myeloid leukemia. Pediatr Blood Cancer. 2014 Oct;61(10):1767-73. doi: 10.1002/pbc.25081. Epub 2014 Jun 24. PubMed PMID: 24962331. Ma H, Takahashi A, Sejimo Y, Adachi A, Kubo N, Isono M, Yoshida Y, Kanai T, Ohno T, Nakano T. Targeting of Carbon Ion-Induced G2 Checkpoint Activation in Lung Cancer Cells Using Wee-1 Inhibitor MK-1775. Radiat Res. 2015 Dec;184(6):660-9. doi: 10.1667/RR14171.1. Epub 2015 Feb 08. PubMed PMID: 26645158. Hirai H, Iwasawa Y, Okada M, Arai T, Nishibata T, Kobayashi M, Kimura T, Kaneko N, Ohtani J, Yamanaka K, Itadani H, Takahashi-Suzuki I, Fukasawa K, Oki H, Nambu T, Jiang J, Sakai T, Arakawa H, Sakamoto T, Sagara T, Yoshizumi T, Mizuarai S, Kotani H. Small-molecule inhibition of Wee1 kinase by MK-1775 selectively sensitizes p53-deficient tumor cells to DNA-damaging agents. Mol Cancer Ther. 2009 Nov;8(11):2992-3000. doi: 10.1158/1535-7163.MCT-09-0463. PubMed PMID: 19887545. Leijen S, van Geel RM, Pavlick AC, Tibes R, Rosen L, Razak AR, Lam R, Demuth T, Rose S, Lee MA, Freshwater T, Shumway S, Liang LW, Oza AM, Schellens JH, Shapiro GI. Phase I Study Evaluating WEE1 Inhibitor AZD1775 As Monotherapy and in Combination With Gemcitabine, Cisplatin, or Carboplatin in Patients With Advanced Solid Tumors. J Clin Oncol. 2016 Dec 20;34(36):4371-4380. doi: 10.1200/JCO.2016.67.5991. Epub 2016 Oct 31. PubMed PMID: 27601554.
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. Diaz RJ, Golbourn B, Shekarforoush M, Smith CA, Rutka JT. Aurora kinase B/C inhibition impairs malignant glioma growth in vivo. J Neurooncol. 2012 Jul;108(3):349-60. doi: 10.1007/s11060-012-0835-2. Epub 2012 Jun 01. PubMed PMID: 22382783.
CD437	Larsson CA, Moyer SM, Liu B, Michel KA, Pant V, Yang P, Wong J, El-Naggar AK, Krahe R, Lozano G. Synergistic and additive effect of retinoic acid in circumventing resistance to p53 restoration. Proc Natl Acad Sci U S A. 2018 02 27;115(9):2198-2203. doi: 10.1073/pnas.1719001115. Epub 2018 Oct 13. PubMed PMID: 29440484; PubMed Central PMCID: PMC5834709.
M3814	Sun Q, Guo Y, Liu X, Czauderna F, Carr MI, Zenke FT, Blaukat A, Vassilev LT. Therapeutic Implications of p53 Status on Cancer Cell Fate Following Exposure to Ionizing Radiation and the DNA-PK Inhibitor M3814. Mol Cancer Res. 2019 12;17(12):2457-2468. doi: 10.1158/1541-7786.MCR-19-0362. Epub 2019 Jul 24. PubMed PMID: 31551253.
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.
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.
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.

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HATÓANYAG NEVE	REFERENCIA
ENTOSPLETINIB	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.
PEVONEDISTAT	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.
BUPARLISIB	Soulières D, Licitra L, Mesía R, Remenár É, Li SH, Karpenko A, Chol M, Wang YA, Solovieff N, Bourdeau L, Sellami D, Faivre S. Molecular Alterations and Buparlisib Efficacy in Patients with Squamous Cell Carcinoma of the Head and Neck: Biomarker Analysis from BERIL-1. Clin Cancer Res. 2018 Jun 1;24(11):2505-2516. doi: 10.1158/1078-0432.CCR-17-2644. Epub 2018 Feb 28. PMID: 29490986.
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.
AMG 900	Carducci M, Shaheen M, Markman B, Hurvitz S, Mahadevan D, Kotasek D, Goodman OB, Rasmussen E, Chow V, Juan G, Friberg GR, Gamelin E, Vogl FD, Desai J. A phase 1, first-in-human study of AMG 900, an orally administered pan-Aurora kinase inhibitor, in adult patients with advanced solid tumors. Invest New Drugs. 2018 12; 36(6):1060-1071. doi: 10.1007/s10637-018-0625-6. Epub 2018 Jun 07. PubMed PMID: 29980894; PubMed Central PMCID: PMC6639057.
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. 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. http://ascopubs.org/doi/abs/10.1200/JCO.2017.35.15_suppl.TPS4150 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.
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. 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. 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. Dosil MA, Mirantes C, Eritja N, Felip I, Navaridas R, Gatius S, Santacana M, Colàs E, Moiola C, Schoenenberger JA, Encinas M, Garí E, Matias-Guiu X, Dolcet X. Palbociclib has antitumour effects on Pten-deficient endometrial neoplasias. J Pathol. 2017 Jun;242(2):152-164. doi: 10.1002/path.4896. Epub 2017 Apr 28. PubMed PMID: 28349562.

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HATÓANYAG NEVE	REFERENCIA
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.
EPRENETAPOPT	Fransson Å, Glaessgen D, Alfredsson J, Wiman KG, Bajalica-Lagercrantz S, Mohell N. Strong synergy with APR-246 and DNA-damaging drugs in primary cancer cells from patients with TP53 mutant High-Grade Serous ovarian cancer. J Ovarian Res. 2016 May 14;9(1):27. doi: 10.1186/s13048-016-0239-6. PubMed PMID: 27179933; PubMed Central PMCID: PMC4868029.
TAK-960	Hikichi Y, Honda K, Hikami K, Miyashita H, Kaieda I, Murai S, Uchiyama N, Hasegawa M, Kawamoto T, Sato T, Ichikawa T, Cao S, Nie Z, Zhang L, Yang J, Kuida K, Kupperman E. TAK-960, a novel, orally available, selective inhibitor of polo-like kinase 1, shows broad-spectrum preclinical antitumor activity in multiple dosing regimens. Mol Cancer Ther. 2012 Mar;11(3):700-9. doi: 10.1158/1535-7163.MCT-11-0762. Epub 2011 Dec 21. PubMed PMID: 22188812.
NMS-P937	Sero V, Tavanti E, Vella S, Hattinger CM, Fanelli M, Michelacci F, Versteeg R, Valsasina B, Gudeman B, Picci P, Serra M. Targeting polo-like kinase 1 by NMS-P937 in osteosarcoma cell lines inhibits tumor cell growth and partially overcomes drug resistance. Invest New Drugs. 2014 Sep 7. [Epub ahead of print] PubMed PMID: 25193492.
GSK-461364	Olmos D, Barker D, Sharma R, Brunetto AT, Yap TA, Taegtmeyer AB, Barriuso J, Medani H, Degenhardt YY, Allred AJ, Smith DA, Murray SC, Lampkin TA, Dar MM, Wilson R, de Bono JS, Blagden SP. Phase I study of GSK461364, a specific and competitive Polo-like kinase 1 inhibitor, in patients with advanced solid malignancies. Clin Cancer Res. 2011 May 15;17(10):3420-30. doi: 10.1158/1078-0432.CCR-10-2946. Epub 2011 Apr 1. PubMed PMID: 21459796.
BI 2536	Oliveira JC, Pezuk JA, Brassesco MS, Morales AG, Queiroz RG, Scrideli CA, Tone LG. PLK1 expression and BI 2536 effects in childhood acute lymphoblastic leukemia. Pediatr Blood Cancer. 2014 Jul;61(7):1227-31. doi: 10.1002/pbc.24978. Epub 2014 Feb 12. PubMed PMID: 24519995.
VOLASERTIB	Gjertsen BT, Schöffski P. Discovery and development of the Polo-like kinase inhibitor volasertib in cancer therapy. Leukemia. 2014 Jul 16. doi: 10.1038/leu.2014.222. [Epub ahead of print] PubMed PMID: 25027517.
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.
PK7088	Liu X, Wilcken R, Joerger AC, Chuckowree IS, Amin J, Spencer J, Fersht AR. Small molecule induced reactivation of mutant p53 in cancer cells. Nucleic Acids Res. 2013 Jul;41(12):6034-44. doi: 10.1093/nar/gkt305. Epub 2013 Nov 29. PubMed PMID: 23630318; PubMed Central PMCID: PMC3695503.
WITHANONE	Sundar D, Yu Y, Katiyar SP, Putri JF, Dhanjal JK, Wang J, Sari AN, Kolettas E, Kaul SC, Wadhwa R. Wild type p53 function in p53Y220C mutant harboring cells by treatment with Ashwagandha derived anticancer withanolides: bioinformatics and experimental evidence. J Exp Clin Cancer Res. 2019 Feb 26;38(1):103. doi: 10.1186/s13046-019-1099-x. Epub 2019 Nov 26. PubMed PMID: 30808373; PubMed Central PMCID: PMC6390572.
WITHAFERIN A	Sundar D, Yu Y, Katiyar SP, Putri JF, Dhanjal JK, Wang J, Sari AN, Kolettas E, Kaul SC, Wadhwa R. Wild type p53 function in p53Y220C mutant harboring cells by treatment with Ashwagandha derived anticancer withanolides: bioinformatics and experimental evidence. J Exp Clin Cancer Res. 2019 Feb 26;38(1):103. doi: 10.1186/s13046-019-1099-x. Epub 2019 Nov 26. PubMed PMID: 30808373; PubMed Central PMCID: PMC6390572.
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	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.

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HATÓANYAG NEVE	REFERENCIA
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.
RUXOLITINIB	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. 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. 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. 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. Yang LP, Keating GM. Ruxolitinib: in the treatment of myelofibrosis. Drugs. 2012 Nov 12;72(16):2117-27. doi: 10.2165 /11209340-000000000-00000. PubMed PMID: 23061804.
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.
BARICITINIB	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. 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.
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.
AZD1480	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. 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.
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.

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HATÓANYAG NEVE	REFERENCIA
AVAPRITINIB	http://www.bloodjournal.org/content/124/21/3217?sso-checked=true
PONATINIB	Gozgit JM, Wong MJ, Wardwell S, Tyner JW, Loriaux MM, Mohemmad QK, Narasimhan NI, Shakespeare WC, Wang F, Druker BJ, Clackson T, Rivera VM. Potent activity of ponatinib (AP24534) in models of FLT3-driven acute myeloid leukemia and other hematologic malignancies. Mol Cancer Ther. 2011 Jun;10(6):1028-35. doi: 10.1158/1535-7163. MCT-10-1044. Epub 2011 Apr 11. PubMed PMID: 21482694; PubMed Central PMCID: PMC3236248.
TELAGLENASTAT	Sayin VI, LeBoeuf SE, Singh SX, Davidson SM, Biancur D, Guzelhan BS, Alvarez SW, Wu WL, Karakousi TR, Zavitsanou AM, Ubriaco J, Muir A, Karagiannis D, Morris PJ, Thomas CJ, Possemato R, Vander Heiden MG, Papagiannakopoulos T. Activation of the NRF2 antioxidant program generates an imbalance in central carbon metabolism in cancer. Elife. 2017 Oct 2;6. pii: e28083. doi: 10.7554/eLife.28083. PubMed PMID: 28967864; PubMed Central PMCID: PMC5624783. Romero R, Sayin VI, Davidson SM, Bauer MR, Singh SX, LeBoeuf SE, Karakousi TR, Ellis DC, Bhutkar A, Sánchez-Rivera FJ, Subbaraj L, Martinez B, Bronson RT, Prigge JR, Schmidt EE, Thomas CJ, Goparaju C, Davies A, Dolgalev I, Heguy A, Allaj V, Poirier JT, Moreira AL, Rudin CM, Pass HI, Vander Heiden MG, Jacks T, Papagiannakopoulos T. Keap1 loss promotes Kras-driven lung cancer and results in dependence on glutaminolysis. Nat Med. 2017 Nov;23 (11):1362-1368. doi: 10.1038/nm.4407. Epub 2017 Oct 2. PubMed PMID: 28967920; PubMed Central PMCID: PMC5677540.
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. 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. 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.
TAS-102	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.
EVEROLIMUS	Constantine C, Vasiliki V, Paraskevi Vasilatou PV, Agathi A, Dionysios D. Successful treatment with the mTOR inhibitor everolimus in a patient with perivascular epithelioid cell tumor. World J Surg Oncol. 2012 Sep 03;10:181. doi: 10.1186/1477-7819-10-181. Epub 2012 Jun 03. PubMed PMID: 22943457; PubMed Central PMCID: PMC3499435 Perez J, Decouvelaere AV, Pointecouteau T, Pissaloux D, Michot JP, Besse A, Blay JY, Dutour A. Inhibition of chondrosarcoma growth by mTOR inhibitor in an in vivo syngeneic rat model. PLoS One. 2012;7(6):e32458. doi: 10.1371/journal.pone.0032458. Epub 2012 Jun 27. PubMed PMID: 22761648; PubMed Central PMCID: PMC3384598. Franz DN. Everolimus in the treatment of subependymal giant cell astrocytomas, angiomyolipomas, and pulmonary and skin lesions associated with tuberous sclerosis complex. Biologics. 2013;7:211-21. doi: 10.2147/BTT.S25095. Epub 2013 Oct 10. Review. PubMed PMID: 24143074; PubMed Central PMCID: PMC3797614. Seront E, Rottey S, Sautois B, Kerger J, D'Hondt LA, Verschaeve V, Canon JL, Dopchie C, Vandenbulcke JM, Whenham N, Goeminne JC, Clausse M, Verhoeven D, Glorieux P, Branders S, Dupont P, Schoonjans J, Feron O, Machiels JP. Phase II study of everolimus in patients with locally advanced or metastatic transitional cell carcinoma of the urothelial tract: clinical activity, molecular response, and biomarkers. Ann Oncol. 2012 Oct;23(10):2663-70. Epub 2012 Apr 3. PubMed PMID: 22473592. Ohtsu A, Ajani JA, Bai YX, Bang YJ, Chung HC, Pan HM, Sahmoud T, Shen L, Yeh KH, Chin K, Muro K, Kim YH, Ferry D, Tebbutt NC, Al-Batran SE, Smith H, Costantini C, Rizvi S, Lebwohl D, Van Cutsem E. Everolimus for previously treated advanced gastric cancer: results of the randomized, double-blind, phase III GRANITE-1 study. J Clin Oncol. 2013 Nov 1;31(31):3935-43. doi: 10.1200/JCO.2012.48.3552. Epub 2013 Sep 16. PubMed PMID: 24043745.

HATÓANYAG NEVE	REFERENCIA
IBRUTINIB	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. 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. 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.
CETUXIMAB	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. Lukan N, Ströbel P, Willer A, Kripp M, Dinter D, Mai S, Hochhaus A, Hofheinz RD. Cetuximab-based treatment of metastatic anal cancer: correlation of response with KRAS mutational status. Oncology. 2009;77(5):293-9. doi: 10.1159/000259615. Epub 2009 Nov 17. PubMed PMID: 19923868. 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.
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. 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.
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.

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HATÓANYAG NEVE	REFERENCIA
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.
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.
VENETOCLAX	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 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. 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. 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.
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.

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HATÓANYAG NEVE	REFERENCIA
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. 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.
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. 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.
ZIV-AFLIBERCEPT	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.
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.

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HATÓANYAG NEVE	REFERENCIA
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.
PANITUMUMAB	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. 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. 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. Schwartzberg LS, Rivera F, Karthaus M, Fasola G, Canon JL, Hecht JR, Yu H, Oliner KS, Go WY. PEAK: a randomized, multicenter phase II study of panitumumab plus modified fluorouracil, leucovorin, and oxaliplatin (mFOLFOX6) or bevacizumab plus mFOLFOX6 in patients with previously untreated, unresectable, wild-type KRAS exon 2 metastatic colorectal cancer. J Clin Oncol. 2014 Jul 20;32(21):2240-7. doi: 10.1200/JCO.2013.53.2473. Epub 2014 Mar 31. PubMed PMID: 24687833.
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.
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.
IPATASERTIB	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.

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HATÓANYAG NEVE	REFERENCIA
METFORMIN	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. 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. 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. 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. Ko EM, Walter P, Jackson A, Clark L, Franasiak J, Bolac C, Havrilesky LJ, Secord AA, Moore DT, Gehrig PA, Bae-Jump V. Metformin is associated with improved survival in endometrial cancer. Gynecol Oncol. 2014 Feb;132(2):438-42. doi: 10.1016/j.ygyno.2013.11.021. Epub 2013 Nov 22. PubMed PMID: 24269517.
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.
NINTEDANIB	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.
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.
VANDETANIB	Leboulleux S, Bastholt L, Krause T, de la Fouchardiere C, Tennvall J, Awada A, Gómez JM, Bonichon F, Leenhardt L, Soufflet C, Licour M, Schlumberger MJ. Vandetanib in locally advanced or metastatic differentiated thyroid cancer: a randomised, double-blind, phase 2 trial. Lancet Oncol. 2012 Sep;13(9):897-905. doi: 10.1016/S1470-2045(12)70335-2. Epub 2012 Aug 14. PubMed PMID: 22898678.
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.
SURUFATINIB	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.
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.

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HATÓANYAG NEVE	REFERENCIA
DUVELISIB	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.
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.
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 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.
OLARATUMAB	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. 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
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.

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HATÓANYAG NEVE	REFERENCIA
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 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.
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.
TEMSIROLIMUS	A A, C C, I I, A L AL, M M, A A, J-M JM, B B. Treatment with the mTOR inhibitor temsirolimus in patients with malignant PEComa. Ann Oncol. 2010 May;21(5):1135-7. doi: 10.1093/annonc/mdq044. Epub 2010 Jun 09. PubMed PMID: 20215136
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. 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.
IDELALISIB	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.
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. 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.
AXITINIB	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. 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.

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HATÓANYAG NEVE	REFERENCIA
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
CABOZANTINIB	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
TOFACITINIB	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.
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.
MK2206	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.
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.
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.
TRAMETINIB	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. KIM, Richard D., et al. SWOG S1310: Randomized phase II trial of single agent MEK inhibitor trametinib vs. 5-fluorouracil or capecitabine in refractory advanced biliary cancer. 2017. Heuck CJ, Jethava Y, Khan R, van Rhee F, Zangari M, Chavan S, Robbins K, Miller SE, Matin A, Mohan M, Ali SM, Stephens PJ, Ross JS, Miller VA, Davies F, Barlogie B, Morgan G. Inhibiting MEK in MAPK pathway-activated myeloma. Leukemia. 2016 Apr;30(4):976-80. doi: 10.1038/leu.2015.208. Epub 2015 Jul 31. PubMed PMID: 26228812; PubMed Central PMCID: PMC4832073.
SELUMETINIB	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.
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.

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HATÓANYAG NEVE	REFERENCIA
LUCITANIB	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.
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.
CERDULATINIB	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.
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	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.
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.
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.
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.
ZALUTUMUMAB	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.
DACOMITINIB	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.
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.
AZD4547	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.
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.
SIROLIMUS	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.

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HATÓANYAG NEVE	REFERENCIA
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.
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.
LAPATINIB	R. K. Ramanathan, C. P. Belani, D. A. Singh, M. Tanaka Jr, H. J. Lenz, Y. Yen, H. L. Kindler, S. Iqbal, J. Longmate, D. R. Gandara. Phase II study of lapatinib, a dual inhibitor of epidermal growth factor receptor (EGFR) tyrosine kinase 1 and 2 (Her2/Neu) in patients (pts) with advanced biliary tree cancer (BTC) or hepatocellular cancer (HCC). A California Consortium (CCC-P) Trial. DOI: 10.1200/jco.2006.24.18_suppl.4010 Journal of Clinical Oncology 24, no. 18_suppl.
TRASTUZUMAB	Moroni M, Stella M, Pedrazzoli P, Pirovano M, Boveri E, Veronese S. c.428T > C (p.V143A) homozygous mutation in TP53 gene as a possible mechanism of resistance to trastuzumab therapy in gastric cancer. Acta Oncol. 2016 Nov; 55(11):1373-1375. Epub 2016 Aug 31. PubMed PMID: 27579625.
ERLOTINIB	Gordon AN, Finkler N, Edwards RP, Garcia AA, Crozier M, Irwin DH, Barrett E. Efficacy and safety of erlotinib HCl, an epidermal growth factor receptor (HER1/EGFR) tyrosine kinase inhibitor, in patients with advanced ovarian carcinoma: results from a phase II multicenter study. Int J Gynecol Cancer. 2005 Sep-Oct;15(5):785-92. PubMed PMID: 16174225. 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. Mody K, Strauss E, Lincer R, Frank RC. Complete response in gallbladder cancer to erlotinib plus gemcitabine does not require mutation of the epidermal growth factor receptor gene: a case report. BMC Cancer. 2010 Oct 20;10:570. doi: 10.1186/1471-2407-10-570. PubMed PMID: 20961434; PubMed Central PMCID: PMC2972285. Pruthi RS, Nielsen M, Heathcote S, Wallen EM, Rathmell WK, Godley P, Whang Y, Fielding J, Schultz H, Grigson G, Smith A, Kim W. A phase II trial of neoadjuvant erlotinib in patients with muscle-invasive bladder cancer undergoing radical cystectomy: clinical and pathological results. BJU Int. 2010 Aug;106(3):349-54. doi: 10.1111/j.1464-410X. 2009.09101.x. Epub 2010 Jan 19. PubMed PMID: 20089114. Nogueira-Rodrigues A, Moralez G, Grazziotin R, Carmo CC, Small IA, Alves FV, Mamede M, Erlich F, Viegas C, Triginelli SA, Ferreira CG. Phase 2 trial of erlotinib combined with cisplatin and radiotherapy in patients with locally advanced cervical cancer. Cancer. 2014 Apr 15;120(8):1187-93. doi: 10.1002/cncr.28471. Epub 2014 Mar 10. PubMed PMID: 24615735.
AFATINIB	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.
MELPHALAN	Tweddle DA, Malcolm AJ, Bown N, Pearson AD, Lunec J. Evidence for the development of p53 mutations after cytotoxic therapy in a neuroblastoma cell line. Cancer Res. 2001 Jan 1;61(1):8-13. PubMed PMID: 11196202.
GEFITINIB	Patel SP, Kim KB, Papadopoulos NE, Hwu WJ, Hwu P, Prieto VG, Bar-Eli M, Zigler M, Dobroff A, Bronstein Y, Bassett RL, Vardeleon AG, Bedikian AY. A phase II study of gefitinib in patients with metastatic melanoma. Melanoma Res. 2011 Aug;21(4):357-63. doi: 10.1097/CMR.0b013e3283471073. PubMed PMID: 21738104; PubMed Central PMCID: PMC3132394. Jakob JA, Kies MS, Glisson BS, Kupferman ME, Liu DD, Lee JJ, El-Naggar AK, Gonzalez-Angulo AM, Blumenschein GR Jr. Phase II study of gefitinib in patients with advanced salivary gland cancers. Head Neck. 2015 May;37(5):644-9. doi: 10.1002/hed.23647. Epub 2015 Mar 30. PubMed PMID: 24585506. Wilken JA, Badri T, Cross S, Raji R, Santin AD, Schwartz P, Branscum AJ, Baron AT, Sakhitab AI, Maihle NJ. EGFR /HER-targeted therapeutics in ovarian cancer. Future Med Chem. 2012 Mar;4(4):447-69. doi: 10.4155/fmc.12.11. Review. PubMed PMID: 22416774; PubMed Central PMCID: PMC4620931. von Minckwitz G, Jonat W, Fasching P, du Bois A, Kleeberg U, Lück HJ, Kettner E, Hilfrich J, Eiermann W, Torode J, Schneeweiss A. A multicentre phase II study on gefitinib in taxane- and anthracycline-pretreated metastatic breast cancer. Breast Cancer Res Treat. 2005 Jan;89(2):165-72. PubMed PMID: 15692759. Baselga J, Albanell J, Ruiz A, Lluch A, Gascón P, Guillém V, González S, Sauleda S, Marimón I, Tabernero JM, Koehler MT, Rojo F. Phase II and tumor pharmacodynamic study of gefitinib in patients with advanced breast cancer. J Clin Oncol. 2005 Aug 10;23(23):5323-33. Epub 2005 Jun 6. PubMed PMID: 15939921.

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HATÓANYAG NEVE	REFERENCIA
FK866	Thakur BK, Dittrich T, Chandra P, Becker A, Kuehnau W, Klusmann JH, Reinhardt D, Welte K. Involvement of p53 in the cytotoxic activity of the NAMPT inhibitor FK866 in myeloid leukemic cells. Int J Cancer. 2013 Feb 15;132(4):766-74. doi: 10.1002/ijc.27726. PubMed PMID: 22815158; PubMed Central PMCID: PMC3562481.
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.
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.
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.
ETOPOSIDE	Brachova P, Thiel KW, Leslie KK. The consequence of oncomorphic TP53 mutations in ovarian cancer. Int J Mol Sci. 2013 Sep 23;14(9):19257-75. doi: 10.3390/ijms140919257. Review. PubMed PMID: 24065105; PubMed Central PMCID: PMC3794832. Tweddle DA, Malcolm AJ, Bown N, Pearson AD, Lunec J. Evidence for the development of p53 mutations after cytotoxic therapy in a neuroblastoma cell line. Cancer Res. 2001 Jan 1;61(1):8-13. PubMed PMID: 11196202. Chamberlain MC. Salvage chemotherapy for recurrent spinal cord ependymona. Cancer. 2002 Sep 1;95(5):997-1002. PubMed PMID: 12209682.
PACLITAXEL	Brachova P, Thiel KW, Leslie KK. The consequence of oncomorphic TP53 mutations in ovarian cancer. Int J Mol Sci. 2013 Sep 23;14(9):19257-75. doi: 10.3390/ijms140919257. Review. PubMed PMID: 24065105; PubMed Central PMCID: PMC3794832.
PATUPILONE	Seagle BL, Yang CP, Eng KH, Dandapani M, Odunsi-Akanji O, Goldberg GL, Odunsi K, Horwitz SB, Shahabi S. TP53 hot spot mutations in ovarian cancer: selective resistance to microtubule stabilizers in vitro and differential survival outcomes from The Cancer Genome Atlas. Gynecol Oncol. 2015 Jul;138(1):159-64. doi: 10.1016/j.ygyno.2015.04.039. Epub 2015 May 6. PubMed PMID: 25958320; PubMed Central PMCID: PMC5303002.
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.
CHOP	Liu YY, Yao SN, Zhao Y, Yao ZH, Ma J, Xia QX, Fu K, Yang SJ. PTEN tumor suppressor plays less prognostic role than P53 tumor suppressor in diffuse large B-cell lymphoma. Leuk Lymphoma. 2010 Sep;51(9):1692-8. doi: 10.3109/10428194.2010.502584. PubMed PMID: 20807096. Young KH, Weisenburger DD, Dave BJ, Smith L, Sanger W, Iqbal J, Campo E, Delabie J, Gascoyne RD, Ott G, Rimsza L, Müller-Hermelink HK, Jaffe ES, Rosenwald A, Staudt LM, Chan WC, Greiner TC. Mutations in the DNA-binding codons of TP53, which are associated with decreased expression of TRAILreceptor-2, predict for poor survival in diffuse large B-cell lymphoma. Blood. 2007 Dec 15;110(13):4396-405. doi: 10.1182/blood-2007-02-072082. Epub 2007 Feb 19. PubMed PMID: 17881637; PubMed Central PMCID: PMC2234786. Young KH, Leroy K, Møller MB, Colleoni GW, Sánchez-Beato M, Kerbauy FR, Haioun C, Eickhoff JC, Young AH, Gaulard P, Piris MA, Oberley TD, Rehrauer WM, Kahl BS, Malter JS, Campo E, Delabie J, Gascoyne RD, Rosenwald A, Rimsza L, Huang J, Braziel RM, Jaffe ES, Wilson WH, Staudt LM, Vose JM, Chan WC, Weisenburger DD, Greiner TC. Structural profiles of TP53 gene mutations predict clinical outcome in diffuse large B-cell lymphoma: an international collaborative study. Blood. 2008 Oct 15;112(8):3088-98. doi: 10.1182/blood-2008-01-129783. Epub 2008 Feb 17. PubMed PMID: 18559976; PubMed Central PMCID: PMC2569165.

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HATÓANYAG NEVE	REFERENCIA
CRIZOTINIB	Zhang Y, Farenholtz KE, Yang Y, Guessous F, Dipierro CG, Calvert VS, Deng J, Schiff D, Xin W, Lee JK, Purow B, Christensen J, Petricoin E, Abounader R. Hepatocyte growth factor sensitizes brain tumors to c-MET kinase inhibition. Clin Cancer Res. 2013 Mar 15;19(6):1433-44. doi: 10.1158/1078-0432.CCR-12-2832. Epub 2013 Feb 5. PubMed PMID: 23386689; PubMed Central PMCID: PMC3602223. Dziadziuszko R, Le AT, Wrona A, Jassem J, Camidge DR, Varella-Garcia M, Aisner DL, Doebele RC. An Activating KIT Mutation Induces Crizotinib Resistance in ROS1-Positive Lung Cancer. J Thorac Oncol. 2016 Aug;11(8):1273-1281. doi: 10.1016/j.jtho.2016.04.001. Epub 2016 Apr 9. PubMed PMID: 27068398; PubMed Central PMCID: PMC4961521. Song P, Zhang F, Li Y, Yang G, Li W, Ying J, Gao S. Concomitant TP53 mutations with response to crizotinib treatment in patients with ALK-rearranged non-small-cell lung cancer. Cancer Med. 2019 04;8(4):1551-1557. doi: 10.1002/cam4.2043. Epub 2019 Jul 07. PubMed PMID: 30843662; PubMed Central PMCID: PMC6488212. Kron A, Alidousty C, Scheffler M, Merkelbach-Bruse S, Seidel D, Riedel R, Ihle MA, Michels S, Nogova L, Fassunke J, Heydt C, Kron F, Ueckeroth F, Serke M, Krüger S, Grohe C, Koschel D, Benedikter J, Kaminsky B, Schaaf B, Braess J, Sebastian M, Kambartel KO, Thomas R, Zander T, Schultheis AM, Büttner R, Wolf J. Impact of TP53 mutation status on systemic treatment outcome in ALK-rearranged non-small-cell lung cancer. Ann Oncol. 2018 10 01;29(10):2068-2075. doi: 10.1093/annonc/mdy333. PubMed PMID: 30165392; PubMed Central PMCID: PMC6225899.
DOXORUBICIN	Chang FL, Lai MD. Various forms of mutant p53 confer sensitivity to cisplatin and doxorubicin in bladder cancer cells. J Urol. 2001 Jul;166(1):304-10. PubMed PMID: 11435891. Capponcelli S, Pedrini E, Cerone MA, Corti V, Fontanesi S, Alessio M, Bachi A, Soddu S, Ribatti D, Picci P, Helman LJ, Cantelli-Forti G, Sangiorgi L. Evaluation of the molecular mechanisms involved in the gain of function of a Li-Fraumeni TP53 mutation. Hum Mutat. 2005 Aug;26(2):94-103. PubMed PMID: 15977174. Anasuya Pal, Laura Gonzalez-Malerva, Seron Eaton, Mayra Guzman, Donald Chow, Hongwei Yin, Jin Park, Karen Anderson, Joshua LaBaer. Functional genomics of TP53 mutations and its impact in breast cancer progression. Proceedings of the Thirty-Seventh Annual CTRC-AACR San Antonio Breast Cancer Symposium: 2014 Dec 9-13; San Antonio, TX. Philadelphia (PA): AACR; Cancer Res 2015;75(9 Suppl):Abstract nr P4-05-07. doi: 10.1158/1538-7445.SABCS14-P4-05-07 Hosain SB, Khiste SK, Uddin MB, Vorubindi V, Ingram C, Zhang S, Hill RA, Gu X, Liu YY. Inhibition of glucosylceramide synthase eliminates the oncogenic function of p53 R273H mutant in the epithelial-mesenchymal transition and induced pluripotency of colon cancer cells. Oncotarget. 2016 Sep 13;7(37):60575-60592. doi: 10.18632/oncotarget.11169. PubMed PMID: 27517620; PubMed Central PMCID: PMC5312403. Tweddle DA, Malcolm AJ, Bown N, Pearson AD, Lunec J. Evidence for the development of p53 mutations after cytotoxic therapy in a neuroblastoma cell line. Cancer Res. 2001 Jan 1;61(1):8-13. PubMed PMID: 11196202.
R-CHOP	Stefancikova L, Moulis M, Fabian P, Vasova I, Zedek F, Ravcukova B, Muzik J, Kuglik P, Vranova V, Falkova I, Hrabalkova R, Smardova J. Prognostic impact of p53 aberrations for R-CHOP-treated patients with diffuse large B-cell lymphoma. Int J Oncol. 2011 Dec;39(6):1413-20. doi: 10.3892/ijo.2011.1170. Epub 2011 Feb 18. PubMed PMID: 21874232. Intlekofer AM, Joffe E, Batlevi CL, Hilden P, He J, Seshan VE, Zelenetz AD, Palomba ML, Moskowitz CH, Portlock C, Straus DJ, Noy A, Horwitz SM, Gerecitano JF, Moskowitz A, Hamlin P, Matasar MJ, Kumar A, van den Brink MR, Knapp KM, Pichardo JD, Nahas MK, Trabucco SE, Mughal T, Copeland AR, Papaemmanuil E, Moarii M, Levine RL, Dogan A, Miller VA, Younes A. Integrated DNA/RNA targeted genomic profiling of diffuse large B-cell lymphoma using a clinical assay. Blood Cancer J. 2018 06 12;8(6):60. doi: 10.1038/s41408-018-0089-0. Epub 2018 Feb 12. PubMed PMID: 29895903; PubMed Central PMCID: PMC5997645. Qin Y, Jiang S, Liu P, Yang J, Yang S, He X, Zhou S, Gui L, Lin J, Du X, Yi Y, Sun Y, Shi Y. Characteristics and Management of TP53-Mutated Diffuse Large B-Cell Lymphoma Patients. Cancer Manag Res. 2020;12:11515-11522. doi: 10.2147/CMAR.S269624. Epub 2020 Feb 10. PubMed PMID: 33204162; PubMed Central PMCID: PMC7666999. Rushton CK, Arthur SE, Alcaide M, Cheung M, Jiang A, Coyle KM, Cleary KLS, Thomas N, Hilton LK, Michaud N, Daigle S, Davidson J, Bushell K, Yu S, Rys RN, Jain M, Shepherd L, Marra MA, Kuruvilla J, Crump M, Mann K, Assouline S, Connors JM, Steidl C, Cragg MS, Scott DW, Johnson NA, Morin RD. Genetic and evolutionary patterns of treatment resistance in relapsed B-cell lymphoma. Blood Adv. 2020 07 14;4(13):2886-2898. doi: 10.1182/bloodadvances.2020001696. PubMed PMID: 32589730; PubMed Central PMCID: PMC7362366. Greenawalt DM, Liang WS, Saif S, Johnson J, Todorov P, Dulak A, Enriquez D, Halperin R, Ahmed A, Saveliev V, Carpten J, Craig D, Barrett JC, Dougherty B, Zinda M, Fawell S, Dry JR, Byth K. Comparative analysis of primary versus relapse/refractory DLBCL identifies shifts in mutation spectrum. Oncotarget. 2017 Nov 21;8(59):99237-99244. doi: 10.18632/oncotarget.18502. Epub 2017 Mar 15. PubMed PMID: 29245897; PubMed Central PMCID: PMC5725088.

BIOMARKEREK ÉS DRIVEREK	REFERENCIA

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BIOMARKEREK ÉS DRIVEREK	REFERENCIA
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. 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. 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. 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.
PDL1 protein overexpression	Zhu J, Wen H, Bi R, Wu Y, Wu X. Prognostic value of programmed death-ligand 1 (PD-L1) expression in ovarian clear cell carcinoma. J Gynecol Oncol. 2017 Nov;28(6):e77. doi: 10.3802/jgo.2017.28.e77. PubMed PMID: 29027395; PubMed Central PMCID: PMC5641527. Song M, Chen D, Lu B, Wang C, Zhang J, Huang L, Wang X, Timmons CL, Hu J, Liu B, Wu X, Wang L, Wang J, Liu H. PTEN loss increases PD-L1 protein expression and affects the correlation between PD-L1 expression and clinical parameters in colorectal cancer. PLoS One. 2013 Jun 13;8(6):e65821. doi: 10.1371/journal.pone.0065821. Print 2013. PubMed PMID: 23785454; PubMed Central PMCID: PMC3681867. De Bacco, Mateus Webber, Andre P. Fay, Gustavo Carvalhal, Josenel Copetti, Bradley Alexander McGregor, Guru Sonpavde, and Mario Wagner. "PD-L1 and p16 expression in penile squamous cell carcinoma from an endemic region." (2019): 515-515. Iacovelli R, Nolè F, Verri E, Renne G, Paglino C, Santoni M, Cossu Rocca M, Giglione P, Aurilio G, Cullurà D, Cascinu S, Porta C. Prognostic Role of PD-L1 Expression in Renal Cell Carcinoma. A Systematic Review and Meta-Analysis. Target Oncol. 2016 Apr;11(2):143-8. doi: 10.1007/s11523-015-0392-7. Review. PubMed PMID: 26429561. Koganemaru S, Inoshita N, Miura Y, Miyama Y, Fukui Y, Ozaki Y, Tomizawa K, Hanaoka Y, Toda S, Suyama K, Tanabe Y, Moriyama J, Fujii T, Matoba S, Kuroyanagi H, Takano T. Prognostic value of programmed death-ligand 1 expression in patients with stage III colorectal cancer. Cancer Sci. 2017 May;108(5):853-858. doi: 10.1111/cas.13229. PubMed PMID: 28267224; PubMed Central PMCID: PMC5448596.
BRCA1-K654fs*47	Kaufman B, Laitman Y, Gronwald J, Lubinski J, Friedman E. Haplotype of the C61G BRCA1 mutation in Polish and Jewish individuals. Genet Test Mol Biomarkers. 2009 Aug;13(4):465-9. doi: 10.1089/gtmb.2009.0001. PubMed PMID: 19594371. Cecener G, Egeli U, Tunca B, Erturk E, Ak S, Gokgoz S, Tasdelen I, Tezcan G, Demirdogen E, Bayram N, Avci N, Evrensel T. BRCA1/2 germline mutations and their clinical importance in Turkish breast cancer patients. Cancer Invest. 2014 Oct;32(8):375-87. doi: 10.3109/07357907.2014.919302. Epub 2014 Jun 2. PubMed PMID: 24884828. Arnold N, Peper H, Bandick K, Kreikemeier M, Karow D, Teegen B, Jonat W. Establishing a control population to screen for the occurrence of nineteen unclassified variants in the BRCA1 gene by denaturing high-performance liquid chromatography. J Chromatogr B Analyt Technol Biomed Life Sci. 2002 Dec 25;782(1-2):99-104. PubMed PMID: 12457999. Waddell N, Ten Haaf A, Marsh A, Johnson J, Walker LC; kConfab Investigators, Gongora M, Brown M, Grover P, Girolami M, Grimmond S, Chenevix-Trench G, Spurdle AB. BRCA1 and BRCA2 missense variants of high and low clinical significance influence lymphoblastoid cell line post-irradiation gene expression. PLoS Genet. 2008 May 23;4(5):e1000080. doi: 10.1371/journal.pgen.1000080. PubMed PMID: 18497862; PubMed Central PMCID: PMC2375115. Zidekova D, Waczulikova I, Dolesova L, Vavrova L, Hamidova O, Lohajova Behulova R, Konecny M. Rapid screening test of most frequent BRCA1/BRCA2 pathogenic variants in the NGS era. Neoplasma. 2018;65(2):309-315. doi: 10.4149/neo_2018_170507N328. PubMed PMID: 29534594.

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BIOMARKEREK ÉS DRIVEREK	REFERENCIA
TP53-M160_A161dup	IARC TP53 Database Shi M, Huang R, Pei C, Jia X, Jiang C, Ren H. TP53 codon 72 polymorphism and glioma risk: A meta-analysis. Oncol Lett. 2012 Mar;3(3):599-606. PubMed PMID: 22740959; PubMed Central PMCID: PMC3362515. Sholl AB, Aisner DL, Behbakht K, Post MD. Novel TP53 gene mutation and correlation with p53 immunohistochemistry in a mixed epithelial carcinoma of the endometrium. Gynecol Oncol Case Rep. 2012 Oct 26; 3:11-3. doi: 10.1016/j.gynor.2012.10.005. eCollection 2012. PubMed PMID: 24371653; PubMed Central PMCID: PMC3862336. Wellcome Trust Sanger Institute Kang HJ, Chun SM, Kim KR, Sohn I, Sung CO. Clinical relevance of gain-of-function mutations of p53 in high-grade serous ovarian carcinoma. PLoS One. 2013 Aug 13;8(8):e72609. doi: 10.1371/journal.pone.0072609. PubMed PMID: 23967324; PubMed Central PMCID: PMC3742716.
KMT2C-C391*	Wellcome Sanger Institute Wellcome Trust Sanger Institute Wellcome Sanger Institute Wellcome Sanger Institute Wellcome Sanger Institute
KIT-E930Q	Wellcome Trust Sanger Institute Wellcome Trust Sanger Institute Wellcome Trust Sanger Institute Wellcome Trust Sanger Institute Vila L, Liu H, Al-Quran SZ, Coco DP, Dong HJ, Liu C. Identification of c-kit gene mutations in primary adenoid cystic carcinoma of the salivary gland. Mod Pathol. 2009 Oct;22(10):1296-302. doi: 10.1038/modpathol.2009.95. Epub 2009 Jul 17. PubMed PMID: 19617878; PubMed Central PMCID: PMC3746033.
NFE2L2-G589D	NCBI ClinVar Wellcome Sanger Institute Fabrizio FP, Sparaneo A, Trombetta D, Muscarella LA. Epigenetic versus Genetic Deregulation of the KEAP1/NRF2 Axis in Solid Tumors: Focus on Methylation and Noncoding RNAs. Oxid Med Cell Longev. 2018 Mar 13;2018: 2492063. doi: 10.1155/2018/2492063. eCollection 2018. Review. PubMed PMID: 29643973; PubMed Central PMCID: PMC5872633. https://cancer.sanger.ac.uk/cosmic/search?q=NFE2L2+D27Y Wellcome Trust Sanger Institute
GNAS-P459R	Wellcome Trust Sanger Institute Wellcome Trust Sanger Institute Wellcome Trust Sanger Institute Wellcome Trust Sanger Institute https://www.ncbi.nlm.nih.gov/clinvar/variation/134493/
KDM5C-S299R	Wellcome Trust Sanger Institute Wellcome Sanger Institute Wellcome Trust Sanger Institute Wellcome Sanger Institute NCBI ClinVar Database

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BIOMARKEREK ÉS DRIVEREK	REFERENCIA
CUL3-R162fs*9	Wellcome Sanger Institute Wellcome Sanger Institute Castro MP, Goldstein N. Mismatch repair deficiency associated with complete remission to combination programmed cell death ligand immune therapy in a patient with sporadic urothelial carcinoma: immunotheranostic considerations. J Immunother Cancer. 2015 Dec 15;3:58. doi: 10.1186/s40425-015-0104-y. eCollection 2015. PubMed PMID: 26674132; PubMed Central PMCID: PMC4678532. Drainas AP, Lambuta RA, Ivanova I, Serçin Ö, Sarropoulos I, Smith ML, Efthymiopoulos T, Raeder B, Stütz AM, Waszak SM, Mardin BR, Korbel JO. Genome-wide Screens Implicate Loss of Cullin Ring Ligase 3 in Persistent Proliferation and Genome Instability in TP53-Deficient Cells. Cell Rep. 2020 Apr 07;31(1):107465. doi: 10.1016/j.celrep.2020.03.029. PubMed PMID: 32268084; PubMed Central PMCID: PMC7166082.
FOXA1-L148V	Wellcome Sanger Institute Wellcome Sanger Institute Wellcome Sanger Institute Li M, Zhang W, Liu C, Shi Y, Tang W, Chen S, Gu H, Yin J, Zhang Z, Jiang P. Forkhead box A1 (FOXA1) tagging polymorphisms and esophageal cancer risk in a Chinese population: a fine-mapping study. Biomarkers. 2016 Sep;21(6):523-9. doi: 10.3109/1354750X.2016.1160425. Epub 2016 Apr 6. PubMed PMID: 27050876.
TENT5C-E299K	Wellcome Trust Sanger Institute Wellcome Sanger Institute
GAS6-V673fs*37	Wellcome Trust Sanger Institute Wellcome Sanger Institute
ZNF703-A514del	Wellcome Trust Sanger Institute Wellcome Trust Sanger Institute
ZNF703-P307S	Wellcome Trust Sanger Institute Wellcome Trust Sanger Institute
AKAP9-Q1373E	Wellcome Sanger Institute
MAGI2-E867K	Wellcome Sanger Institute
BRCA1-D430N	Wellcome Sanger Institute
OTOP1-V69M	Wellcome Trust Sanger Institute
KLHL6-Q317L	Wellcome Trust Sanger Institute
SEC16A-T1001I	Wellcome Trust Sanger Institute
PCBP1-N84S	Wellcome Trust Sanger Institute
KMT2C-R380L	Wellcome Trust Sanger Institue Yang B, Luo L, Luo W, Zhou Y, Yang C, Xiong T, Li X, Meng X, Li L, Zhang X, Wang Z, Wang Z. The genomic dynamics during progression of lung adenocarcinomas. J Hum Genet. 2017 Aug;62(8):783-788. doi: 10.1038/jhg.2017.40. Epub 2017 Jan 06. PubMed PMID: 28381877; PubMed Central PMCID: PMC5537414. Cho SJ, Yoon C, Lee JH, Chang KK, Lin JX, Kim YH, Kook MC, Aksoy BA, Park DJ, Ashktorab H, Smoot DT, Schultz N, Yoon SS. KMT2C Mutations in Diffuse-Type Gastric Adenocarcinoma Promote Epithelial-to-Mesenchymal Transition. Clin Cancer Res. 2018 Dec 15;24(24):6556-6569. doi: 10.1158/1078-0432.CCR-17-1679. Epub 2018 Aug 14. PubMed PMID: 30108106; PubMed Central PMCID: PMC6295255.
KIT-M541L	LOVD database SNPeffect database Krüger S, Emig M, Lohse P, Ehninger G, Hochhaus A, Schackert HK. The c-kit (CD117) sequence variation M541L, but not N564K, is frequent in the general population, and is not associated with CML in Caucasians. Leukemia. 2006 Feb;20(2):354-5; discussion 356-7. PubMed PMID: 16307017. Dufresne A, Bertucci F, Penel N, Le Cesne A, Bui B, Tubiana-Hulin M, Ray-Coquard I, Cupissol D, Chevreau C, Perol D, Goncalves A, Jimenez M, Bringuier PP, Blay JY. Identification of biological factors predictive of response to imatinib mesylate in aggressive fibromatosis. Br J Cancer. 2010 Aug 10;103(4):482-5. doi: 10.1038/sj.bjc.6605783. Epub 2010 Jul 27. PubMed PMID: 20664593; PubMed Central PMCID: PMC2939782. Gonçalves A, Monges G, Yang Y, Palmerini F, Dubreuil P, Noguchi T, Jacquemier J, Di Stefano D, Delpero JR, Sobol H, Bertucci F. Response of a KIT-positive extra-abdominal fibromatosis to imatinib mesylate and KIT genetic analysis. J Natl Cancer Inst. 2006 Apr 19;98(8):562-3. PubMed PMID: 16622127.
GNAT2-A5V	NCBI ClinVar Database

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BIOMARKEREK ÉS DRIVEREK	REFERENCIA
WNK2-H758N	NCBI ClinVar
EPHA5-A672T	Wellcome Sanger Institute http://snpeffect.switchlab.org/mutation/EPHA5_HUMAN/VAR_042144
NOTCH1-R1279H	Wellcome Sanger Institute McBride KL, Riley MF, Zender GA, Fitzgerald-Butt SM, Towbin JA, Belmont JW, Cole SE. NOTCH1 mutations in individuals with left ventricular outflow tract malformations reduce ligand-induced signaling. Hum Mol Genet. 2008 Sep 15;17(18):2886-93. doi: 10.1093/hmg/ddn187. Epub 2008 Jun 30. PubMed PMID: 18593716; PubMed Central PMCID: PMC2722892. NCBI ClinVar

TARGET GÉNEK	REFERENCIA
CD274 vad típus	Strickland KC, Howitt BE, Shukla SA, Rodig S, Ritterhouse LL, Liu JF, Garber JE, Chowdhury D, Wu CJ, D'Andrea AD, Matulonis UA, Konstantinopoulos PA. Association and prognostic significance of BRCA1/2-mutation status with neoantigen load, number of tumor-infiltrating lymphocytes and expression of PD-1/PD-L1 in high grade serous ovarian cancer. Oncotarget. 2016 Mar 22;7(12):13587-98. doi: 10.18632/oncotarget.7277. PubMed PMID: 26871470; PubMed Central PMCID: PMC4924663. 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. 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. Aguiar PN Jr, De Mello RA, Hall P, Tadokoro H, Lima Lopes G. PD-L1 expression as a predictive biomarker in advanced non-small-cell lung cancer: updated survival data. Immunotherapy. 2017 May;9(6):499-506. doi: 10.2217/imt-2016-0150. PubMed PMID: 28472902.
PD-1 vad típus	Shields LBE, Gordinier ME. Pembrolizumab in Recurrent Squamous Cell Carcinoma of the Vulva: Case Report and Review of the Literature. Gynecol Obstet Invest. 2019;84(1):94-98. doi: 10.1159/000491090. Epub 2018 Feb 17. PubMed PMID: 30016784. Aguiar PN Jr, De Mello RA, Hall P, Tadokoro H, Lima Lopes G. PD-L1 expression as a predictive biomarker in advanced non-small-cell lung cancer: updated survival data. Immunotherapy. 2017 May;9(6):499-506. doi: 10.2217/imt-2016-0150. PubMed PMID: 28472902. Strickland KC, Howitt BE, Shukla SA, Rodig S, Ritterhouse LL, Liu JF, Garber JE, Chowdhury D, Wu CJ, D'Andrea AD, Matulonis UA, Konstantinopoulos PA. Association and prognostic significance of BRCA1/2-mutation status with neoantigen load, number of tumor-infiltrating lymphocytes and expression of PD-1/PD-L1 in high grade serous ovarian cancer. Oncotarget. 2016 Mar 22;7(12):13587-98. doi: 10.18632/oncotarget.7277. PubMed PMID: 26871470; PubMed Central PMCID: PMC4924663. 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. Tang B, Yan X, Sheng X, Si L, Cui C, Kong Y, Mao L, Lian B, Bai X, Wang X, Li S, Zhou L, Yu J, Dai J, Wang K, Hu J, Dong L, Song H, Wu H, Feng H, Yao S, Chi Z, Guo J. Safety and clinical activity with an anti-PD-1 antibody JS001 in advanced melanoma or urologic cancer patients. J Hematol Oncol. 2019 01 14;12(1):7. doi: 10.1186/s13045-018-0693-2. Epub 2019 Feb 14. PubMed PMID: 30642373; PubMed Central PMCID: PMC6332582.
CTLA4 vad típus	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.

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TARGET GÉNEK	REFERENCIA
PARP1 vad típus	McGonigle S, Chen Z, Wu J, Ackermann K, Tendyke K, Moniz G, et al. Abstract 4688: E7449: A novel PARP inhibitor enhances the efficacy of radiotherapy and chemotherapy and has potent single agent anticancer activity in BRCA-deficient tumors. Cancer Res. 2012 Apr 15;72(8 Supplement):4688–4688. Anantha RW, Simhadri S, Foo TK, Miao S, Liu J, Shen Z, Ganesan S, Xia B. Functional and mutational landscapes of BRCA1 for homology-directed repair and therapy resistance. Elife. 2017 Apr 11;6. pii: e21350. doi: 10.7554/eLife.21350. PubMed PMID: 28398198; PubMed Central PMCID: PMC5432210. Drew Y, Ledermann J, Hall G, Rea D, Glasspool R, Highley M, Jayson G, Sludden J, Murray J, Jamieson D, Halford S, Acton G, Backholer Z, Mangano R, Boddy A, Curtin N, Plummer R. Phase 2 multicentre trial investigating intermittent and continuous dosing schedules of the poly(ADP-ribose) polymerase inhibitor rucaparib in germline BRCA mutation carriers with advanced ovarian and breast cancer. Br J Cancer. 2016 Mar 29;114(7):723-30. doi: 10.1038/bjc.2016.41. Epub 2016 Mar 22. Erratum in: Br J Cancer. 2016 Jun 14;114(12):e21. PubMed PMID: 27002934; PubMed Central PMCID: PMC4882768. Ledermann JA, Drew Y, Kristeleit RS. Homologous recombination deficiency and ovarian cancer. Eur J Cancer. 2016 Jun;60:49-58. doi: 10.1016/j.ejca.2016.03.005. Epub 2016 Apr 9. Review. PubMed PMID: 27065456. Livraghi L, Garber JE. PARP inhibitors in the management of breast cancer: current data and future prospects. BMC Med. 2015 Aug 13;13:188. doi: 10.1186/s12916-015-0425-1. Review. PubMed PMID: 26268938; PubMed Central PMCID: PMC4535298.
KIT vad típus	Hochhaus A, Baccarani M, Giles FJ, le Coutre PD, Müller MC, Reiter A, Santanastasio H, Leung M, Novick S, Kantarjian HM. Nilotinib in patients with systemic mastocytosis: analysis of the phase 2, open-label, single-arm nilotinib registration study. J Cancer Res Clin Oncol. 2015 Nov;141(11):2047-60. doi: 10.1007/s00432-015-1988-0. Epub 2015 May 23. PubMed PMID: 26002753; PubMed Central PMCID: PMC4768228. Zermati Y, De Sepulveda P, Féger F, Létard S, Kersual J, Castéran N, Gorochov G, Dy M, Ribadeau Dumas A, Dorgham K, Parizot C, Bieche Y, Vidaud M, Lortholary O, Arock M, Hermine O, Dubreuil P. Effect of tyrosine kinase inhibitor STI571 on the kinase activity of wild-type and various mutated c-kit receptors found in mast cell neoplasms. Oncogene. 2003 Feb 6;22(5):660-4. PubMed PMID: 12569358. Smith BD, Kaufman MD, Lu WP, Gupta A, Leary CB, Wise SC, Rutkoski TJ, Ahn YM, Al-Ani G, Bulfer SL, Caldwell TM, Chun L, Ensinger CL, Hood MM, McKinley A, Patt WC, Ruiz-Soto R, Su Y, Telikepalli H, Town A, Turner BA, Vogeti L, Vogeti S, Yates K, Janku F, Abdul Razak AR, Rosen O, Heinrich MC, Flynn DL. Ripretinib (DCC-2618) Is a Switch Control Kinase Inhibitor of a Broad Spectrum of Oncogenic and Drug-Resistant KIT and PDGFRA Variants. Cancer Cell. 2019 May 13;35(5):738-751.e9. doi: 10.1016/j.ccell.2019.04.006. PubMed PMID: 31085175. Lyle M, Long GV. Diagnosis and treatment of KIT-mutant metastatic melanoma. J Clin Oncol. 2013 Sep 10;31(26):3176-81. doi: 10.1200/JCO.2013.50.4662. Epub 2013 Aug 12. PubMed PMID: 23940219.
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. Chen Z, Xiao Z, Gu WZ, Xue J, Bui MH, Kovar P, Li G, Wang G, Tao ZF, Tong Y, Lin NH, Sham HL, Wang JY, Sowin TJ, Rosenberg SH, Zhang H. Selective Chk1 inhibitors differentially sensitize p53-deficient cancer cells to cancer therapeutics. Int J Cancer. 2006 Dec 15;119(12):2784-94. PubMed PMID: 17019715. 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. Koniaras K, Cuddihy AR, Christopoulos H, Hogg A, O'Connell MJ. Inhibition of Chk1-dependent G2 DNA damage checkpoint radiosensitizes p53 mutant human cells. Oncogene. 2001 Nov 8;20(51):7453-63. PubMed PMID: 11709716.
PARP2 vad típus	McGonigle S, Chen Z, Wu J, Ackermann K, Tendyke K, Moniz G, et al. Abstract 4688: E7449: A novel PARP inhibitor enhances the efficacy of radiotherapy and chemotherapy and has potent single agent anticancer activity in BRCA-deficient tumors. Cancer Res. 2012 Apr 15;72(8 Supplement):4688–4688.
WEE1 vad típus	Hirai H, Iwasawa Y, Okada M, Arai T, Nishibata T, Kobayashi M, Kimura T, Kaneko N, Ohtani J, Yamanaka K, Itadani H, Takahashi-Suzuki I, Fukasawa K, Oki H, Nambu T, Jiang J, Sakai T, Arakawa H, Sakamoto T, Sagara T, Yoshizumi T, Mizuarai S, Kotani H. Small-molecule inhibition of Wee1 kinase by MK-1775 selectively sensitizes p53-deficient tumor cells to DNA-damaging agents. Mol Cancer Ther. 2009 Nov;8(11):2992-3000. doi: 10.1158/1535-7163.MCT-09-0463. PubMed PMID: 19887545. Leijen S, van Geel RM, Pavlick AC, Tibes R, Rosen L, Razak AR, Lam R, Demuth T, Rose S, Lee MA, Freshwater T, Shumway S, Liang LW, Oza AM, Schellens JH, Shapiro GI. Phase I Study Evaluating WEE1 Inhibitor AZD1775 As Monotherapy and in Combination With Gemcitabine, Cisplatin, or Carboplatin in Patients With Advanced Solid Tumors. J Clin Oncol. 2016 Dec 20;34(36):4371-4380. doi: 10.1200/JCO.2016.67.5991. Epub 2016 Oct 31. PubMed PMID: 27601554.
ATR vad típus	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.
CDK4 vad típus	Zou X, Ray D, Aziyu A, Christov K, Boiko AD, Gudkov AV, Kiyokawa H. Cdk4 disruption renders primary mouse cells resistant to oncogenic transformation, leading to Arf/p53-independent senescence. Genes Dev. 2002 Nov 15;16(22):2923-34. PubMed PMID: 12435633; PubMed Central PMCID: PMC187486.

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TARGET GÉNEK	REFERENCIA
RARG vad típus	Larsson CA, Moyer SM, Liu B, Michel KA, Pant V, Yang P, Wong J, El-Naggar AK, Krahe R, Lozano G. Synergistic and additive effect of retinoic acid in circumventing resistance to p53 restoration. Proc Natl Acad Sci U S A. 2018 02 27; 115(9):2198-2203. doi: 10.1073/pnas.1719001115. Epub 2018 Oct 13. PubMed PMID: 29440484; PubMed Central PMCID: PMC5834709.
PLK1 vad típus	Degenhardt Y, Greshock J, Laquerre S, Gilmartin AG, Jing J, Richter M, Zhang X, Bleam M, Halsey W, Hughes A, Moy C, Liu-Sullivan N, Powers S, Bachman K, Jackson J, Weber B, Wooster R. Sensitivity of cancer cells to Plk1 inhibitor GSK461364A is associated with loss of p53 function and chromosome instability. Mol Cancer Ther. 2010 Jul;9(7):2079-89. doi: 10.1158/1535-7163.MCT-10-0095. Epub 2010 Jun 22. PubMed PMID: 20571075.
PRKDC vad típus	Sun Q, Guo Y, Liu X, Czauderna F, Carr MI, Zenke FT, Blaukat A, Vassilev LT. Therapeutic Implications of p53 Status on Cancer Cell Fate Following Exposure to Ionizing Radiation and the DNA-PK Inhibitor M3814. Mol Cancer Res. 2019 12;17(12):2457-2468. doi: 10.1158/1541-7786.MCR-19-0362. Epub 2019 Jul 24. PubMed PMID: 31551253.
CDK1 vad típus	Bhattacharya S, Ray RM, Johnson LR. Cyclin-dependent kinases regulate apoptosis of intestinal epithelial cells. Apoptosis. 2014 Mar;19(3):451-66. doi: 10.1007/s10495-013-0942-3. PubMed PMID: 24242917; PubMed Central PMCID: PMC3945523.
CDK9 vad típus	Bhattacharya S, Ray RM, Johnson LR. Cyclin-dependent kinases regulate apoptosis of intestinal epithelial cells. Apoptosis. 2014 Mar;19(3):451-66. doi: 10.1007/s10495-013-0942-3. PubMed PMID: 24242917; PubMed Central PMCID: PMC3945523.
CDK2 vad típus	Bhattacharya S, Ray RM, Johnson LR. Cyclin-dependent kinases regulate apoptosis of intestinal epithelial cells. Apoptosis. 2014 Mar;19(3):451-66. doi: 10.1007/s10495-013-0942-3. PubMed PMID: 24242917; PubMed Central PMCID: PMC3945523.
AURKB vad típus	Diaz RJ, Golbourn B, Shekarforoush M, Smith CA, Rutka JT. Aurora kinase B/C inhibition impairs malignant glioma growth in vivo. J Neurooncol. 2012 Jul;108(3):349-60. doi: 10.1007/s11060-012-0835-2. Epub 2012 Jun 01. PubMed PMID: 22382783.
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.
JAK2 vad típus	Huang Z, Ruan HB, Zhang ZD, Chen W, Lin Z, Zeng H, Gao X. Mutation in the first Ig-like domain of Kit leads to JAK2 activation and myeloproliferation in mice. Am J Pathol. 2014 Jan;184(1):122-32. doi: 10.1016/j.ajpath.2013.09.019. Epub 2013 Nov 7. PubMed PMID: 24211109.
glutaminase vad típus	Sayin VI, LeBoeuf SE, Singh SX, Davidson SM, Biancur D, Guzelhan BS, Alvarez SW, Wu WL, Karakousi TR, Zavitsanou AM, Ubriaco J, Muir A, Karagiannis D, Morris PJ, Thomas CJ, Possemato R, Vander Heiden MG, Papagiannakopoulos T. Activation of the NRF2 antioxidant program generates an imbalance in central carbon metabolism in cancer. Elife. 2017 Oct 2;6. pii: e28083. doi: 10.7554/eLife.28083. PubMed PMID: 28967864; PubMed Central PMCID: PMC5624783. Romero R, Sayin VI, Davidson SM, Bauer MR, Singh SX, LeBoeuf SE, Karakousi TR, Ellis DC, Bhutkar A, Sánchez-Rivera FJ, Subbaraj L, Martinez B, Bronson RT, Prigge JR, Schmidt EE, Thomas CJ, Goparaju C, Davies A, Dolgalev I, Heguy A, Allaj V, Poirier JT, Moreira AL, Rudin CM, Pass HI, Vander Heiden MG, Jacks T, Papagiannakopoulos T. Keap1 loss promotes Kras-driven lung cancer and results in dependence on glutaminolysis. Nat Med. 2017 Nov;23(11):1362-1368. doi: 10.1038/nm.4407. Epub 2017 Oct 2. PubMed PMID: 28967920; PubMed Central PMCID: PMC5677540.
PRKACA vad típus	http://www.fasebj.org/content/31/1_Supplement/lb527.short
ATM vad típus	Drainas AP, Lambuta RA, Ivanova I, Serçin Ö, Sarropoulos I, Smith ML, Efthymiopoulos T, Raeder B, Stütz AM, Waszak SM, Mardin BR, Korbel JO. Genome-wide Screens Implicate Loss of Cullin Ring Ligase 3 in Persistent Proliferation and Genome Instability in TP53-Deficient Cells. Cell Rep. 2020 Apr 07;31(1):107465. doi: 10.1016/j.celrep.2020.03.029. PubMed PMID: 32268084; PubMed Central PMCID: PMC7166082.

DRIVER ÉS TARGET GÉNEK LEÍRÁSA

DRIVER GÉNEK

Név	Leírás
AMPH	May participate in mechanisms of regulated exocytosis in synapses and certain endocrine cell types. May control the properties of the membrane associated cytoskeleton.
AXL	Receptor tyrosine kinase that transduces signals from the extracellular matrix into the cytoplasm by binding growth factor GAS6 and which is thus regulating many physiological processes including cell survival, cell proliferation, migration and differentiation. Ligand binding at the cell surface induces dimerization and autophosphorylation of AXL. Following activation by ligand, ALX binds and induces tyrosine phosphorylation of PI3-kinase subunits PIK3R1, PIK3R2 and PIK3R3; but also GRB2, PLCG1, LCK and PTPN11. Other downstream substrate candidates for AXL are CBL, NCK2, SOCS1 and TNS2. Recruitment of GRB2 and phosphatidylinositol 3 kinase regulatory subunits by AXL leads to the downstream activation of the AKT kinase. GAS6/AXL signaling plays a role in various processes such as endothelial cell survival during acidification by preventing apoptosis, optimal cytokine signaling during human natural killer cell development, hepatic regeneration, gonadotropin-releasing hormone neuron survival and migration, platelet activation, or regulation of thrombotic responses. Plays also an important role in inhibition of Toll-like receptors (TLRs)-mediated innate immune response. In case of filovirus infection, seems to function as a cell entry factor.

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DRIVER GÉNEK

Név	Leírás
BRCA1	E3 ubiquitin-protein ligase that specifically mediates the formation of Lys-6-linked polyubiquitin chains and plays a central role in DNA repair by facilitating cellular responses to DNA damage. It is unclear whether it also mediates the formation of other types of polyubiquitin chains. The E3 ubiquitin-protein ligase activity is required for its tumor suppressor function. The BRCA1-BARD1 heterodimer coordinates a diverse range of cellular pathways such as DNA damage repair, ubiquitination and transcriptional regulation to maintain genomic stability. Regulates centrosomal microtubule nucleation. Required for normal cell cycle progression from G2 to mitosis. Required for appropriate cell cycle arrests after ionizing irradiation in both the S-phase and the G2 phase of the cell cycle. Involved in transcriptional regulation of P21 in response to DNA damage. Required for FANCD2 targeting to sites of DNA damage. May function as a transcriptional regulator. Inhibits lipid synthesis by binding to inactive phosphorylated ACACA and preventing its dephosphorylation. Contributes to homologous recombination repair (HRR) via its direct interaction with PALB2, fine-tunes recombinational repair partly through its modulatory role in the PALB2-dependent loading of BRCA2-RAD51 repair machinery at DNA breaks. Component of the BRCA1-RBBP8 complex which regulates CHEK1 activation and controls cell cycle G2/M checkpoints on DNA damage via BRCA1-mediated ubiquitination of RBBP8.
CCNE1	Essential for the control of the cell cycle at the G1/S (start) transition.
EPHA5	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 most probably constitutes the cognate/functional ligand for EPHA5. Functions as an axon guidance molecule during development and may be involved in the development of the retinotectal, entorhino-hippocampal and hippocamposeptal pathways. Together with EFNA5 plays also a role in synaptic plasticity in adult brain through regulation of synaptogenesis. In addition to its function in the nervous system, the interaction of EPHA5 with EFNA5 mediates communication between pancreatic islet cells to regulate glucose-stimulated insulin secretion (By similarity).
FGF14	Probably involved in nervous system development and function
GAS6	Ligand for tyrosine-protein kinase receptors AXL, TYRO3 and MER whose signaling is implicated in cell growth and survival, cell adhesion and cell migration. GAS6/AXL signaling plays a role in various processes such as endothelial cell survival during acidification by preventing apoptosis, optimal cytokine signaling during human natural killer cell development, hepatic regeneration, gonadotropin-releasing hormone neuron survival and migration, platelet activation, or regulation of thrombotic responses.2 Publications (Microbial infection) Can bridges virus envelope phosphatidylserine to the TAM receptor tyrosine kinase Axl to mediate viral entry by apoptotic mimicry (PubMed:21501828). Plays a role in Dengue cell entry by apoptotic mimicry (PubMed:23084921). Plays a role in Vaccinia virus cell entry by apoptotic mimicry (PubMed:21501828). Plays a role in ebolavirus and marburgvirus cell entry by apoptotic mimicry (PubMed:17005688).
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.
GNAT2	Guanine nucleotide-binding proteins (G proteins) are involved as modulators or transducers in various transmembrane signaling systems. Transducin is an amplifier and one of the transducers of a visual impulse that performs the coupling between rhodopsin and cGMP-phosphodiesterase.
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).
KIT	Tyrosine-protein kinase that acts as cell-surface receptor for the cytokine KITLG/SCF and plays an essential role in the regulation of cell survival and proliferation, hematopoiesis, stem cell maintenance, gametogenesis, mast cell development, migration and function, and in melanogenesis. In response to KITLG/SCF binding, KIT can activate several signaling pathways. Phosphorylates PIK3R1, PLCG1, SH2B2/APS and CBL. Activates the AKT1 signaling pathway by phosphorylation of PIK3R1, the regulatory subunit of phosphatidylinositol 3-kinase. Activated KIT also transmits signals via GRB2 and activation of RAS, RAF1 and the MAP kinases MAPK1/ERK2 and/or MAPK3/ERK1. Promotes activation of STAT family members STAT1, STAT3, STAT5A and STAT5B. Activation of PLCG1 leads to the production of the cellular signaling molecules diacylglycerol and inositol 1,4,5-trisphosphate. KIT signaling is modulated by protein phosphatases, and by rapid internalization and degradation of the receptor. Activated KIT promotes phosphorylation of the protein phosphatases PTPN6/SHP-1 and PTPRU, and of the transcription factors STAT1, STAT3, STAT5A and STAT5B. Promotes phosphorylation of PIK3R1, CBL, CRK (isoform Crk-II), LYN, MAPK1 /ERK2 and/or MAPK3/ERK1, PLCG1, SRC and SHC1.
KLHL6	Involved in B-lymphocyte antigen receptor signaling and germinal center formation.
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.
NFE2L2	Transcription activator that binds to antioxidant response (ARE) elements in the promoter regions of target genes. Important for the coordinated up-regulation of genes in response to oxidative stress. May be involved in the transcriptional activation of genes of the beta-globin cluster by mediating enhancer activity of hypersensitive site 2 of the beta-globin locus control region.

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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).
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).
PCBP1	Single-stranded nucleic acid binding protein that binds preferentially to oligo dC
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.
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.
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.
SPEG	Isoform 3 may have a role in regulating the growth and differentiation of arterial smooth muscle cells.
TP53	Acts as a tumor suppressor in many tumor types; induces growth arrest or apoptosis depending on the physiological circumstances and cell type. Involved in cell cycle regulation as a trans-activator that acts to negatively regulate cell division by controlling a set of genes required for this process. One of the activated genes is an inhibitor of cyclin-dependent kinases. Apoptosis induction seems to be mediated either by stimulation of BAX and FAS antigen expression, or by repression of Bcl-2 expression. In cooperation with mitochondrial PPIF is involved in activating oxidative stress-induced necrosis; the function is largely independent of transcription. Induces the transcription of long intergenic non-coding RNA p21 (lincRNA-p21) and lincRNA-Mkln1. LincRNA-p21 participates in TP53-dependent transcriptional repression leading to apoptosis and seem to have to effect on cell-cycle regulation. Implicated in Notch signaling cross-over. Prevents CDK7 kinase activity when associated to CAK complex in response to DNA damage, thus stopping cell cycle progression. Isoform 2 enhances the transactivation activity of isoform 1 from some but not all TP53-inducible promoters. Isoform 4 suppresses transactivation activity and impairs growth suppression mediated by isoform 1. Isoform 7 inhibits isoform 1-mediated apoptosis. Regulates the circadian clock by repressing CLOCK-ARNTL/BMAL1-mediated transcriptional activation of PER2 (PubMed:24051492).
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.
ZNF703	Transcriptional corepressor which does not bind directly to DNA and may regulate transcription through recruitment of histone deacetylases to gene promoters. Regulates cell adhesion, migration and proliferation. May be required for segmental gene expression during hindbrain development.

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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.
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.
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 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

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	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 mitogenenic 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.
CDK9	Protein kinase involved in the regulation of transcription. Member of the cyclin-dependent kinase pair (CDK9/cyclin-T) complex, also called positive transcription elongation factor b (P-TEFb), which facilitates the transition from abortive to productive elongation by phosphorylating the CTD (C-terminal domain) of the large subunit of RNA polymerase II (RNAP II) POLR2A, SUPT5H and RDBP. This complex is inactive when in the 7SK snRNP complex form. Phosphorylates EP300, MYOD1, RPB1/POLR2A and AR, and the negative elongation factors DSIF and NELF. Regulates cytokine inducible transcription networks by facilitating promoter recognition of target transcription factors (e.g. TNF-inducible RELA/p65 activation and IL-6-inducible STAT3 signaling). Promotes RNA synthesis in genetic programs for cell growth, differentiation and viral pathogenesis. P-TEFb is also involved in cotranscriptional histone modification, mRNA processing and mRNA export. Modulates a complex network of chromatin modifications including histone H2B monoubiquitination (H2Bub1), H3 lysine 4 trimethylation (H3K4me3) and H3K36me3; integrates phosphorylation during transcription with chromatin modifications to control co-transcriptional histone mRNA processing. The CDK9/cyclin-K complex has also a kinase activity towards CTD of RNAP II and can substitute for CDK9/cyclin-T P-TEFb in vitro. Replication stress response protein; the CDK9/cyclin-K complex is required for genome integrity maintenance, by promoting cell cycle recovery from replication arrest and limiting single-stranded DNA amount in response to replication stress, thus reducing the breakdown of stalled replication forks and avoiding DNA damage. In addition, probable function in DNA repair of isoform 2 via interaction with KU70/XRCC6. Promotes cardiac myocyte enlargement. RPB1/POLR2A phosphorylation on Ser-2 in CTD activates transcription. AR phosphorylation modulates AR transcription factor promoter selectivity and cell growth. DSIF and NELF phosphorylation promotes transcription by inhibiting their negative effect. The phosphorylation of MYOD1 enhances its transcriptional activity and thus promotes muscle differentiation.
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

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	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.
glutaminase	Catalyzes the first reaction in the primary pathway for the renal catabolism of glutamine. Plays a role in maintaining acid-base homeostasis. Regulates the levels of the neurotransmitter glutamate in the brain. Isoform 2 lacks catalytic activity.
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.
KIT	Tyrosine-protein kinase that acts as cell-surface receptor for the cytokine KITLG/SCF and plays an essential role in the regulation of cell survival and proliferation, hematopoiesis, stem cell maintenance, gametogenesis, mast cell development, migration and function, and in melanogenesis. In response to KITLG/SCF binding, KIT can activate several signaling pathways. Phosphorylates PIK3R1, PLCG1, SH2B2/APS and CBL. Activates the AKT1 signaling pathway by phosphorylation of PIK3R1, the regulatory subunit of phosphatidylinositol 3-kinase. Activated KIT also transmits signals via GRB2 and activation of RAS, RAF1 and the MAP kinases MAPK1/ERK2 and/or MAPK3/ERK1. Promotes activation of STAT family members STAT1, STAT3, STAT5A and STAT5B. Activation of PLCG1 leads to the production of the cellular signaling molecules diacylglycerol and inositol 1,4,5-trisphosphate. KIT signaling is modulated by protein phosphatases, and by rapid internalization and degradation of the receptor. Activated KIT promotes phosphorylation of the protein phosphatases PTPN6/SHP-1 and PTPRU, and of the transcription factors STAT1, STAT3, STAT5A and STAT5B. Promotes phosphorylation of PIK3R1, CBL, CRK (isoform Crk-II), LYN, MAPK1 /ERK2 and/or MAPK3/ERK1, PLCG1, SRC and SHC1.
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.
PARP2	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
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.
PLK1	Serine/threonine-protein kinase that performs several important functions throughout M phase of the cell cycle, including the regulation of centrosome maturation and spindle assembly, the removal of cohesins from chromosome arms, the inactivation of anaphase-promoting complex/cyclosome (APC/C) inhibitors, and the regulation of mitotic exit and cytokinesis. Polo-like kinase proteins acts by binding and phosphorylating proteins are that already phosphorylated on a specific motif recognized by the POLO box domains. Phosphorylates BORA, BUB1B/BUBR1, CCNB1, CDC25C, CEP55, ECT2, ERCC6L, FBXO5/EMI1, FOXM1, KIF20A/MKLP2, CENPU, NEDD1,

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TARGET GÉNEK

Név	Leírás
	NINL, NPM1, NUDC, PKMYT1/MYT1, KIZ, PPP1R12A/MYPT1, PRC1, RACGAP1/CYK4, SGOL1, STAG2/SA2, TEX14, TOPORS, p73/TP73, TPT1 and WEE1. Plays a key role in centrosome functions and the assembly of bipolar spindles by phosphorylating KIZ, NEDD1 and NINL. NEDD1 phosphorylation promotes subsequent targeting of the gamma-tubulin ring complex (gTuRC) to the centrosome, an important step for spindle formation. Phosphorylation of NINL component of the centrosome leads to NINL dissociation from other centrosomal proteins. Involved in mitosis exit and cytokinesis by phosphorylating CEP55, ECT2, KIF20A/MKLP2, CENPU, PRC1 and RACGAP1. Recruited at the central spindle by phosphorylating and docking PRC1 and KIF20A/MKLP2; creates its own docking sites on PRC1 and KIF20A/MKLP2 by mediating phosphorylation of sites subsequently recognized by the POLO box domains. Phosphorylates RACGAP1, thereby creating a docking site for the Rho GTP exchange factor ECT2 that is essential for the cleavage furrow formation. Promotes the central spindle recruitment of ECT2. Plays a central role in G2/M transition of mitotic cell cycle by phosphorylating CCNB1, CDC25C, FOXM1, CENPU, PKMYT1/MYT1, PPP1R12A /MYPT1 and WEE1. Part of a regulatory circuit that promotes the activation of CDK1 by phosphorylating the positive regulator CDC25C and inhibiting the negative regulators WEE1 and PKMYT1/MYT1. Also acts by mediating phosphorylation of cyclin-B1 (CCNB1) on centrosomes in prophase. Phosphorylates FOXM1, a key mitotic transcription regulator, leading to enhance FOXM1 transcriptional activity. Involved in kinetochore functions and sister chromatid cohesion by phosphorylating BUB1B/BUBR1, FBXO5/EMI1 and STAG2/SA2. PLK1 is high on non-attached kinetochores suggesting a role of PLK1 in kinetochore attachment or in spindle assembly checkpoint (SAC) regulation. Required for kinetochore localization of BUB1B. Regulates the dissociation of cohesin from chromosomes by phosphorylating cohesin subunits such as STAG2/SA2. Phosphorylates SGOL1: required for spindle pole localization of isoform 3 of SGOL1 and plays a role in regulating its centriole cohesion function. Mediates phosphorylation of FBXO5/EMI1, a negative regulator of the APC/C complex during prophase, leading to FBXO5/EMI1 ubiquitination and degradation by the proteasome. Acts as a negative regulator of p53 family members: phosphorylates TOPORS, leading to inhibit the sumoylation of p53/TP53 and simultaneously enhance the ubiquitination and subsequent degradation of p53/TP53. Phosphorylates the transactivation domain of the transcription factor p73/TP73, leading to inhibit p73/TP73-mediated transcriptional activation and pro-apoptotic functions. Phosphorylates BORA, and thereby promotes the degradation of BORA. Contributes to the regulation of AURKA function. Also required for recovery after DNA damage checkpoint and entry into mitosis. Phosphorylates MISP, leading to stabilization of cortical and astral microtubule attachments required for proper spindle positioning (PubMed:8991084, PubMed:11202906, PubMed:12207013, PubMed:12447691, PubMed:12524548, PubMed: 12738781, PubMed:12852856, PubMed:12939256, PubMed:14532005, PubMed:14734534, PubMed:15070733, PubMed:15148369, PubMed:15469984, PubMed:16198290, PubMed:16247472, PubMed:16980960, PubMed: 17081991, PubMed:17351640, PubMed:17376779, PubMed:17617734, PubMed:18174154, PubMed:18331714, PubMed: 18418051, PubMed:18477460, PubMed:18521620, PubMed:1
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 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).
PRKDC	Serine/threonine-protein kinase that acts as a molecular sensor for DNA damage. Involved in DNA non-homologous end joining (NHEJ) required for double-strand break (DSB) repair and V(D)J recombination. Must be bound to DNA to express its catalytic properties. Promotes processing of hairpin DNA structures in V(D)J recombination by activation of the hairpin endonuclease artemis (DCLRE1C). The assembly of the DNA-PK complex at DNA ends is also required for the NHEJ ligation step. Required to protect and align broken ends of DNA. May also act as a scaffold protein to aid the localization of DNA repair proteins to the site of damage. Found at the ends of chromosomes, suggesting a further role in the maintenance of telomeric stability and the prevention of chromosomal end fusion. Also involved in modulation of transcription. Recognizes the substrate consensus sequence [ST]-Q. Phosphorylates Ser-139 of histone variant H2AX/H2AFX, thereby regulating DNA damage response mechanism. Phosphorylates DCLRE1C, c-Abl/ABL1, histone H1, HSPCA, c-jun/JUN, p53/TP53, PARP1, POU2F1, DHX9, SRF, XRCC1, XRCC1, XRCC4, XRCC5, XRCC6, WRN, MYC and RFA2. Can phosphorylate C1D not only in the presence of linear DNA but also in the presence of supercoiled DNA. Ability to phosphorylate p53/TP53 in the presence of supercoiled DNA is dependent on C1D. Contributes to the determination of the circadian period length by antagonizing phosphorylation of CRY1 Ser-588 and increasing CRY1 protein stability, most likely through an indirect machanism. Interacts with CRY1 and CRY2; negatively regulates CRY1 phosphorylation.
RARG	Receptor for retinoic acid. Retinoic acid receptors bind as heterodimers to their target response elements in response to their ligands, all-trans or 9-cis retinoic acid, and regulate gene expression in various biological processes. The RAR/RXR heterodimers bind to the retinoic acid response elements (RARE) composed of tandem 5'-AGGTCA-3' sites known as DR1-DR5. In the absence of ligand, acts mainly as an activator of gene expression due to weak binding to corepressors. Required for limb bud development. In concert with RARA or RARB, required for skeletal growth, matrix homeostasis and growth plate function (By similarity).
WEE1	

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DRIVER ÉS TARGET GÉNEK LEÍRÁSA

TARGET GÉNEK

Név	Leírás
	Acts as a negative regulator of entry into mitosis (G2 to M transition) by protecting the nucleus from cytoplasmically activated cyclin B1-complexed CDK1 before the onset of mitosis by mediating phosphorylation of CDK1 on Tyr-15. Specifically phosphorylates and inactivates cyclin B1-complexed CDK1 reaching a maximum during G2 phase and a minimum as cells enter M phase. Phosphorylation of cyclin B1-CDK1 occurs exclusively on Tyr-15 and phosphorylation of monomeric CDK1 does not occur. Its activity increases during S and G2 phases and decreases at M phase when it is hyperphosphorylated. A correlated decrease in protein level occurs at M/G1 phase, probably due to its degradation

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

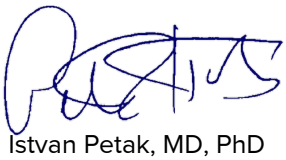
KLINIKAI VIZSGÁLATBAN ELÉRHETŐ HATÓANYAGOK (445): 17-AAG, 4SC-201, 4SC-202, 4SC-203, AAL881, AB-010, ABBV-221, ABT-414, ABT-494, ABT-700, ABT-767, ABT-806, ABTL0812, AC0010MA, AC-480, ACE-041, ACP-319, ACY-1215, ACY-241, ADU-623, AEB071, AEE788, AG-014699, AG-120, AG-881, AGI-5198, AKN-028, ALLITINIB, 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	
NÉV	Anonymous



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