ONCOMPASS™ REPORT

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Realtime Oncology
Molecular Treatment Calculator™

Oncompass Report

A Realtime Oncology Molecular Treatment Calculator számításaival

AZONOSÍTÓ	429397
NÉV	Anonymous

BETEG ADATAI

Oncompass™ ID:
Név: Anonymous
Születési dátum: 1954

Primer daganat lokalizációja: gastric
Szövettani típus: adenocarcinoma
Metasztázis lokalizációja: liver, lymph node

SZAKÉRTŐK

Molekuláris Farmakológus: Dr. Peták István
Genetikai Tanácsadó: Déri Júlia, MSc
Konzulens Orvos: Dr. Pajkos Gábor
Molekuláris Biológus: Várkondi Edit, PhD
Szakértő: Dr. Szuszán Marianna
Betegút Koordinátor: Molnár Katalin
molekuláris biológus: Boldizsár Ákos, PhD
Biofizikus: Lakatos Dóra, PhD

PATOLÓGIAI ÉS MOLEKULÁRIS DIAGNOSZTIKAI VIZSGÁLATOK

Mintaazonosító: XXX
Minta eredete: primer tumor
Tumorarány: 40%
Tumortípus: gyomor adenocarcinoma

Elvégzett vizsgálatok:
NGS - 591 gén
MSI - MSS
TMB - HIGH
IHC - PDL1 (Overexpresszió: 80%)
FISH - PIK3CA (Nem amplifikált)

Korábban elvégzett vizsgálatok:
IHC - HER2 (Normál expresszió)

KORÁBBI KEZELÉSEK

1. vonal - FOLFIRINOX

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ÖSSZEFOGLALÁS

Elkészült XXX (gyomor adenocarcinoma) Oncompass Riportja digitális terápia tervezés és célzott terápiás lehetőségek feltárása céljából.
NGS-591/MSI/PD-L1 alapú molekuláris profil vizsgálat a XXX primer tumor szöveti mintából készült 40%-os tumorarány mellett. NGS során a következő eredmények szignifikánsak:
A tumor TMB-H (5,75), PD-L1 80% pozitív ugynakkor MSS.
A vizsgált mintában a szekvencia analízis (NGS) során kapott 1 megabázisra vonatkozó mutációk száma (TMB) 5,75. Az adatbázisunkban lévő kalkulált TMB értékek (n=576) eloszlása alapján az eseteink 89%-ában ennél alacsonyabb TMB értéket kaptunk. Pembrolizumab FDA törzskönyvezett PD-L1 pozitív gyomor daganatban illetve TMB-H szolid tumorban. Molekuláris profil alapján immunterápiára rezisztencia mutációt nem detektáltunk.
PIK3CA-E545K driver (AF 40%) egy ismert aktiváló mutáció, mely esetén a daganat molekuláris profiljával pozitív asszociációban említhetőek a PIK3CA/AKT/mTOR gátló hatóanyagok. Az ALPELISIB és a COPANLISIB (FDA) törzskönyvezett PIK3CA gátló hatóanyagok. Forgalomban lévő mTOR-gátló készítmény az EVEROLIMUS, a METFORMIN, SIROLIMUS és a TEMSIROLIMUS.

A szövettan alapján a 2. vonalban on-label elérhető ramucirumab és paclitaxel kombináció nem kontraindikált metforminnal kiegészítve.
A szövettan és molekuláris profil ismeretében célzott FDA törzskönyvezett terápiás opció: pembrolizumab plusz metformin off-label.

MOLEKULÁRIS CÉLPONT ELEMZÉS

MOLEKULÁRIS ALTERÁCIÓK

TMB-H driver (AEL: 796,72, AF/TR: NA/40%),
PDL1 protein overexpression driver (AEL: 493,34, AF/TR: NA/40%),
PIK3CA-E545K driver (AEL: 251,73, AF/TR: 35.85%/40%),
FBXW7-E449Q VUS, driver gén (AEL: 4,90, AF/TR: 13.23%/40%),
FGFR3-P795L VUS, driver gén (AEL: 3,83, AF/TR: 13.06%/40%),
ARID1A-S558fs*65 VUS, driver gén (AEL: 2,43, AF/TR: 13.23%/40%),
ABL1-T653R VUS, driver gén (AEL: 2,36, AF/TR: 9.59%/40%),
KMT2C-G908C driver (AEL: 1,73, AF/TR: 8.7%/40%),
KMT2C-G3106_K3109del VUS, driver gén (AEL: 1,72, AF/TR: 12.89%/40%),
MUC16-S14437F VUS, driver gén (AEL: 0,51, AF/TR: 49%/40%),
PTPRD-D778N VUS, driver gén (AEL: 0,12, AF/TR: 6.3%/40%),
LAMA2-T821M VUS, driver gén (AEL: 0,10, AF/TR: 49.22%/40%),
SBDS-C119S VUS, driver gén (AEL: 0,10, AF/TR: 14.61%/40%),
CDC73-K524T VUS, driver gén (AEL: 0,09, AF/TR: 15.78%/40%),
SPRED1-E63* VUS, driver gén (AEL: 0,06, AF/TR: 12.99%/40%),
FOXP1-M188T VUS, driver gén (AEL: 0,02, AF/TR: 52.22%/40%),
SLIT2-A502V driver (AEL: 0,01, AF/TR: 57.99%/40%),
BCL6-E164D ellentmondásos driver (AEL: 0,00, AF/TR: 59.31%/40%),
PAX7-R221Q ellentmondásos driver (AEL: 0,00, AF/TR: 53.49%/40%),
BCOR loss presence ismeretlen jelentőségű variáns (AEL: 0,00, AF/TR: NA/40%),
BAZ2B-G2005fs*4 ismeretlen jelentőségű variáns (AEL: 0,00, AF/TR: 15.99%/40%),
CYLD-R315del ismeretlen jelentőségű variáns (AEL: 0,00, AF/TR: 39.94%/40%),
NEK2-R164T ismeretlen jelentőségű variáns (AEL: 0,00, AF/TR: 3.12%/40%),
GRM8-A222fs*49 ismeretlen jelentőségű variáns (AEL: 0,00, AF/TR: 11.98%/40%),
RBM10 loss presence ismeretlen jelentőségű variáns (AEL: 0,00, AF/TR: NA/40%),
GRM8-Y663C ismeretlen jelentőségű variáns (AEL: 0,00, AF/TR: 49.17%/40%),
MST1R-W1271fs*11 ismeretlen jelentőségű variáns (AEL: 0,00, AF/TR: 3.06%/40%),
CCDC178-T657A ismeretlen jelentőségű variáns (AEL: 0,00, AF/TR: 46.98%/40%),
PIK3C2B-F1029L nem driver (AEL: -0,01, AF/TR: 55.59%/40%),
PTGFR-M155I nem driver (AEL: -0,01, AF/TR: 46.61%/40%),
SDHD-H50R nem driver (AEL: -2,65, AF/TR: 48.37%/40%),
SDHA-L649FS*4 nem driver (AEL: -4,99, AF/TR: 11.25%/40%),
BCL9-G302D nem driver (AEL: -5,00, AF/TR: 47.92%/40%),
APEX1-Q51H nem driver (AEL: -5,53, AF/TR: 47.85%/40%),
MAP3K4-H906P nem driver (AEL: -9,98, AF/TR: 50.19%/40%),
FANCD2-F386V nem driver (AEL: -14,99, AF/TR: 11.44%/40%)

INDIREKT CÉLPONT GÉNEK

CD274 vad típus (AEL: 1700,55),
- MUC16-S14437F driver (AEL: 0,51) ;
- TMB-H driver (AEL: 796,72) ;
- PDL1 protein overexpression driver (AEL: 493,34) ;
- ARID1A-S558fs*65 driver (AEL: 2,43)

PD-1 vad típus (AEL: 1372,75),
- MUC16-S14437F driver (AEL: 0,51) ;
- PDL1 protein overexpression driver (AEL: 493,34) ;
- TMB-H driver (AEL: 796,72)

CTLA4 vad típus (AEL: 803,49),
- TMB-H driver (AEL: 796,72) ;
- MUC16-S14437F driver (AEL: 0,51)

PIK3CA vad típus (AEL: 475,28),
- PIK3CA-E545K driver (AEL: 251,73)

MTOR vad típus (AEL: 277,97),
- FBXW7-E449Q driver (AEL: 4,90) ;
- PIK3CA-E545K driver (AEL: 251,73)

AKT1 vad típus (AEL: 258,85),
- ARID1A-S558fs*65 driver (AEL: 2,43) ;
- PIK3CA-E545K driver (AEL: 251,73)

AKT2 vad típus (AEL: 252,83),
- PIK3CA-E545K driver (AEL: 251,73)

CTNNB1 vad típus (AEL: 252,16),
- PIK3CA-E545K driver (AEL: 251,73)

AKT3 vad típus (AEL: 252,09),
- PIK3CA-E545K driver (AEL: 251,73)

FGFR3 vad típus (AEL: 173,81),
- FGFR3-P795L driver (AEL: 3,83)

NOTCH1 vad típus (AEL: 6,04),
- FBXW7-E449Q driver (AEL: 4,90)

BRD4 vad típus (AEL: 5,59),
- KMT2C-G908C driver (AEL: 1,73) ;
- KMT2C-G3106_K3109del driver (AEL: 1,72)

MCL1 vad típus (AEL: 5,35),
- FBXW7-E449Q driver (AEL: 4,90)

EZH2 vad típus (AEL: 4,92),
- ARID1A-S558fs*65 driver (AEL: 2,43)

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MOLEKULÁRIS CÉLPONT ELEMZÉS	
	PARP1 vad típus (AEL: 3,88), • ARID1A-S558fs*65 driver (AEL: 2,43) YES1 vad típus (AEL: 2,95), • ARID1A-S558fs*65 driver (AEL: 2,43) KDM1A vad típus (AEL: 2,73), • ARID1A-S558fs*65 driver (AEL: 2,43) STAT3 vad típus (AEL: 0,99) • PTPRD-D778N driver (AEL: 0,12)

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DAGANAT MOLEKULÁRIS PROFILJÁVAL POZITÍV KAPCSOLATBAN ÁLLÓ HATÓANYAGOK

FORGALOMBAN LÉVŐ
9 listázott hatóanyag (összesen 88)

PEMBROLIZUMAB (esophagus - squamous cell carcinoma [FDA]; rectum - bármely szövettan [FDA+EMA]; skin - squamous cell carcinoma [FDA]; gastroesophageal junction - adenocarcinoma [FDA]; gastric - adenocarcinoma [FDA]; bármely tumor - urothelial carcinoma [FDA+EMA]; bármely tumor - malignant melanoma [FDA+EMA]; lung - adenocarcinoma [FDA+EMA]; endometrium - bármely szövettan [FDA]; skin - Merkel cell carcinoma (MCC) [FDA]; bármely tumor - renal cell carcinoma [FDA+EMA]; cervix - bármely szövettan [FDA]; colon - bármely szövettan [FDA+EMA]; head-neck - squamous cell carcinoma [FDA+EMA]; breast - bármely szövettan [FDA]; lung - non-small cell carcinoma [FDA+EMA]; bármely tumor - mediastinal B-cell lymphoma [FDA]; bármely tumor - endometrioid carcinoma [FDA]; liver - hepatocellular carcinoma [FDA]; bármely tumor - Hodgkin lymphoma [FDA+EMA]) (AEL: 10775,40)
- PD-L1 protein overexpression driver (AEL: 493,34) ;
- PD-L1 vad típus target (AEL: 1700,55) ;
- TMB-H driver (AEL: 796,72) ;
- PD-1 vad típus target (AEL: 1372,75)

ATEZOLIZUMAB (liver - hepatocellular carcinoma [FDA+EMA]; bármely tumor - urothelial carcinoma [FDA+EMA]; breast - bármely szövettan [FDA+EMA]; lung - non-small cell carcinoma [FDA+EMA]; bármely tumor - malignant melanoma [FDA]; lung - small cell carcinoma [FDA+EMA]) (AEL: 3616,77)
- PD-L1 protein overexpression driver (AEL: 493,34) ;
- PD-L1 vad típus target (AEL: 1700,55)

AVELUMAB (ureter - bármely szövettan [FDA+EMA]; skin - Merkel cell carcinoma (MCC) [FDA+EMA]; bladder - urothelial carcinoma [FDA+EMA]; bladder - bármely szövettan [FDA+EMA]; kidney - renal cell carcinoma [FDA+EMA]) (AEL: 3240,29)
- PD-L1 protein overexpression driver (AEL: 493,34) ;
- TMB-H driver (AEL: 796,72) ;
- PD-L1 vad típus target (AEL: 1700,55)

DURVALUMAB (lung - non-small cell carcinoma [FDA+EMA]; lung - small cell carcinoma [FDA+EMA]; bármely tumor - urothelial carcinoma [FDA]) (AEL: 2327,42)
- PD-L1 protein overexpression driver (AEL: 493,34) ;
- PD-L1 vad típus target (AEL: 1700,55)

NIVOLUMAB (esophagus - squamous cell carcinoma [FDA+EMA]; bármely tumor - urothelial carcinoma [FDA+EMA]; lung - non-small cell carcinoma [FDA+EMA]; bone marrow - Hodgkin lymphoma [FDA+EMA]; head-neck - squamous cell carcinoma [FDA+EMA]; bármely tumor - malignant melanoma [FDA+EMA]; colon - bármely szövettan [FDA]; liver - hepatocellular carcinoma [FDA]; kidney - renal cell carcinoma [FDA+EMA]; pleura - mesothelioma [FDA]; rectum - bármely szövettan [FDA]) (AEL: 2309,57)
- PD-1 vad típus target (AEL: 1372,75) ;
- PD-L1 protein overexpression driver (AEL: 493,34)

DOSTARLIMAB (endometrium - bármely szövettan [EMA]; bármely tumor - endometrioid carcinoma [EMA]) (AEL: 1372,95)
- PD-1 vad típus target (AEL: 1372,75)

CEMIPLIMAB (skin - basal cell carcinoma [FDA]; lung - adenocarcinoma [FDA]; skin - squamous cell carcinoma [FDA+EMA]; lung - squamous cell carcinoma [FDA]) (AEL: 1372,85)
- PD-1 vad típus target (AEL: 1372,75)

IPILIMUMAB (liver - hepatocellular carcinoma [FDA]; rectum - bármely szövettan [FDA]; pleura - mesothelioma [FDA]; skin - malignant melanoma [FDA+EMA]; colon - bármely szövettan [FDA]; lung - adenocarcinoma [FDA+EMA]; kidney - renal cell carcinoma [FDA+EMA]) (AEL: 809,34)
- CTLA4 vad típus target (AEL: 803,49)

ALPELISIB (breast - bármely szövettan [FDA+EMA]) (AEL: 736,69)
- PIK3CA-E545K driver (AEL: 251,73) ;
- PIK3CA vad típus target (AEL: 475,28)

DAGANAT MOLEKULÁRIS PROFILJÁVAL NEGATÍV KAPCSOLATBAN ÁLLÓ HATÓANYAGOK

FORGALOMBAN LÉVŐ
10 listázott hatóanyag (összesen 35)

CETUXIMAB (rectum - bármely szövettan [FDA+EMA]; head-neck - squamous cell carcinoma [FDA+EMA]; colon - bármely szövettan [FDA+EMA]) (AEL: -667,94)
- PIK3CA-E545K driver (AEL: -251,73) ;
- FGFR3-P795L driver (AEL: -3,83) ;
- FBXW7-E449Q driver (AEL: -4,90) ;
- EGFR vad típus target (AEL: -297,76)

PANITUMUMAB (rectum - bármely szövettan [FDA+EMA]; colon - bármely szövettan [FDA+EMA]) (AEL: -635,05)
- FBXW7-E449Q driver (AEL: -4,90) ;
- EGFR vad típus target (AEL: -297,76) ;
- PIK3CA-E545K driver (AEL: -251,73)

LAPATINIB (breast - bármely szövettan [FDA+EMA]) (AEL: -574,12)
- ERBB2 vad típus target (AEL: -256,09) ;
- PIK3CA-E545K driver (AEL: -251,73) ;
- AKT1 vad típus target (AEL: 258,85) ;
- EGFR vad típus target (AEL: -297,76)

NERATINIB (breast - bármely szövettan [FDA+EMA]) (AEL: -553,84)
- EGFR vad típus target (AEL: -297,76) ;
- ERBB2 vad típus target (AEL: -256,09)

AFATINIB (lung - squamous cell carcinoma [FDA+EMA]; lung - non-small cell carcinoma [FDA+EMA]; lung - adenocarcinoma [FDA+EMA]) (AEL: -553,56)
- ERBB2 vad típus target (AEL: -256,09) ;
- EGFR vad típus target (AEL: -297,76)

ERLOTINIB (lung - squamous cell carcinoma [FDA+EMA]; lung - non-small cell carcinoma [FDA+EMA]; lung - adenocarcinoma [FDA+EMA]; pancreas - bármely szövettan [FDA+EMA]) (AEL: -545,43)
- PIK3CA-E545K driver (AEL: -251,73) ;
- EGFR vad típus target (AEL: -297,76)

TRASTUZUMAB (breast - bármely szövettan [FDA+EMA]; gastric - adenocarcinoma [FDA+EMA]; gastroesophageal junction - adenocarcinoma [FDA+EMA]) (AEL: -517,95)
- PIK3CA-E545K driver (AEL: -251,73) ;
- ERBB2 vad típus target (AEL: -256,09)

GEFITINIB (lung - non-small cell carcinoma [FDA+EMA]; lung - adenocarcinoma [FDA+EMA]; lung - squamous cell carcinoma [FDA+EMA]) (AEL: -305,44)
- FBXW7-E449Q driver (AEL: -4,90) ;
- EGFR vad típus target (AEL: -297,76)

OSIMERTINIB (lung - non-small cell carcinoma [FDA+EMA]; lung - adenocarcinoma [FDA+EMA]; lung - squamous cell carcinoma [FDA+EMA]) (AEL: -297,76)
- EGFR vad típus target (AEL: -297,76)

DACOMITINIB (lung - non-small cell carcinoma [FDA+EMA]; lung - squamous cell carcinoma [FDA+EMA]; lung - adenocarcinoma [FDA+EMA]) (AEL: -297,68)
- EGFR vad típus target (AEL: -297,76)

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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 143)* TORIPALIMAB (AEL: 2006,08) • PD-1 vad típus target (AEL: 1372,75) ; • PD-L1 protein overexpression driver (AEL: 493,34) SINTILIMAB (AEL: 1906,08) • PD-L1 protein overexpression driver (AEL: 493,34) ; • PD-1 vad típus target (AEL: 1372,75) CS1001 (AEL: 1700,81) • PD-L1 vad típus target (AEL: 1700,55) BINTRAFUSP ALFA (AEL: 1700,55) • PD-L1 vad típus target (AEL: 1700,55) PACMILIMAB (AEL: 1700,55) • PD-L1 vad típus target (AEL: 1700,55) MDX-1105 (AEL: 1700,55) • PD-L1 vad típus target (AEL: 1700,55) camrelizumab (AEL: 1373,65) • PD-1 vad típus target (AEL: 1372,75) TISLELIZUMAB (AEL: 1373,23) • PD-1 vad típus target (AEL: 1372,75) GEPTANOLIMAB (AEL: 1372,95) • PD-1 vad típus target (AEL: 1372,75) ABBV-181 (AEL: 1372,75) • PD-1 vad típus target (AEL: 1372,75)	KLINIKAI FEJLESZTÉS ALATT *10 listázott hatóanyag (összesen 68)* ALLITINIB (AEL: -553,84) • EGFR vad típus target (AEL: -297,76) ; • ERBB2 vad típus target (AEL: -256,09) AV-412 (AEL: -553,84) • EGFR vad típus target (AEL: -297,76) ; • ERBB2 vad típus target (AEL: -256,09) CUDC-101 (AEL: -553,84) • ERBB2 vad típus target (AEL: -256,09) ; • EGFR vad típus target (AEL: -297,76) PELITINIB (AEL: -553,84) • EGFR vad típus target (AEL: -297,76) ; • ERBB2 vad típus target (AEL: -256,09) TAK-285 (AEL: -553,84) • EGFR vad típus target (AEL: -297,76) ; • ERBB2 vad típus target (AEL: -256,09) EPERTINIB (AEL: -553,84) • EGFR vad típus target (AEL: -297,76) ; • ERBB2 vad típus target (AEL: -256,09) JNJ-26483327 (AEL: -553,84) • EGFR vad típus target (AEL: -297,76) ; • ERBB2 vad típus target (AEL: -256,09) AEE788 (AEL: -297,76) • EGFR vad típus target (AEL: -297,76) SAPITINIB (AEL: -297,76) • EGFR vad típus target (AEL: -297,76) MEHD7945A (AEL: -297,76) • EGFR vad típus target (AEL: -297,76)

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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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

ABL1-T653R, APEX1-Q51H, ARID1A-S558FS*65, BAZ2B-G2005FS*4, BCL6-E164D, BCL9-G302D, CCDC178-T657A, CDC73-K524T, CYLD-R315DEL, FANCD2-F386V, FBXW7-E449Q, FGFR3-P795L, FOXP1-M188T, GRM8-A222FS*49, GRM8-Y663C, KMT2C-G3106_K3109DEL, KMT2C-G908C, LAMA2-T821M, MAP3K4-H906P, MST1R-W1271FS*11, MUC16-S14437F, NEK2-R164T, PAX7-R221Q, PIK3C2B-F1029L, PIK3CA-E545K, PTGFR-M155I, PTPRD-D778N, SBDS-C119S, SDHA-L649FS*4, SDHD-H50R, SLIT2-A502V, SPRED1-E63*

VAD TÍPUSÚ GÉNEK

ABCB1, ABCC2, ABL2, ABRAXAS1, ACVR1B, ACVRL1, ADGRB3, AGTRAP, AIP, AKAP9, AKT1, AKT2, AKT3, ALK, AMER1, AMPH, APC, AR, ARAF, ARFRP1, ARID1B, ARID2, ASXL1, ATM, ATP11B, ATP4A, ATP6V0D2, ATR, ATRX, AURKA, AURKB, AXIN1, AXIN2, AXL, B2M, BAP1, BARD1, BAX, BCL2, BCL2L1, BCL2L2, BCOR, BCORL1, BCR, BIM, BIRC2, BIRC3, BLM, BMPR1A, BRAF, BRCA1, BRCA2, BRD4, BRIP1, BTG1, BTK, BUB1B, CARD11, CASP8, CASR, CBFB, CBL, CBLB, CBLC, CCDC6, CCND1, CCND2, CCND3, CCNE1, CD74, CD79A, CD79B, CDA, CDC27, 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, CUL3, 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, EPHA5, EPHA7, EPHB1, ERBB2, ERBB3, ERBB4, ERCC1, ERCC2, ERCC3, ERCC4, ERCC5, ERG, ERRFI1, ESR1, ESR2, ESRP1, ETV6, EXOC2, EXT1, EXT2, EZH2, EZR, FANCA, FANCB, FANCC, FANCE, FANCF, FANCG, FANCI, FANCL, FANCM, FAS, FAT1, FAT3, FBXO11, FBXO32, FGF10, FGF14, FGF19, FGF23, FGF3, FGF4, FGF5, FGF6, FGF9, FGFR1, FGFR2, FGFR4, FH, FLCN, FLT1, FLT3, FLT4, FN1, FOXA1, FOXL2, FOXO1, FRS2, FSTL5, FUBP1, FZD3, G6PD, GABRA6, GALNT17, GAS6, GATA1, GATA2, GATA3, GATA4, GATA6, GEN1, GID4, GLI1, GNA11, GNA13, GNAI2, GNAQ, GNAS, GNAT2, GOPC, GPC3, GPR78, GREM1, GRIN2A, GRM3, 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, KDM5C, KDM6A, KDR, KEAP1, KEL, KIAA1549, KIF5B, KIT, KLF6, KLHL6, KMT2A, KMT2D, KNSTRN, KRAS, KREMEN1, LCK, LMO1, LPAR2, LRP1B, LRRK2, LTK, LYN, LZTR1, MAGI2, MAGI3, MAGOH, MAP2K1, MAP2K2, MAP2K4, MAP3K1, MAP4K3, MAP7, MAPK1, MAPK3, MAS1L, MAX, MCL1, MDM2, MDM4, MED12, MED13, MEF2B, MEN1, MET, MIER3, MITF, MLH1, MLLT3, MPL, MRE11, MSH2, MSH3, MSH6, MTOR, MUTYH, MYC, MYCL1, MYCN, MYD88, MYO18A, MYO1B, NBN, NCOA2, NCOR1, NF1, NF2, NFE2L2, NFKBIA, NIPA2, NKX2-1, NKX2-8, NKX3-1, NOTCH1, NOTCH2, NOTCH3, NPM1, NRAS, NRCAM, NRG1, NRP2, NSD1, NT5C2, NTRK1, NTRK2, NTRK3, NUP93, OR5L1, OTOP1, PAK3, PALB2, PAX3, PAX5, PBRM1, PCBP1, PCGF2, PD-L1, PDGFRA, PDGFRB, PDK1, PDL2, PDZRN3, PHF6, PHOX2B, PIK3CB, PIK3CD, PIK3CG, 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, PTPN11, PTPN12, 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, SCN11A, SDC4, SDHAF2, SDHB, SDHC, SEC16A, SEPT9, SETBP1, SETD2, SF1, SF3A1, SF3B1, SH2B3, SHH, SHOC2, SLC22A1, SLC22A2, SLC31A1, SLC34A2, SLC45A3, SLC7A8, SLC9A9, SLCO1B1, SLX4, SMAD2, SMAD3, SMAD4, SMARCA4, SMARCB1, SMARCE1, SMC1A, SMC3, SMO, SNCAIP, SOCS1, SOS1, SOX10, SOX2, SOX9, SPEG, SPEN, SPOP, SPTA1, SRC, SRSF2, SSTR1, STAG2, STAT3, STAT4, STK11, SUFU, SUZ12, SYK, SYNE3, TACC3, TAF1, TAS2R38, TBX20, TBX3, TCERG1, TCF7L2, TENT5C, TERC, TERT, TET2, TFG, TGFBR2, THSD7B, TIAF1, TMEM127, TMPRSS2, TNFAIP3, TNFRSF14, TOP1, TOP2A, TP53, TP53BP1, TP63, TPM3, TPM4, TPMT, TRAF5, TRIO, TRRAP, TSC1, TSC2, TSHR, TYK2, U2AF1, U2AF2, UBR3, UGT1A1, USP16, USP25, VCL, VEGFA, VHL, WDCP, WEE1, WISP3, WNK2, WRN, WT1, WWP1, XPA, XPC, XPO1, XRCC2, YAP1, YES1, ZBED4, ZBTB2, ZFHX3, ZIC3, ZMYM3, ZNF2, ZNF217, ZNF226, ZNF473, ZNF595, ZNF703, ZRSR2

FISH/CNA/IHC POZITÍV GÉNEK

BCOR LOSS PRESENCE, PD-L1 PROTEIN OVEREXPRESSION, RBM10 LOSS PRESENCE

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, 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, RAF1 TRANSLOCATION ABSENCE, RARA TRANSLOCATION ABSENCE, RET TRANSLOCATION ABSENCE, ROS1 TRANSLOCATION ABSENCE, TACC1 TRANSLOCATION ABSENCE, TACC3 TRANSLOCATION ABSENCE

MOLEKULÁRIS BIOLÓGIAI INTERPRETÁCIÓ

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Oncompass Report

A Realtime Oncology Molecular Treatment Calculator számításaival

AZONOSÍTÓ	429397
NÉV	Anonymous

RÉSZLETES MOLEKULÁRIS PROFIL

MOLEKULÁRIS ALTERÁCIÓK

TMB-H driver (AEL: 796,72, AF/TR: NA/40%),
PDL1 protein overexpression driver (AEL: 493,34, AF/TR: NA/40%),
PIK3CA-E545K driver (AEL: 251,73, AF/TR: 35.85%/40%),
FBXW7-E449Q VUS, driver gén (AEL: 4,90, AF/TR: 13.23%/40%),
FGFR3-P795L VUS, driver gén (AEL: 3,83, AF/TR: 13.06%/40%),
ARID1A-S558fs*65 VUS, driver gén (AEL: 2,43, AF/TR: 13.23%/40%),
ABL1-T653R VUS, driver gén (AEL: 2,36, AF/TR: 9.59%/40%),
KMT2C-G908C driver (AEL: 1,73, AF/TR: 8.7%/40%),
KMT2C-G3106_K3109del VUS, driver gén (AEL: 1,72, AF/TR: 12.89%/40%),
MUC16-S14437F VUS, driver gén (AEL: 0,51, AF/TR: 49%/40%),
PTPRD-D778N VUS, driver gén (AEL: 0,12, AF/TR: 6.3%/40%),
LAMA2-T821M VUS, driver gén (AEL: 0,10, AF/TR: 49.22%/40%),
SBDS-C119S VUS, driver gén (AEL: 0,10, AF/TR: 14.61%/40%),
CDC73-K524T VUS, driver gén (AEL: 0,09, AF/TR: 15.78%/40%),
SPRED1-E63* VUS, driver gén (AEL: 0,06, AF/TR: 12.99%/40%),
FOXP1-M188T VUS, driver gén (AEL: 0,02, AF/TR: 52.22%/40%),
SLIT2-A502V driver (AEL: 0,01, AF/TR: 57.99%/40%),
BCL6-E164D ellentmondásos driver (AEL: 0,00, AF/TR: 59.31%/40%),
PAX7-R221Q ellentmondásos driver (AEL: 0,00, AF/TR: 53.49%/40%),
BCOR loss presence ismeretlen jelentőségű variáns (AEL: 0,00, AF/TR: NA/40%),
BAZ2B-G2005fs*4 ismeretlen jelentőségű variáns (AEL: 0,00, AF/TR: 15.99%/40%),
CYLD-R315del ismeretlen jelentőségű variáns (AEL: 0,00, AF/TR: 39.94%/40%),
NEK2-R164T ismeretlen jelentőségű variáns (AEL: 0,00, AF/TR: 3.12%/40%),
GRM8-A222fs*49 ismeretlen jelentőségű variáns (AEL: 0,00, AF/TR: 11.98%/40%),
RBM10 loss presence ismeretlen jelentőségű variáns (AEL: 0,00, AF/TR: NA/40%),
GRM8-Y663C ismeretlen jelentőségű variáns (AEL: 0,00, AF/TR: 49.17%/40%),
MST1R-W1271fs*11 ismeretlen jelentőségű variáns (AEL: 0,00, AF/TR: 3.06%/40%),
CCDC178-T657A ismeretlen jelentőségű variáns (AEL: 0,00, AF/TR: 46.98%/40%),
PIK3C2B-F1029L nem driver (AEL: -0,01, AF/TR: 55.59%/40%),
PTGFR-M155I nem driver (AEL: -0,01, AF/TR: 46.61%/40%),
SDHD-H50R nem driver (AEL: -2,65, AF/TR: 48.37%/40%),
SDHA-L649FS*4 nem driver (AEL: -4,99, AF/TR: 11.25%/40%),
BCL9-G302D nem driver (AEL: -5,00, AF/TR: 47.92%/40%),
APEX1-Q51H nem driver (AEL: -5,53, AF/TR: 47.85%/40%),
MAP3K4-H906P nem driver (AEL: -9,98, AF/TR: 50.19%/40%),
FANCD2-F386V nem driver (AEL: -14,99, AF/TR: 11.44%/40%)

INDIREKT CÉLPONT GÉNEK

CD274 vad típus (AEL: 1700,55),
- MUC16-S14437F driver (AEL: 0,51) ;
- TMB-H driver (AEL: 796,72) ;
- PDL1 protein overexpression driver (AEL: 493,34) ;
- ARID1A-S558fs*65 driver (AEL: 2,43)

PD-1 vad típus (AEL: 1372,75),
- MUC16-S14437F driver (AEL: 0,51) ;
- PDL1 protein overexpression driver (AEL: 493,34) ;
- TMB-H driver (AEL: 796,72)

CTLA4 vad típus (AEL: 803,49),
- TMB-H driver (AEL: 796,72) ;
- MUC16-S14437F driver (AEL: 0,51)

PIK3CA vad típus (AEL: 475,28),
- PIK3CA-E545K driver (AEL: 251,73)

MTOR vad típus (AEL: 277,97),
- FBXW7-E449Q driver (AEL: 4,90) ;
- PIK3CA-E545K driver (AEL: 251,73)

AKT1 vad típus (AEL: 258,85),
- ARID1A-S558fs*65 driver (AEL: 2,43) ;
- PIK3CA-E545K driver (AEL: 251,73)

AKT2 vad típus (AEL: 252,83),
- PIK3CA-E545K driver (AEL: 251,73)

CTNNB1 vad típus (AEL: 252,16),
- PIK3CA-E545K driver (AEL: 251,73)

AKT3 vad típus (AEL: 252,09),
- PIK3CA-E545K driver (AEL: 251,73)

FGFR3 vad típus (AEL: 173,81),
- FGFR3-P795L driver (AEL: 3,83)

NOTCH1 vad típus (AEL: 6,04),
- FBXW7-E449Q driver (AEL: 4,90)

BRD4 vad típus (AEL: 5,59),
- KMT2C-G908C driver (AEL: 1,73) ;
- KMT2C-G3106_K3109del driver (AEL: 1,72)

MCL1 vad típus (AEL: 5,35),
- FBXW7-E449Q driver (AEL: 4,90)

EZH2 vad típus (AEL: 4,92),
- ARID1A-S558fs*65 driver (AEL: 2,43)

PARP1 vad típus (AEL: 3,88),
- ARID1A-S558fs*65 driver (AEL: 2,43)

YES1 vad típus (AEL: 2,95),
- ARID1A-S558fs*65 driver (AEL: 2,43)

KDM1A vad típus (AEL: 2,73),
- ARID1A-S558fs*65 driver (AEL: 2,43)

STAT3 vad típus (AEL: 0,99)
- PTPRD-D778N driver (AEL: 0,12)

MOLEKULÁRIS BIOLÓGIAI INTERPRETÁCIÓ

A tumor mutational burden (TMB) vizsgálat eredménye (magas TMB)

A vizsgált mintában a szekvencia analízis (NGS) során kapott 1 megabázisra vonatkozó mutációk száma (TMB) 5,75. Az adatbázisunkban lévő kalkulált TMB értékek (n=576) eloszlása alapján az eseteink 89%-ában ennél alacsonyabb TMB értéket kaptunk.

A TMB érték klinikai interpretációja egyelőre nem egyértelmű, az eredmény tájékoztató jellegű.

A magas TMB érték pozitív asszociációban áll a PD-1 és PD-L1 inhibitorokra adott válasszal különböző tumortípusokban.

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MOLEKULÁRIS BIOLÓGIAI INTERPRETÁCIÓ

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

PD-L1 overexpresszió
A metszeten PD-L1 22 C3 pharmDX antitesttel immunhisztokémiai reakciót végeztünk. A daganatsejtek 80%-a pozitív.

PD-L1 overexpresszió - targetek
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

Immunterápiák gyomordaganatban és gastroesophageális junctio (GEJ) carcinomában
A PD-L1 expresszió hiánya jobb prognózissal mutat összefüggést gyomorrákban (1).
Egy fázis I vizsgálat eredménye szerint a PD-L1 expresszió szintje összefüggést mutatott a pembrolizumab (PD-1 gátló) kezelésre adott válaszadással. A vizsgálatban csak PD-L1 pozitív betegek vehettek részt (2). PD-L1 pozitív gyomor- és GEJ tumoros betegek számára törzskönyvezte az FDA a PEMBROLIZUMAB PD-1 gátló hatóanyagot. Egy fázis II vizsgálat eredménye szerint előzetesen kezelt PD-L1 pozitív gyomor és GEJ daganatos betegek között a pembrolizumab monoterápia 11,6%-os válaszadási arányt eredményezett (3).

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MOLEKULÁRIS BIOLÓGIAI INTERPRETÁCIÓ

A KEYNOTE-062 fázis III-mas klinikai vizsgálatban PD-L1 pozitív gyomor és GEJ daganatos betegek között az első vonalas pembrolizumab terápia nem eredményezett kedvezőbb teljes túlélést (overall survival, OS) és progressziómentes túlélést (progression-free survival, PFS), a kemoterápiával összehasonlítva (4).
A pembrolizumab és fluoropyrimidine-alapú kemoterápia kombinációt az FDA elsőbbségi felülvizsgálat (priority review) alá sorolta lokálisan előrehaladott, irreszekábilis vagy metasztatikus nyelőcső és gastroesophageális junctio daganatok elsővonalbeli kezelése esetén a KEYNOTE-590 klinikai vizsgálat eredményei alapján.

Nivolumab (PD-1 gátló) terápia fázis III vizsgálatban PD-L1 státusz szerint nem szelektált előzetesen kezelt gyomorrákos és GEJ carcinomás betegpopuláción a placebónál szignifikánsan hosszabb OS-t és PFS-t, valamint magasabb válaszadási arányt eredményezett (5). A PD-L1 pozitív és a PD-L1 negatív betegcsoportban is hosszabb volt a medián PFS a nivolumab karon, mint a placebo karon. A fázis III CheckMate 577 vizsgálatban az adjuváns nivolumab kezelés megnövekedett betegségmentes túlélést (DFS) eredményezett reszekált esophagealis vagy GEJ daganatos betegek esetén neoadjuváns kemoradiációs terápiát követően a placebóhoz képest. Az előzetes eredmények alapján a medián DFS 22,4 és 11,0 hónap volt a nivolumab (n=532) és a placebo (n=262) kezelés esetén (6). A vizsgálat eredményei alapján az FDA elsőbbségi felülvizsgálat (priority review) alá sorolta a nivolumab adjuváns terápiát nyelőcső vagy GEJ betegek számára reszekciót követően.
A nivolumab és regorafenib kombinációja 44%-os válaszadási arányt ért el (ORR, 11/25) többszörösen előkezelt, mikroszatellita stabil gyomordaganatos betegek körében egy fázis I-es klinikai vizsgálatban (ahol a KRAS mutációs státuszt nem vizsgálták) (7).
Egy fázis I/II vizsgálat szerint a nivolumab + paclitaxel + ramucirumab kombináció ígéretesnek bizonyult másodvonalas kezelésként gyomortumoros betegek körében (8). Az ORR 37,2%, a medián PFS 5,1 volt.
A CheckMate 649 fázis III-mas klinikai vizsgálatban PD-L1 pozitív gyomor és GEJ daganatos betegek között az első vonalas nivolumab + kemoterápia kombinációs kezelés statisztikailag szignifikáns javulást eredményezett az OS-ben és a PFS-ben a kemoterápiával összehasonlítva (medián OS: 13,8 és 11,6 hónap; medián PFS: 7,7 és 6,1 hónap) (9). A vizsgálat eredményei alapján az FDA elsőbbségi felülvizsgálat alá sorolta a nivolumab és kemoterápia kombinációt elsővonalas kezelésként metasztatikus gyomor, GEJ daganat és nyelőcső adenocarcinoma indikációkban.
Egy fázis III-mas klinikai vizsgálatban (ATTRACTION-4) HER2 negatív gyomor és GEJ daganatos betegek között az első vonalas nivolumab + kemoterápia kombinációs kezelés statisztikailag szignifikáns javulást eredményezett a PFS-ben a kemoterápiával összehasonlítva (medián PFS: 10,5 és 8,3 hónap), azonban az OS-ben nem eredményezett statisztikailag szignifikáns javulást (medián OS: 17,5 és 17,2 hónap) (10).

Az EPOC1706 fázis II klinikai vizsgálatban a lenvatinib (multi tirozin-kináz inhibitor) és pembrolizumab kombinációja antitumor aktivitást mutatott előrehaladott gyomordaganatos beteg esetén első- és másodvonalas terápiaként. A vizsgálatba bevont 29 betegből 20-nál (69%) tapasztaltak objektív választ (1 teljes válasz (CR) és 19 részleges válasz (PR)), 9 esetben (31%) pedig stabil betegséget, a medián PFS 7,1 hónap volt. A PD-L1 overexpresszióval rendelkező betegek esetén a válaszadási ráta 84% volt, míg a PD-L1 normál expresszióval rendelkezőeknél 40% (11).
Az FDA "orphan drug" besorolásban részesítette az APX005M hatóanyagot (monoklonális antitest, amely stimulálja a daganatellenes immunválaszt) gastroesophageális junctio daganat indikációban.

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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-csökkenést okozó genetikai eltérés jelenléte. Daganatképződéssel összefüggésbe hozható gének, melyek feltehetően alacsonyabb kópiaszámban vannak jelen, a BCOR és az RBM10 (n=0).

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.

BCOR kópiaszámvesztés

A BCOR tumorszupresszor gén egy transzkripciós korepresszor fehérjét kódol, amely a HDAC1, HDAC3 és HDAC5 gének által kódolt fehérjékkel közösen fejti ki génexpressziót gátló funkcióját.

Szintetikus letális kapcsolat miatt a MET target gén pozitív asszociációban említhető funkcióvesztő BCOR mutációk esetén (1).

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RBM10 funkcióvesztés

Az RBM10 az RBM10 transzkripciós faktort kódolja, mely egy RNS-kötő és alternatív splicing szabályozó fehérje. RBM10 mutációk gyakoriak tüdő adenocarcinomában, és gyakran a fehérje funkcióvesztését eredményezik. Egy preklinikai vizsgálatban azt találták, hogy az RBM10 tumorszupresszorként gátolta a NOTCH szignalizációt és sejt proliferációt a NUMB alternatív splicing szabályozásán keresztül (1).

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Az újgenerációs szekvenálás (NGS) eredménye

591 gén NGS szekvenálása 6002 genetikai variánst mutatott ki a mintában. A molekuláris profilba feltöltött 32 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.

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- CANCER DRIVER VARIANTS: Olyan mutációk azonosítását teszi lehetővé, amelyek valószínűsíthetően tumorigenezishez vagy metasztázisok kialakulásához vezetnek. Kiválasztottuk azokat a variánsokat, amelyek szakirodalmi adatok szerint daganat kialakulásához köthető útvonalakat, szabályozó egységeket vagy sejtes folyamatokat érintenek. Továbbá kiválasztásra kerültek azok a variánsok is, amelyekről a szakirodalomban szerepel daganat-indikációban leírt adat.

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

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

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

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

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

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

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

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.

PIK3CA-E545K

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A variáns a COSMIC adatbázisban nagy esetszámmal szerepel. A ClinVar adatbázisban patogén/valószínűsíthetően patogén, a LOVD adatbázisban domináns patogén alterációként szerepel. A szakirodalom szerint ismert, hotspot pozíciót érintő driver variáns (1-3). A mutációt hordozó fehérje megnövekedett PIK3CA kináz aktivitást mutat, onkogenikus transzformáló képességgel rendelkezik (4).
Egy tanulmányban 52 méhnyakrákos beteg (46 PIK3CA vad típusú, 6 PIK3CA E542K és E545K mutáns) PET/CT felvételét vizsgálva, a PIK3CA mutáns betegek esetén jelentősen megemelkedett glükózanyagcsere-aktivitást tapasztaltak a vad típusúakhoz képest. A PIK3CA mutáció és a megnövekedett proliferáció és glükóz-anyagcsere közötti összefüggést további in vitro és xenograft modellekkel támasztották alá (5).

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PIK3CA mutáns gén - célpontok

A PIK3CA (phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha) a PI3K-Akt jelátviteli útvonal részeként fontos szerepet tölt be a sejtproliferációban és a sejtek túlélésében, így a tumorigenezis során is.
PIK3CA génben detektált driver mutáció esetén a daganat molekuláris profiljával pozitív asszociációban említhetőek a PIK3CA/AKT/mTOR gátló hatóanyagok (1-3).
Az ALPELISIB és a COPANLISIB (FDA) törzskönyvezett PIK3CA gátló hatóanyagok. Forgalomban lévő mTOR-gátló készítmény az EVEROLIMUS, a METFORMIN, SIROLIMUS és a TEMSIROLIMUS. Az EVEROLIMUS emlő indikációban törzskönyvezett. A METFORMIN és a SIROLIMUS tumor indikációban nem törzskönyvezett. A TEMSIROLIMUS vesesejtes carcinoma indikációban elfogadott hatóanyag.
A TASELISIB fejlesztés alatt álló PIK3CA gátló hatóanyag fázis I vizsgálatban 36%-os válaszadási arányt eredményezett PIK3CA mutáns szolid tumoros betegek között, míg egyetlen PIK3CA vad típusú betegnél sem írtak le válaszadást (4). Egy nagyobb fázis I vizsgálatban többszörösen előkezelt PIK3CA mutáns szolid tumoros betegek között a taselisib 8,9%-os válaszadási arányt ért el (5). Az ALPELISIB kezelés PIK3CA mutáns vagy amplifikált szolid tumoros betegek között 6%-os válaszadási arányt és 58,2%-os betegség kontroll arányt ért el (6).

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

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ARID1A-S558fs*65

Ez a mutáció alacsony frekvenciával szerepel a COSMIC adatbázisban (n<5). A leolvasási kereteltolódást okozó mutáció (frameshift mutation) következtében egy jelentősen rövidebb fehérjeváltozatot kódoló ARID1A variáns jön létre, így a funkcióvesztés nagymértékben valószínűsíthető. A legújabb irodalmi adatok szerint a mutáció jelentősége ismeretlen.

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ARID1A mutáns gén - célpontok

Az ARID1A elvesztése esetén csökken a mismatch repair funkció. Az ARID1A deficiencia preklinikai vizsgálatban, továbbá gyomor- és colorectalis daganatos betegekben korrelált a mikroszatellita instabilitással (1, 2). Egy vizsgálatban gasztrointesztinális eredetű tumorokból származó adatokat elemeztek és az ARID1A mutáns daganatok esetén magasabb TMB értéket, valamint magasabb PD-L1 expressziót tapasztaltak (3). Preklinikai adatok szerint ARID1A mutáns ováriumtumoros egér modelleken hatékony volt a PD-L1 gátló immunterápia alkalmazása, míg vad típusú ARID1A esetén nem (1). További pozitív asszociációban említhető célpont gének az EZH2 (4), a YES1 (5), a PI3K/AKT (6) és a PARP (7). A forgalomban lévő dasatinibbel szintetikus letális hatás volt kimutatható ARID1A vesztés esetén (5). A TAZEMETOSTAT FDA által elfogadott EZH2 gátló hatóanyag. Forgalomban lévő PD-L1 gátlók az AVELUMAB, az ATEZOLIZUMAB és a DURVALUMAB. Forgalomban lévő YES1 gátló a DASATINIB. Forgalomban lévő PI3K gátlók az IDEALISIB, ALPELISIB és az FDA által törzskönyvezett COPANLISIB és DUVELISIB. Forgalomban lévő PARP gátló gyógyszerek az OLAPARIB, RUCAPARIB, TALAZOPARIB és a NIRAPARIB.

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KMT2C-G908C

A mutáció alacsony esetszámmal (n<20) szerepel a COSMIC adatbázisban. A szakirodalomban nem szerepel adat a funkcionális jelentőségéről.

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:

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LAMA2-T821M

A LAMA2-T821M egy misszensz alteráció az EGF kötő doménben. A ClinVar adatbázisában főként bizonytalan jelentőségű vagy feltehetően benignus klasszifikációval szerepel germline megbetegedésekkel asszociációban.

LAMA2 mutáns gén

A LAMA2 gén tumorszupresszor funkcióval bíró laminin alegységet kódol (1), csíravonalas alterációi daganatos megbetegedések kialakulására és izomdisztrófiára hajlamosítanak (2).

Jelenleg nincs olyan hatóanyag, amely összefüggésbe hozható LAMA2 mutációkkal.

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SPRED1-E63*

A korai STOP kodon megjelenését eredményező mutáció (nonsense mutation) következtében egy jelentősen rövidebb fehérjeváltozatot kódoló SPRED1 variáns jön létre, így a funkcióvesztés nagymértékben valószínűsíthető.

SPRED1 mutáns gén

A SPRED1 gén által kódolt SPRED1 fehérje a Sprouty fehérjecsalád tagja. A SPRED1 a MAPK szignalizációs útvonal negatív regulátora, ezáltal tumorszuppresszor funkcióval rendelkezhet.

Egy vizsgálatban melyben 43 melanomás mintát elemezve az esetek 37%-ban ez az útvonal felszabadult a SPRED1 gátlás alól, ami a daganat kialakulásához vezetett. Preklinikai vizsgálatokban a SPREAD1 knockdown a MAPK útvonal aktiválódásához és fokozott sejt osztódáshoz vezetett, valamint rezisztenciát okozott KIT tirozin-kináz gátlókra. Mely eredmények tovább támogatják a SPRED1 tumorszuppresszor funkcióját (1).

A SPRED1 funkcióvesztő (LoF) mutációi különböző daganattípusokkal, különösen leukémiával asszociáltak. A SPRED1 csíravonalas LoF mutációkról ismert, hogy a fejlődési rendellenességgel járó Legius-szindrómát, mely az I-es típusú neurofibromatózis egy altípusa, okoznak (2, 3).

A SPRED1 mutációk a rákok körülbelül 2% -ában fordulnak elő (TCGA). Jelenleg nem ismertek mutációs hotspot régiók a SPRED1 gén esetén (2).

Egy tanulmányban 230 akut limfoblasztos/mieloid leukémiás beteg esetén vizsgálták a SPRED1 mutációs és expressziós státuszát. Egy Legius-szindrómás beteg esetén SPRED1 LoF frameshift mutációt detektáltak, valamint a leukémia blasztok kariotípusa SPRED1 heterozigozitás-vesztést mutatott, mely a remissziót követően normális kariotípusúvá alakult (3).

A SPRED1 a miR196a mikroRNS közvetlen célpontja, ER+ emlő daganatokban a miR196a overexpressziója mellett a SPRED1 expresszió jelentősen csökkent (4).

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SDHD-H50R

A ClinVar adatbázisban 6 alkalommal benignus, 6 alkalommal valószínűsíthetően benignus és 1 alkalommal bizonytalan jelentőségű besorolással szerepel.

Egy preklinikai eredmény szerint ez a mutáció pajzsmirigydaganat sejtekben apoptózis rezisztenciát és nagyobb mértékű migrációt indukciójával hozzájárul a tumorigenezishez (1). Hatását a PTEN tumorszupresszor gátlásán keresztül fejti ki, és bosutinib SRC inhibitor kezelés hatására az SDHD mutáció tumorigenikus következményei megszüntethetőek PTEN vad típusú sejtekben (1).

Referenciák:

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SDHD mutáns gén

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Az SDHD tumorszupresszor gén (1, 2). Funkcióvesztő mutációi pheochromocitomában és paragangliomában gyakoriak, hozzájárulnak a tumorképződéshez. Több hatóanyagcsoport érdemes lehet tesztelni SDH deficiens tumorokban a tudományos irodalom szerint, de egyik csoportról sem bizonyították eddig, hogy szelektív hatékonyságot mutatna SDHD mutáns daganatokban. Ilyen hatóanyagcsoportok az angiogenezisgátlók, a HIF gátlók, az mTOR gátlók, a DNS demetiláló anyagok, a DNS alkiláló anyagok, a PARP gátlók, a HDAC gátlók és az immunterápiák. PTEN-t expresszáló SDHD deficiens sejteken a buparlisib SRC gátló hatóanyag bizonyult hatékonynak (4).

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SDHA-L649fs*4

A variáns szerepel a COSMIC adatbázisban. A LOVD adatbázisban 1 esetben benignus, 3 esetben vélhetően benignus variánsként, és 1 esetben VUS-ként szerepel.

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

A variáns szerepel a dbSNP adatbázisban (rs112307877), leírták már csíravonalas mutációként. A neoantigén képződésről és az immunterápiák hatékonyságának várható növekedéséről csak szomatikus mutációk esetén beszélhetünk. A tumor mintán végzett NGS vizsgálat nem alkalmas a szomatikus és a csíravonalas variánsok megkülönböztetésére.

A variánst leírták egy tanulmányban, mely 2 paraganglioma esetet tartalmaz, és szomatikus mutációként jellemezték. A vizsgálatban elvégzett IHC analízis alapján mindkét esetben csökkent SDHB expressziót találtak, míg az SDHA expresszió megtartottnak bizonyult (2).

Referenciák:

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SDHA mutáns gén - célpontok

Szakirodalmi adatok szerint a tumorszupresszor gén funkcióvesztő mutációi hozzájárulnak daganatok kialakulásához (1-4). Jelenleg nem ismert olyan fogalomban lévő hatóanyag, ami az SDHA gén mutációival pozitív asszociációban említhető.

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(1) Pantaleo MA et al., SDHA loss-of-function mutations in KIT-PDGFRA wild-type gastrointestinal stromal tumors identified by massively parallel sequencing. J Natl Cancer Inst. 2011 Jun 22;103(12):983-7. Epub 2011 Apr 19. PubMed PMID: 21505157

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MST1R-W1271fs*11

A MST1R-W1271fs*11 egy funkciónális doméneken kívül eső frameshift mutáció. A leolvasási kereteltolódást okozó mutáció (frameshift mutation) következtében egy jelentősen rövidebb fehérjeváltozatot kódoló MST1R variáns jön létre, így a funkcióvesztés nagymértékben valószínűsíthető. Ez a mutáció nem szerepel sem a COSMIC sem a ClinVar adatbázisokban. A legújabb irodalmi adatok szerint a mutáció jelentősége ismeretlen. Az MST1R egy receptor tirozin kinázt kódol, amely a makrofág stimuláló fehérje receptoraként működik, és részt vesz a sejtek migrációjában és differenciálódásában (1). Az MST1R overexpresszióját összefüggésbe hozták a hasnyálmirigy daganatok progressziójával (2). Funkcióvesztésével kapcsolatban jelenleg nincs ismert célzott terápia.

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BAZ2B-G2005fs*4

Ez a mutáció nem szerepel sem a COSMIC sem a ClinVar adatbázisokban. A BAZ2B-G1969fs*4 egy funkcionális doméneken kívül eső frameshift mutáció. A leolvasási kereteltolódást okozó mutáció (frameshift mutation) következtében egy jelentősen rövidebb fehérjeváltozatot kódoló BAZ2B variáns jön létre, így a funkcióvesztés nagymértékben valószínűsíthető. A legújabb irodalmi adatok szerint a mutáció jelentősége ismeretlen.

BAZ2B gén

A BAZ2B a BAZ fehérje család tagja. PHD-ujjat tartalmaznak egy homológ bromodomén közelében a fehérje C-terminális részén (1). A BAZ2B funkciójáról nincs ismert adat, eltekintve a bromodomén nemrégiben közzétett hisztonkötési preferenciáitól (2). A GSK2801-et a GSK és az SGC közötti együttműködésének keretein belül vizsgálva kiderült, hogy a BAZ2A és a BAZ2B erős, szelektív bromodomain inhibitora, amely az acetil-lizinekkel kompetitív kötődési modellben hat. In vitro és állatmodellekben is hatékony inhibitor (3).

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SLIT2-A502V

A COSMIC adatbázisban alacsony esetszámmal szerepel (n<5). Az alteráció a fehérje funkcionális alegységén kívüli aminosav cserét eredményez, melynek funkcionális jelentőségéről nem érhető el adat.

GRM8-A222fs*49

Ez a mutáció nem szerepel sem a COSMIC sem a ClinVar adatbázisokban. A GRM8-A222fs*49 egy frameshift mutáció. A leolvasási kereteltolódást okozó mutáció (frameshift mutation) következtében egy jelentősen rövidebb fehérjeváltozatot kódoló GRM8 variáns jön létre, így a funkcióvesztés nagymértékben valószínűsíthető. A legújabb irodalmi adatok szerint a mutáció jelentősége ismeretlen.

Célzott hatóanyagok gyomordaganat indikációban molekuláris profiltól függetlenül

Gyomor daganat indikációban törzskönyvezett a VEGFR2 gátló RAMUCIRUMAB.

Egy 665 gyomor és gastroesophagealis daganatos beteget involváló fázis III vizsgálatban paclitaxellel kombinált ramucirumab kezelés mellett 9,6 hónapos teljes túlélést (overall survival, OS) mértek, a placebo + kemoterápiás kezelés esetében tapasztalt 7,4 hónappal szemben (1). Egy másik vizsgálatba 355 beteget vontak be. A ramucirumab és legjobb szupportív kezelés (BSC) csoport esetén szignifikánsan magasabb OS-t mértek, mint a placebo + BSC csoportban (5,2 hónap vs 3,8 hónap) (2).

Egy "real-world" study eredményei alapján az apatinib (multi tirozin-kináz inhibitor) ígéretes hatékonyságot mutatott gyomordaganatos betegek (n=1000) körében különböző vonalú kezelések esetén (3). Az apatinib "orphan drug" besorolásban részesült az EMA és az FDA által gyomordaganat indikációban.

A Lonsurf kemoterápiás hatóanyag törzskönyvezett legalább két vonal kezelésen átesett gyomor és GEJ adenocarcinomás betegek számára. Fázis 3 vizsgálatban a Lonsurf kezelés 5.7 hónapos medián teljes túlélést eredményezett többszörösen előkezelt gyomor vagy GEJ daganatos betegek között, míg a placebo karon a medián teljes túlélés 3.6 hónap volt (4).

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A Realtime Oncology Molecular Treatment Calculator számításaival

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BCL9-G302D	NCBI ClinVar

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Oncompass Report

A Realtime Oncology Molecular Treatment Calculator számításaival

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TARGET GÉNEK	REFERENCIA
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DRIVER ÉS TARGET GÉNEK LEÍRÁSA

DRIVER GÉNEK

Név	Leírás
ABL1	Non-receptor tyrosine-protein kinase that plays a role in many key processes linked to cell growth and survival such as cytoskeleton remodeling in response to extracellular stimuli, cell motility and adhesion, receptor endocytosis, autophagy, DNA damage response and apoptosis. Coordinates actin remodeling through tyrosine phosphorylation of proteins controlling cytoskeleton dynamics like WASF3 (involved in branch formation); ANXA1 (involved in membrane anchoring); DBN1, DBNL, CTTN, RAPH1 and ENAH (involved in signaling); or MAPT and PXN (microtubule-binding proteins). Phosphorylation of WASF3 is critical for the stimulation of lamellipodia formation and cell migration. Involved in the regulation of cell adhesion and motility through phosphorylation of key regulators of these processes such as BCAR1, CRK, CRKL, DOK1, EFS or NEDD9. Phosphorylates multiple receptor tyrosine kinases and more particularly promotes endocytosis of EGFR, facilitates the formation of neuromuscular synapses through MUSK, inhibits PDGFRB-mediated chemotaxis and modulates the endocytosis of activated B-cell receptor complexes. Other substrates which are involved in endocytosis regulation are the caveolin (CAV1) and RIN1. Moreover, ABL1 regulates the CBL family of ubiquitin ligases that drive receptor down-regulation and actin remodeling. Phosphorylation of CBL leads to increased EGFR stability. Involved in late-stage autophagy by regulating positively the trafficking and function of lysosomal components. ABL1 targets to mitochondria in response to oxidative stress and thereby mediates mitochondrial dysfunction and cell death. ABL1 is also translocated in the nucleus where it has DNA-binding activity and is involved in DNA-damage response and apoptosis. Many substrates are known mediators of DNA repair: DDB1, DDB2, ERCC3, ERCC6, RAD9A, RAD51, RAD52 or WRN. Activates the proapoptotic pathway when the DNA damage is too severe to be repaired. Phosphorylates TP73, a primary regulator for this type of damage-induced apoptosis. Phosphorylates the caspase CASP9 on Tyr-153 and regulates its processing in the apoptotic response to DNA damage. Phosphorylates PSMA7 that leads to an inhibition of proteasomal activity and cell cycle transition blocks. ABL1 acts also as a regulator of multiple pathological signaling cascades during infection. Several known tyrosine-phosphorylated microbial proteins have been identified as ABL1 substrates. This is the case of A36R of Vaccinia virus, Tir (translocated intimin receptor) of pathogenic E.coli and possibly Citrobacter, CagA (cytotoxin-associated gene A) of H.pylori, or AnkA (ankyrin repeat-containing protein A) of A.phagocytophilum. Pathogens can highjack ABL1 kinase signaling to reorganize the host actin cytoskeleton for multiple purposes, like facilitating intracellular movement and host cell exit. Finally, functions as its own regulator through autocatalytic activity as well as through phosphorylation of its inhibitor, ABI1.
APEX1	Multifunctional protein that plays a central role in the cellular response to oxidative stress. The two major activities of APEX1 in DNA repair and redox regulation of transcriptional factors. Functions as a apurinic/apyrimidinic (AP) endodeoxyribonuclease in the DNA base excision repair (BER) pathway of DNA lesions induced by oxidative and alkylating agents. Initiates repair of AP sites in DNA by catalyzing hydrolytic incision of the phosphodiester backbone immediately adjacent to the damage, generating a single-strand break with 5'-deoxyribose phosphate and 3'-hydroxyl ends. Does also incise at AP sites in the DNA strand of DNA/RNA hybrids, single-stranded DNA regions of R-loop structures, and single-stranded RNA molecules. Has a 3'-5' exoribonuclease activity on mismatched deoxyribonucleotides at the 3' termini of nicked or gapped DNA molecules during short-patch BER. Possesses a DNA 3' phosphodiesterase activity capable of removing lesions (such as phosphoglycolate) blocking the 3' side of DNA strand breaks. May also play a role in the epigenetic regulation of gene expression by participating in DNA demethylation. Acts as a loading factor for POLB onto non-incised AP sites in DNA and stimulates the 5'-terminal deoxyribose 5'-phosphate (dRp) excision activity of POLB. Plays a role in the protection from granzymes-mediated cellular repair leading to cell death. Also involved in the DNA cleavage step of class switch recombination (CSR). On the other hand, APEX1 also exerts reversible nuclear redox activity to regulate DNA binding affinity and transcriptional activity of transcriptional factors by controlling the redox status of their DNA-binding domain, such as the FOS/JUN AP-1 complex after exposure to IR. Involved in calcium-dependent down-regulation of parathyroid hormone (PTH) expression by binding to negative calcium response elements (nCaREs). Together with HNRNPL or the dimer XRCC5/XRCC6, associates with nCaRE, acting as an activator of transcriptional repression. Stimulates the YBX1-mediated MDR1 promoter activity, when acetylated at Lys-6 and Lys-7, leading to drug resistance. Acts also as an endoribonuclease involved in the control of single-stranded RNA metabolism. Plays a role in regulating MYC mRNA turnover by preferentially cleaving in between UA and CA dinucleotides of the MYC coding region determinant (CRD). In association with NMD1, plays a role in the rRNA quality control process during cell cycle progression. Associates, together with YBX1, on the MDR1 promoter. Together with NPM1, associates with rRNA. Binds DNA and RNA.

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Név	Leírás
ARID1A	Involved in transcriptional activation and repression of select genes by chromatin remodeling (alteration of DNA-nucleosome topology). Binds DNA non-specifically. Belongs to the neural progenitors-specific chromatin remodeling complex (npBAF complex) and the neuron-specific chromatin remodeling complex (nBAF complex). During neural development a switch from a stem/progenitor to a post-mitotic chromatin remodeling mechanism occurs as neurons exit the cell cycle and become committed to their adult state. The transition from proliferating neural stem/progenitor cells to post-mitotic neurons requires a switch in subunit composition of the npBAF and nBAF complexes. As neural progenitors exit mitosis and differentiate into neurons, npBAF complexes which contain ACTL6A/BAF53A and PHF10/BAF45A, are exchanged for homologous alternative ACTL6B/BAF53B and DPF1 /BAF45B or DPF3/BAF45C subunits in neuron-specific complexes (nBAF). The npBAF complex is essential for the self-renewal/proliferative capacity of the multipotent neural stem cells. The nBAF complex along with CREST plays a role regulating the activity of genes essential for dendrite growth (By similarity).
BAZ2B	May play a role in transcriptional regulation interacting with ISWI.
BCL6	Transcriptional repressor mainly required for germinal center (GC) formation and antibody affinity maturation which has different mechanisms of action specific to the lineage and biological functions. Forms complexes with different corepressors and histone deacetylases to repress the transcriptional expression of different subsets of target genes. Represses its target genes by binding directly to the DNA sequence 5-TTCCTAGAA-3 (BCL6-binding site) or indirectly by repressing the transcriptional activity of transcription factors. In GC B-cells, represses genes that function in differentiation, inflammation, apoptosis and cell cycle control, also autoregulates its transcriptional expression and up-regulates, indirectly, the expression of some genes important for GC reactions, such as AICDA, through the repression of microRNAs expression, like miR155. An important function is to allow GC B-cells to proliferate very rapidly in response to T-cell dependent antigens and tolerate the physiological DNA breaks required for immunglobulin class switch recombination and somatic hypermutation without inducing a p53/TP53-dependent apoptotic response. In follicular helper CD4(+) T-cells (T(FH) cells), promotes the expression of T(FH)-related genes but inhibits the differentiation of T(H)1, T(H)2 and T(H)17 cells. Also required for the establishment and maintenance of immunological memory for both T- and B-cells. Suppresses macrophage proliferation through competition with STAT5 for STAT-binding motifs binding on certain target genes, such as CCL2 and CCND2. In response to genotoxic stress, controls cell cycle arrest in GC B-cells in both p53/TP53-dependedent and -independent manners. Besides, also controls neurogenesis through the alteration of the composition of NOTCH-dependent transcriptional complexes at selective NOTCH targets, such as HES5, including the recruitment of the deacetylase SIRT1 and resulting in an epigenetic silencing leading to neuronal differentiation.
BCOR	Transcriptional corepressor. May specifically inhibit gene expression when recruited to promoter regions by sequence-specific DNA-binding proteins such as BCL6 and MLLT3. This repression may be mediated at least in part by histone deacetylase activities which can associate with this corepressor. Involved in the repression of TFAP2A; impairs binding of BCL6 and KDM2B to TFAP2A promoter regions. Via repression of TFAP2A acts as a negative regulator of osteo-dentiogenic capacity in adult stem cells; the function implies inhibition of methylation on histone H3 Lys-4 (H3K4me3) and Lys-36 (H3K36me2).
CDC73	Tumor suppressor probably involved in transcriptional and post-transcriptional control pathways. May be involved in cell cycle progression through the regulation of cyclin D1/PRAD1 expression. Component of the PAF1 complex (PAF1C) which has multiple functions during transcription by RNA polymerase II and is implicated in regulation of development and maintenance of embryonic stem cell pluripotency. PAF1C associates with RNA polymerase II through interaction with POLR2A CTD non-phosphorylated and Ser-2- and Ser-5-phosphorylated forms and is involved in transcriptional elongation, acting both indepentently and synergistically with TCEA1 and in cooperation with the DSIF complex and HTATSF1. PAF1C is required for transcription of Hox and Wnt target genes. PAF1C is involved in hematopoiesis and stimulates transcriptional activity of KMT2A/MLL1; it promotes leukemogenesis through association with KMT2A/MLL1-rearranged oncoproteins, such as KMT2A/MLL1-MLLT3/AF9 and KMT2A /MLL1-MLLT1/ENL. PAF1C is involved in histone modifications such as ubiquitination of histone H2B and methylation on histone H3 Lys-4 (H3K4me3). PAF1C recruits the RNF20/40 E3 ubiquitin-protein ligase complex and the E2 enzyme UBE2A or UBE2B to chromatin which mediate monoubiquitination of Lys-120 of histone H2B (H2BK120ub1); UB2A/B-mediated H2B ubiquitination is proposed to be coupled to transcription. PAF1C is involved in mRNA 3 end formation probably through association with cleavage and poly(A) factors. In case of infection by influenza A strain H3N2, PAF1C associates with viral NS1 protein, thereby regulating gene transcription. Connects PAF1C with the cleavage and polyadenylation specificity factor (CPSF) complex and the cleavage stimulation factor (CSTF) complex, and with Wnt signaling. Involved in polyadenylation of mRNA precursors.
CYLD	Protease that specifically cleaves Lys-63-linked polyubiquitin chains. Has endodeubiquitinase activity. Plays an important role in the regulation of pathways leading to NF-kappa-B activation (PubMed:12917689, PubMed: 12917691). Contributes to the regulation of cell survival, proliferation and differentiation via its effects on NF-kappa-B activation (PubMed:12917690). Negative regulator of Wnt signaling (PubMed:20227366). Inhibits HDAC6 and thereby promotes acetylation of alpha-tubulin and stabilization of microtubules (PubMed:19893491). Plays a role in the regulation of microtubule dynamics, and thereby contributes to the regulation of cell proliferation, cell polarization, cell migration, and angiogenesis (PubMed:18222923, PubMed:20194890). Required for normal cell cycle progress and normal cytokinesis (PubMed:17495026, PubMed:19893491). Inhibits nuclear translocation of NF-kappa-B. Plays a role in the regulation of inflammation and the innate immune response, via its effects on NF-kappa-B activation (PubMed:18636086). Dispensable for the maturation of intrathymic natural killer cells, but required for the continued survival of immature natural killer cells. Negatively regulates TNFRSF11A signaling and osteoclastogenesis (By similarity). Involved in the regulation of ciliogenesis, allowing ciliary basal bodies to migrate and dock to the plasma membrane; this process does not depend on NF-kappa-B activation (By similarity).
FANCD2	Required for maintenance of chromosomal stability. Promotes accurate and efficient pairing of homologs during meiosis. Involved in the repair of DNA double-strand breaks, both by homologous recombination and single-strand annealing. May participate in S phase and G2 phase checkpoint activation upon DNA damage. Plays a role in preventing breakage and loss of missegregating chromatin at the end of cell division, particularly after replication stress. Required for the targeting, or stabilization, of BLM to non-centromeric abnormal structures induced by replicative stress. Promotes BRCA2/FANCD1 loading onto damaged chromatin. May also be involved in B-cell immunoglobulin isotype switching.

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Név	Leírás
FBXW7	Substrate recognition component of an SCF (SKP1-CUL1-F-box protein) E3 ubiquitin-protein ligase complex which mediates the ubiquitination and subsequent proteasomal degradation of target proteins. Recognizes and binds phosphorylated sites/phosphodegrons within target proteins and thereafter bring them to the SCF complex for ubiquitination (PubMed:17434132). Identified substrates include cyclin-E (CCNE1 or CCNE2), JUN, MYC, NOTCH1 released notch intracellular domain (NICD), and probably PSEN1 (PubMed:11565034, PubMed:12354302, PubMed:11585921, PubMed:15103331, PubMed:14739463, PubMed:17558397, PubMed:17873522, PubMed:22608923). Acts as a negative regulator of JNK signaling by binding to phosphorylated JUN and promoting its ubiquitination and subsequent degradation (PubMed:14739463).
FGFR3	Tyrosine-protein kinase that acts as cell-surface receptor for fibroblast growth factors and plays an essential role in the regulation of cell proliferation, differentiation and apoptosis. Plays an essential role in the regulation of chondrocyte differentiation, proliferation and apoptosis, and is required for normal skeleton development. Regulates both osteogenesis and postnatal bone mineralization by osteoblasts. Promotes apoptosis in chondrocytes, but can also promote cancer cell proliferation. Required for normal development of the inner ear. Phosphorylates PLCG1, CBL and FRS2. Ligand binding leads to the activation of several signaling cascades. Activation of PLCG1 leads to the production of the cellular signaling molecules diacylglycerol and inositol 1,4,5-trisphosphate. Phosphorylation of FRS2 triggers recruitment of GRB2, GAB1, PIK3R1 and SOS1, and mediates activation of RAS, MAPK1/ERK2, MAPK3/ERK1 and the MAP kinase signaling pathway, as well as of the AKT1 signaling pathway. Plays a role in the regulation of vitamin D metabolism. Mutations that lead to constitutive kinase activation or impair normal FGFR3 maturation, internalization and degradation lead to aberrant signaling. Over-expressed or constitutively activated FGFR3 promotes activation of PTPN11/SHP2, STAT1, STAT5A and STAT5B. Secreted isoform 3 retains its capacity to bind FGF1 and FGF2 and hence may interfere with FGF signaling.
FOXP1	Transcriptional repressor (PubMed:18347093). Can act with CTBP1 to synergistically repress transcription but CTPBP1 is not essential (By similarity). Plays an important role in the specification and differentiation of lung epithelium. Acts cooperatively with FOXP4 to regulate lung secretory epithelial cell fate and regeneration by restricting the goblet cell lineage program; the function may involve regulation of AGR2. Essential transcriptional regulator of B-cell development. Involved in regulation of cardiac muscle cell proliferation. Involved in the columnar organization of spinal motor neurons. Promotes the formation of the lateral motor neuron column (LMC) and the preganglionic motor column (PGC) and is required for respective appropriate motor axon projections. The segment-appropriate generation of spinal chord motor columns requires cooperation with other Hox proteins. Can regulate PITX3 promoter activity; may promote midbrain identity in embryonic stem cell-derived dopamine neurons by regulating PITX3. Negatively regulates the differentiation of T follicular helper cells T(FH)s. Involved in maintainance of hair follicle stem cell quiescence; the function probably involves regulation of FGF18 (By similarity). Represses transcription of various pro-apoptotic genes and cooperates with NF-kappa B-signaling in promoting B-cell expansion by inhibition of caspase-dependent apoptosis (PubMed:25267198). Binds to CSF1R promoter elements and is involved in regulation of monocyte differentiation and macrophage functions; repression of CSF1R in monocytes seems to involve NCOR2 as corepressor (PubMed:15286807, PubMed:18799727, PubMed:18347093). Involved in endothelial cell proliferation, tube formation and migration indicative for a role in angiogenesis; the role in neovascularization seems to implicate suppression of SEMA5B (PubMed:24023716). Can negatively regulate androgen receptor signaling (PubMed:18640093). Isoform 8: Involved in transcriptional regulation in embryonic stem cells (ESCs). Stimulates expression of transcription factors that are required for pluripotency and decreases expression of differentiation-associated genes. Has distinct DNA-binding specifities as compared to the canonical form and preferentially binds DNA with the sequence 5-CGATACAA-3 (or closely related sequences) (PubMed:21924763). Promotes ESC self-renewal and pluripotency (By similarity).
KMT2C	Histone methyltransferase. Methylates Lys-4 of histone H3. H3 Lys-4 methylation represents a specific tag for epigenetic transcriptional activation. Central component of the MLL2/3 complex, a coactivator complex of nuclear receptors, involved in transcriptional coactivation. KMT2C/MLL3 may be a catalytic subunit of this complex. May be involved in leukemogenesis and developmental disorder.
LAMA2	Binding to cells via a high affinity receptor, laminin is thought to mediate the attachment, migration and organization of cells into tissues during embryonic development by interacting with other extracellular matrix components.
MAP3K4	Component of a protein kinase signal transduction cascade. Activates the CSBP2, P38 and JNK MAPK pathways, but not the ERK pathway. Specifically phosphorylates and activates MAP2K4 and MAP2K6.
MST1R	Receptor tyrosine kinase that transduces signals from the extracellular matrix into the cytoplasm by binding to MST1 ligand. Regulates many physiological processes including cell survival, migration and differentiation. Ligand binding at the cell surface induces autophosphorylation of RON on its intracellular domain that provides docking sites for downstream signaling molecules. Following activation by ligand, interacts with the PI3-kinase subunit PIK3R1, PLCG1 or the adapter GAB1. Recruitment of these downstream effectors by RON leads to the activation of several signaling cascades including the RAS-ERK, PI3 kinase-AKT, or PLCgamma-PKC. RON signaling activates the wound healing response by promoting epithelial cell migration, proliferation as well as survival at the wound site. Plays also a role in the innate immune response by regulating the migration and phagocytic activity of macrophages. Alternatively, RON can also promote signals such as cell migration and proliferation in response to growth factors other than MST1 ligand.
MUC16	Thought to provide a protective, lubricating barrier against particles and infectious agents at mucosal surfaces.
NEK2	Protein kinase which is involved in the control of centrosome separation and bipolar spindle formation in mitotic cells and chromatin condensation in meiotic cells. Regulates centrosome separation (essential for the formation of bipolar spindles and high-fidelity chromosome separation) by phosphorylating centrosomal proteins such as CROCC, CEP250 and NINL, resulting in their displacement from the centrosomes. Regulates kinetochore microtubule attachment stability in mitosis via phosphorylation of NDC80. Involved in regulation of mitotic checkpoint protein complex via phosphorylation of CDC20 and MAD2L1. Plays an active role in chromatin condensation during the first meiotic division through phosphorylation of HMGA2. Phosphorylates: PPP1CC; SGO1; NECAB3 and NPM1. Essential for localization of MAD2L1 to kinetochore and MAPK1 and NPM1 to the centrosome. Phosphorylates CEP68 and CNTLN directly or indirectly (PubMed:24554434). NEK2-mediated phosphorylation of CEP68 promotes CEP68 dissociation from the centrosome and its degradation at the onset of mitosis (PubMed:25704143). Involved in the regulation of centrosome disjunction (PubMed:26220856).

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Név	Leírás
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.
PIK3CA	Phosphoinositide-3-kinase (PI3K) that phosphorylates PtdIns (Phosphatidylinositol), PtdIns4P (Phosphatidylinositol 4-phosphate) and PtdIns(4,5)P2 (Phosphatidylinositol 4,5-bisphosphate) to generate phosphatidylinositol 3,4,5-trisphosphate (PIP3). PIP3 plays a key role by recruiting PH domain-containing proteins to the membrane, including AKT1 and PDPK1, activating signaling cascades involved in cell growth, survival, proliferation, motility and morphology. Participates in cellular signaling in response to various growth factors. Involved in the activation of AKT1 upon stimulation by receptor tyrosine kinases ligands such as EGF, insulin, IGF1, VEGFA and PDGF. Involved in signaling via insulin-receptor substrate (IRS) proteins. Essential in endothelial cell migration during vascular development through VEGFA signaling, possibly by regulating RhoA activity. Required for lymphatic vasculature development, possibly by binding to RAS and by activation by EGF and FGF2, but not by PDGF. Regulates invadopodia formation in breast cancer cells through the PDPK1-AKT1 pathway. Participates in cardiomyogenesis in embryonic stem cells through a AKT1 pathway. Participates in vasculogenesis in embryonic stem cells through PDK1 and protein kinase C pathway. Has also serine-protein kinase activity: phosphorylates PIK3R1 (p85alpha regulatory subunit), EIF4EBP1 and HRAS.
PTGFR	Receptor for prostaglandin F2-alpha (PGF2-alpha). The activity of this receptor is mediated by G proteins which activate a phosphatidylinositol-calcium second messenger system. Initiates luteolysis in the corpus luteum (By similarity). Isoforms 2 to 7 do not bind PGF2-alpha but are proposed to modulate signaling by participating in variant receptor complexes; heterodimers between isoform 1 and isoform 5 are proposed to be a receptor for prostamides including the synthetic analog bimatoprost.
PTPRD	Can bidirectionally induce pre- and post-synaptic differentiation of neurons by mediating interaction with IL1RAP and IL1RAPL1 trans-synaptically. Involved in pre-synaptic differentiation through interaction with SLITRK2.
SDHA	Flavoprotein (FP) subunit of succinate dehydrogenase (SDH) that is involved in complex II of the mitochondrial electron transport chain and is responsible for transferring electrons from succinate to ubiquinone (coenzyme Q). Can act as a tumor suppressor.
SDHD	Membrane-anchoring subunit of succinate dehydrogenase (SDH) that is involved in complex II of the mitochondrial electron transport chain and is responsible for transferring electrons from succinate to ubiquinone (coenzyme Q).
SPRED1	Tyrosine kinase substrate that inhibits growth-factor-mediated activation of MAP kinase. Negatively regulates hematopoiesis of bone marrow (By similarity).

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

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Név	Leírás
AKT3	AKT3 is one of 3 closely related serine/threonine-protein kinases (AKT1, AKT2 and AKT3) called the AKT kinase, and which regulate many processes including metabolism, proliferation, cell survival, growth and angiogenesis. This is mediated through serine and/or threonine phosphorylation of a range of downstream substrates. Over 100 substrate candidates have been reported so far, but for most of them, no isoform specificity has been reported. AKT3 is the least studied AKT isoform. It plays an important role in brain development and is crucial for the viability of malignant glioma cells. AKT3 isoform may also be the key molecule in up-regulation and down-regulation of MMP13 via IL13. Required for the coordination of mitochondrial biogenesis with growth factor-induced increases in cellular energy demands. Down-regulation by RNA interference reduces the expression of the phosphorylated form of BAD, resulting in the induction of caspase-dependent apoptosis.
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
CTLA4	Inhibitory receptor acting as a major negative regulator of T-cell responses. The affinity of CTLA4 for its natural B7 family ligands, CD80 and CD86, is considerably stronger than the affinity of their cognate stimulatory coreceptor CD28.
CTNNB1	Key downstream component of the canonical Wnt signaling pathway. In the absence of Wnt, forms a complex with AXIN1, AXIN2, APC, CSNK1A1 and GSK3B that promotes phosphorylation on N-terminal Ser and Thr residues and ubiquitination of CTNNB1 via BTRC and its subsequent degradation by the proteasome. In the presence of Wnt ligand, CTNNB1 is not ubiquitinated and accumulates in the nucleus, where it acts as a coactivator for transcription factors of the TCF/LEF family, leading to activate Wnt responsive genes. Involved in the regulation of cell adhesion. Acts as a negative regulator of centrosome cohesion. Involved in the CDK2/PTPN6/CTNNB1/CEACAM1 pathway of insulin internalization. Blocks anoikis of malignant kidney and intestinal epithelial cells and promotes their anchorage-independent growth by down-regulating DAPK2. Disrupts PML function and PML-NB formation by inhibiting RANBP2-mediated sumoylation of PML (PubMed:17524503, PubMed:18077326, PubMed:18086858, PubMed:18957423, PubMed:21262353, PubMed:22647378, PubMed:22699938, PubMed:22155184). Promotes neurogenesis by maintaining sympathetic neuroblasts within the cell cycle (By similarity).
EZH2	Polycomb group (PcG) protein. Catalytic subunit of the PRC2/EED-EZH2 complex, which methylates Lys-9 (H3K9me) and Lys-27 (H3K27me) of histone H3, leading to transcriptional repression of the affected target gene. Able to mono-, di- and trimethylate Lys-27 of histone H3 to form H3K27me1, H3K27me2 and H3K27me3, respectively. Compared to EZH2-containing complexes, it is more abundant in embryonic stem cells and plays a major role in forming H3K27me3, which is required for embryonic stem cell identity and proper differentiation. The PRC2/EED-EZH2 complex may also serve as a recruiting platform for DNA methyltransferases, thereby linking two epigenetic repression systems. Genes repressed by the PRC2/EED-EZH2 complex include HOXC8, HOXA9, MYT1, CDKN2A and retinoic acid target genes. EZH2 can also methylate non-histone proteins such as the transcription factor GATA4 and the nuclear receptor RORA. Regulates the circadian clock via histone methylation at the promoter of the circadian genes. Essential for the CRY1/2-mediated repression of the transcriptional activation of PER1/2 by the CLOCK-ARNTL/BMAL1 heterodimer; involved in the di and trimethylation of Lys-27 of histone H3 on PER1/2 promoters which is necessary for the CRY1/2 proteins to inhibit transcription.
FGFR3	Tyrosine-protein kinase that acts as cell-surface receptor for fibroblast growth factors and plays an essential role in the regulation of cell proliferation, differentiation and apoptosis. Plays an essential role in the regulation of chondrocyte differentiation, proliferation and apoptosis, and is required for normal skeleton development. Regulates both osteogenesis and postnatal bone mineralization by osteoblasts. Promotes apoptosis in chondrocytes, but can also promote cancer cell proliferation. Required for normal development of the inner ear. Phosphorylates PLCG1, CBL and FRS2. Ligand binding leads to the activation of several signaling cascades. Activation of PLCG1 leads to the production of the cellular signaling molecules diacylglycerol and inositol 1,4,5-trisphosphate. Phosphorylation of FRS2 triggers recruitment of GRB2, GAB1, PIK3R1 and SOS1, and mediates activation of RAS, MAPK1/ERK2, MAPK3/ERK1 and the MAP kinase signaling pathway, as well as of the AKT1 signaling pathway. Plays a role in the regulation of vitamin D metabolism. Mutations that lead to constitutive kinase activation or impair normal FGFR3 maturation, internalization and degradation lead to aberrant signaling. Over-expressed or constitutively activated FGFR3 promotes activation of PTPN11/SHP2, STAT1, STAT5A and STAT5B. Secreted isoform 3 retains its capacity to bind FGF1 and FGF2 and hence may interfere with FGF signaling.
KDM1A	This gene encodes a nuclear protein containing a SWIRM domain, a FAD-binding motif, and an amine oxidase domain. This protein is a component of several histone deacetylase complexes, though it silences genes by functioning as a histone demethylase. Alternative splicing results in multiple transcript variants. [provided by RefSeq, Apr 2009]
MCL1	Involved in the regulation of apoptosis versus cell survival, and in the maintenance of viability but not of proliferation. Mediates its effects by interactions with a number of other regulators of apoptosis. Isoform 1 inhibits apoptosis. Isoform 2 promotes apoptosis.

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DRIVER ÉS TARGET GÉNEK LEÍRÁSA

TARGET GÉNEK

Név	Leírás
MTOR	Serine/threonine protein kinase which is a central regulator of cellular metabolism, growth and survival in response to hormones, growth factors, nutrients, energy and stress signals. MTOR directly or indirectly regulates the phosphorylation of at least 800 proteins. Functions as part of 2 structurally and functionally distinct signaling complexes mTORC1 and mTORC2 (mTOR complex 1 and 2). Activated mTORC1 up-regulates protein synthesis by phosphorylating key regulators of mRNA translation and ribosome synthesis. This includes phosphorylation of EIF4EBP1 and release of its inhibition toward the elongation initiation factor 4E (eiF4E). Moreover, phosphorylates and activates RPS6KB1 and RPS6KB2 that promote protein synthesis by modulating the activity of their downstream targets including ribosomal protein S6, eukaryotic translation initiation factor EIF4B, and the inhibitor of translation initiation PDCD4. Stimulates the pyrimidine biosynthesis pathway, both by acute regulation through RPS6KB1-mediated phosphorylation of the biosynthetic enzyme CAD, and delayed regulation, through transcriptional enhancement of the pentose phosphate pathway which produces 5-phosphoribosyl-1-pyrophosphate (PRPP), an allosteric activator of CAD at a later step in synthesis, this function is dependent on the mTORC1 complex. Regulates ribosome synthesis by activating RNA polymerase III-dependent transcription through phosphorylation and inhibition of MAF1 an RNA polymerase III-repressor. In parallel to protein synthesis, also regulates lipid synthesis through SREBF1/SREBP1 and LPIN1. To maintain energy homeostasis mTORC1 may also regulate mitochondrial biogenesis through regulation of PPARGC1A. mTORC1 also negatively regulates autophagy through phosphorylation of ULK1. Under nutrient sufficiency, phosphorylates ULK1 at Ser-758, disrupting the interaction with AMPK and preventing activation of ULK1. Also prevents autophagy through phosphorylation of the autophagy inhibitor DAP. mTORC1 exerts a feedback control on upstream growth factor signaling that includes phosphorylation and activation of GRB10 a INSR-dependent signaling suppressor. Among other potential targets mTORC1 may phosphorylate CLIP1 and regulate microtubules. As part of the mTORC2 complex MTOR may regulate other cellular processes including survival and organization of the cytoskeleton. Plays a critical role in the phosphorylation at Ser-473 of AKT1, a pro-survival effector of phosphoinositide 3-kinase, facilitating its activation by PDK1. mTORC2 may regulate the actin cytoskeleton, through phosphorylation of PRKCA, PXN and activation of the Rho-type guanine nucleotide exchange factors RHOA and RAC1A or RAC1B. mTORC2 also regulates the phosphorylation of SGK1 at Ser-422.
NOTCH1	Functions as a receptor for membrane-bound ligands Jagged1, Jagged2 and Delta1 to regulate cell-fate determination. Upon ligand activation through the released notch intracellular domain (NICD) it forms a transcriptional activator complex with RBPJ/RBPSUH and activates genes of the enhancer of split locus. Affects the implementation of differentiation, proliferation and apoptotic programs. Involved in angiogenesis; negatively regulates endothelial cell proliferation and migration and angiogenic sprouting. Involved in the maturation of both CD4+ and CD8+ cells in the thymus. Important for follicular differentiation and possibly cell fate selection within the follicle. During cerebellar development, functions as a receptor for neuronal DNER and is involved in the differentiation of Bergmann glia. Represses neuronal and myogenic differentiation. May play an essential role in postimplantation development, probably in some aspect of cell specification and/or differentiation. May be involved in mesoderm development, somite formation and neurogenesis. May enhance HIF1A function by sequestering HIF1AN away from HIF1A. Required for the THBS4 function in regulating protective astrogenesis from the subventricular zone (SVZ) niche after injury. Involved in determination of left/right symmetry by modulating the balance between motile and immotile (sensory) cilia at the left-right organiser (LRO).
PARP1	Involved in the base excision repair (BER) pathway, by catalyzing the poly(ADP-ribosyl)ation of a limited number of acceptor proteins involved in chromatin architecture and in DNA metabolism. This modification follows DNA damages and appears as an obligatory step in a detection/signaling pathway leading to the reparation of DNA strand breaks. Mediates the poly(ADP-ribosyl)ation of APLF and CHFR. Positively regulates the transcription of MTUS1 and negatively regulates the transcription of MTUS2/TIP150. With EEF1A1 and TXK, forms a complex that acts as a T-helper 1 (Th1) cell-specific transcription factor and binds the promoter of IFN-gamma to directly regulate its transcription, and is thus involved importantly in Th1 cytokine production. Required for PARP9 and DTX3L recruitment to DNA damage sites. PARP1-dependent PARP9-DTX3L-mediated ubiquitination promotes the rapid and specific recruitment of 53BP1/TP53BP1, UIMC1/RAP80, and BRCA1 to DNA damage sites.
PD-1	Inhibitory cell surface receptor involved in the regulation of T-cell function during immunity and tolerance. Upon ligand binding, inhibits T-cell effector functions in an antigen-specific manner. Possible cell death inducer, in association with other factors.
PD-L1	Involved in the costimulatory signal, essential for T-cell proliferation and production of IL10 and IFNG, in an IL2-dependent and a PDCD1-independent manner. Interaction with PDCD1 inhibits T-cell proliferation and cytokine production.
PIK3CA	Phosphoinositide-3-kinase (PI3K) that phosphorylates PtdIns (Phosphatidylinositol), PtdIns4P (Phosphatidylinositol 4-phosphate) and PtdIns(4,5)P2 (Phosphatidylinositol 4,5-bisphosphate) to generate phosphatidylinositol 3,4,5-trisphosphate (PIP3). PIP3 plays a key role by recruiting PH domain-containing proteins to the membrane, including AKT1 and PDPK1, activating signaling cascades involved in cell growth, survival, proliferation, motility and morphology. Participates in cellular signaling in response to various growth factors. Involved in the activation of AKT1 upon stimulation by receptor tyrosine kinases ligands such as EGF, insulin, IGF1, VEGFA and PDGF. Involved in signaling via insulin-receptor substrate (IRS) proteins. Essential in endothelial cell migration during vascular development through VEGFA signaling, possibly by regulating RhoA activity. Required for lymphatic vasculature development, possibly by binding to RAS and by activation by EGF and FGF2, but not by PDGF. Regulates invadopodia formation in breast cancer cells through the PDPK1-AKT1 pathway. Participates in cardiomyogenesis in embryonic stem cells through a AKT1 pathway. Participates in vasculogenesis in embryonic stem cells through PDK1 and protein kinase C pathway. Has also serine-protein kinase activity: phosphorylates PIK3R1 (p85alpha regulatory subunit), EIF4EBP1 and HRAS.
STAT3	Signal transducer and transcription activator that mediates cellular responses to interleukins, KITLG/SCF and other growth factors. May mediate cellular responses to activated FGFR1, FGFR2, FGFR3 and FGFR4. Binds to the interleukin-6 (IL-6)-responsive elements identified in the promoters of various acute-phase protein genes. Activated by IL31 through IL31RA. Cytoplasmic STAT3 represses macroautophagy by inhibiting EIF2AK2/PKR activity. Plays an important role in host defense in methicillin-resistant S.aureus lung infection by regulating the expression of the antimicrobial lectin REG3G (By similarity).

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Oncompass Report

A Realtime Oncology Molecular Treatment Calculator számításaival

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NÉV	Anonymous

DRIVER ÉS TARGET GÉNEK LEÍRÁSA

TARGET GÉNEK

Név	Leírás
YES1	Non-receptor protein tyrosine kinase that is involved in the regulation of cell growth and survival, apoptosis, cell-cell adhesion, cytoskeleton remodeling, and differentiation. Stimulation by receptor tyrosine kinases (RTKs) including EGRF, PDGFR, CSF1R and FGFR leads to recruitment of YES1 to the phosphorylated receptor, and activation and phosphorylation of downstream substrates. Upon EGFR activation, promotes the phosphorylation of PARD3 to favor epithelial tight junction assembly. Participates in the phosphorylation of specific junctional components such as CTNND1 by stimulating the FYN and FER tyrosine kinases at cell-cell contacts. Upon T-cell stimulation by CXCL12, phosphorylates collapsin response mediator protein 2/DPYSL2 and induces T-cell migration. Participates in CD95L/FASLG signaling pathway and mediates AKT-mediated cell migration. Plays a role in cell cycle progression by phosphorylating the cyclin-dependent kinase 4/CDK4 thus regulating the G1 phase. Also involved in G2/M progression and cytokinesis.

FÜGGELÉK

CÉLZOTT HATÓANYAGOK

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

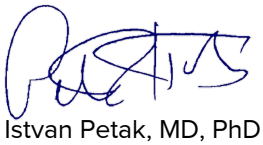
KLINIKAI VIZSGÁLATBAN ELÉRHETŐ HATÓANYAGOK (445): 17-AAG, 4SC-201, 4SC-202, 4SC-203, AAL881, AB-010, ABBV-221, ABT-414, ABT-494, ABT-700, ABT-767, ABT-806, ABTL0812, AC0010MA, AC-480, ACE-041, ACP-319, ACY-1215, ACY-241, ADU-623, AEB071, AEE788, AG-014699, AG-120, AG-881, AGI-5198, AKN-028, ALLITINIB,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

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

Oncompass Report

A Realtime Oncology Molecular Treatment Calculator számításaival

AZONOSÍTÓ	429397
NÉV	Anonymous



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