ONCOMPASS™ REPORT

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Realtime Oncology
Molecular Treatment Calculator™

Oncompass Report

A Realtime Oncology Molecular Treatment Calculator számításaival

AZONOSÍTÓ	430735
NÉV	Anonymous

BETEG ADATAI

Oncompass™ ID:
Név: Anonymous
Születési dátum: 1965

Primer daganat lokalizációja: colon
Szövettani típus: adenocarcinoma
Metasztázis lokalizációja: peritoneum

SZAKÉRTŐK

Molekuláris Farmakológus: Dr. Peták István
Genetikai Tanácsadó: Déri Júlia, MSc
Molekuláris Biológus: Várkondi Edit, PhD
Konzulens Orvos: Dr. Pajkos Gábor
Szakértő: Dr. Rácz Anna
Betegút Koordinátor: Gligorovics Rita
Kezelőorvos:
Biológus: Sipos Anna, MSc
Biofizikus: Lakatos Dóra, PhD

PATOLÓGIAI ÉS MOLEKULÁRIS DIAGNOSZTIKAI VIZSGÁLATOK

Az Oncompass vizsgálatot a XXX azonosítójú, primer tumorból származó szövettani mintából végeztük.
Tumorarány: 50%
Tumortípus és szövettan: colon adenocarcinoma

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

Korábbi molekuláris diagnosztikai vizsgálatok eredménye:
Sanger - BRAF (Vad típusú gén), KRAS (Mutáns gén)

KORÁBBI KEZELÉSEK

1. vonal - BEVACIZUMAB + FOLFIRI
adjuváns terápia: 5FU

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ÖSSZEFOGLALÁS

A colon adenocc. 2019. műtéti mintájából származó szöveti mintát vizsgáltuk 50 % tumorarány mellett.
Az 591 génes NGS vizsgálat sikeresen lefutott.
Immunterápia hatékonyságára vonatkozó biomarkerek:
MSI: stabil (MSS)
Tumor mutational burden (TMB) alacsony (1,0, 18%-ban kapunk ennél alacsonyabb értéket)
PD-L1 negatív.

KRAS-Q61H, PIK3CA-N345K, PTEN-N323fs*2, GNAS-R844C, APC-Q1328*, APC-N741S a legfontosabb detektált génhibák.
- A KRAS génhiba jól ismert, rezisztenciát okoz többféle célzott terápiára, célba vételére nincs törzskönyvezett lehetőség, EGFR-gátlásra rezisztenciát okoz, egy esettanulmány szerint TRAMETINIB (MEK-gátló) célba veszi. A KRAS mutáns CRC daganatoknál megfigyelték a metformin hatékonyságát.
- PIK3CA-N345K mutáció jól ismert patogén mutáció, mTOR-gátlók veszik célba. A PIK3CA mutáns CRC daganatokban az aszpirin kedvező hatását látták.
KRAS és PIK3CA együttes mutációk esetén sem a MEK-gátlók, sem az mTOR-gátlók nem hatékonyak monoterápiaként, de együttadásukkor szinergizmus is megfigyelhető.
- PTEN frameshift mutációja patogén, rezisztenciát okoz PIK3CA-gátlókra, EGFR-gátlásra, immunterápiára, de preklinikai eredmények szerint PTEN vesztés esetén a MEK + mTOR kombinált gátlás szinergisztikus hatású.
- a GNAS mutáció is patogén, megcélzásával kapcsolatban fejlesztés alatt álló szerek említhetőek.
- az APC mutáció jellemző vastagbél daganatokra, a fenti STOP mutáció ismerten patogén. COX2-gátlókkal vagy aszpirinnel vehető célba.

Összefoglalva: KRAS mutáció esetén célzott terápia csak a későbbi vonalakban merül fel, mert a kemoterápiától nagyobb eredményesség várható. A KRAS mutáció előfordulása gyakori colon adenocc.-ban, EGFR gátlás nem hatékony ilyen profil esetén (EGFR-gátlás ellen szól a PIK3CA és a PTEN mutáció is).
A felvetődő célzott kezelések hatékonysága klinikailag jelenleg nem alátámasztott, de preklinikai adatok alapján a KRAS mutáció inkább kombinációkkal vehető célba. A célzott terápia nem törzskönyvezett, a NEAK egyedi méltányossági kérelem elbírálásakor dönthet a finanszírozásukról. Preklinikai adatok alapján javasolja a Realtime Oncology Calculator első helyen a MEK-gátlót, a KRAS mutációt célba inkább MEK-gátlós kombinációjuk venné, pl. **TRAMETINIB + EVEROLIMUS** vagy **TRAMETINIB + METFORMIN**. A MEKi + mTOR inhibitor kombináció mellett szól mind a PIK3CA, mind a PTEN mutáció, mindkettőt az mTOR-gátlók célba veszik, de KRAS mutáció mellett csak MEK-gátlóval kiegészítve hatékonyak, de úgy szinergizmust is megfigyeltek.
A kemoterápiák kiegészítésére javasolható **ASPIRIN** és **METFORMIN**, az ASPIRIN és PIK3CA mutáció valamint az APC mutáció összefüggését is írja a szakirodalom, a METFORMINt inkább a KRAS mutációval kapcsolatban említik, de mint mTOR gátló hatású szer, a PTEN és PIK3CA génhibát is célba veszi.
Immunterápia hatékonyságára nem utal egyik biomarker sem (MSS, alacsony TMB), sőt, a PTEN mutáció rezisztenciát is okozhat rá.

A kezelőorvos javaslatára szívesen írunk EMK-t, OGYÉI kérelmet, ha a kezelési stratégiába illeszthető.

MOLEKULÁRIS CÉLPONT ELEMZÉS

MOLEKULÁRIS ALTERÁCIÓK

KRAS-Q61H driver (AEL: 236,74, AF/TR: 10.24%/50%),
PIK3CA-N345K driver (AEL: 69,80, AF/TR: 9.43%/50%),
PTEN-N323fs*2 driver (AEL: 24,48, AF/TR: 18.13%/50%),
GNAS-R844C driver (AEL: 16,95, AF/TR: 7.99%/50%),
APC-Q1328* driver (AEL: 6,04, AF/TR: 18.05%/50%),
APC-N741S driver (AEL: 5,99, AF/TR: 59.78%/50%),
PRKN-E309* VUS, driver gén (AEL: 1,55, AF/TR: 8.16%/50%),
CHEK2-Y159H VUS, driver gén (AEL: 1,52, AF/TR: 47.08%/50%),
KMT2D-T2949A VUS, driver gén (AEL: 1,37, AF/TR: 50.34%/50%),
INPP4B-V594A driver (AEL: 0,41, AF/TR: 99.58%/50%),
EPHA3-C928F VUS, driver gén (AEL: 0,12, AF/TR: 50.09%/50%),
WNK2-V2107I VUS, driver gén (AEL: 0,11, AF/TR: 57.98%/50%),
RECQL5-S958R VUS, driver gén (AEL: 0,07, AF/TR: 47.42%/50%),
CSMD3-E13D VUS, driver gén (AEL: 0,03, AF/TR: 47.86%/50%),
PIK3CG-N522S driver (AEL: 0,03, AF/TR: 53.25%/50%),
SLIT2-S849T VUS, driver gén (AEL: 0,01, AF/TR: 10.53%/50%),
GATA6-G540fs*5 VUS, driver gén (AEL: 0,01, AF/TR: 9.87%/50%),
THSD7B-R353H ellentmondásos driver (AEL: 0,00, AF/TR: 47.07%/50%),
BCL6-E164D ellentmondásos driver (AEL: 0,00, AF/TR: 44.04%/50%),

INDIREKT CÉLPONT GÉNEK

PIK3CA vad típus (AEL: 268,59),
- PTEN-N323fs*2 driver (AEL: -24,48) ;
- PRKN-E309* driver (AEL: 1,55) ;
- PIK3CA-N345K driver (AEL: 69,80)

CDK4 vad típus (AEL: 244,10),
- KRAS-Q61H driver (AEL: 236,74)

XPO1 vad típus (AEL: 242,44),
- KRAS-Q61H driver (AEL: 236,74)

RAF1 vad típus (AEL: 240,61),
- KRAS-Q61H driver (AEL: 236,74)

SOS1 vad típus (AEL: 238,58),
- KRAS-Q61H driver (AEL: 236,74)

MAPK3 vad típus (AEL: 238,19),
- KRAS-Q61H driver (AEL: 236,74)

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MIER3-A529V ismeretlen jelentőségű variáns (AEL: 0,00, AF/TR: 45.13%/50%),
SEC16A-G2247R ismeretlen jelentőségű variáns (AEL: 0,00, AF/TR: 59.67%/50%),
SYNE3-P559T ismeretlen jelentőségű variáns (AEL: 0,00, AF/TR: 54.48%/50%),
OTOP1-G407D ismeretlen jelentőségű variáns (AEL: 0,00, AF/TR: 13.92%/50%),
MYO18A-R2034Q ismeretlen jelentőségű variáns (AEL: 0,00, AF/TR: 47.36%/50%),
SEC16A-R1214C nem driver (AEL: -0,03, AF/TR: 46.7%/50%),
TET2-M1701I nem driver (AEL: -24,90, AF/TR: 49.47%/50%)

MAPK1 vad típus (AEL: 238,19),
- KRAS-Q61H driver (AEL: 236,74)

CDC7 vad típus (AEL: 237,91),
- KRAS-Q61H driver (AEL: 236,74)

PLK1 vad típus (AEL: 237,74),
- KRAS-Q61H driver (AEL: 236,74)

CNKSR1 vad típus (AEL: 237,59),
- KRAS-Q61H driver (AEL: 236,74)

DNMT1 vad típus (AEL: 237,59),
- KRAS-Q61H driver (AEL: 236,74)

PTPN11 vad típus (AEL: 237,54),
- KRAS-Q61H driver (AEL: 236,74)

Hsp90 vad típus (AEL: 237,49),
- KRAS-Q61H driver (AEL: 236,74)

FAK vad típus (AEL: 237,24),
- KRAS-Q61H driver (AEL: 236,74)

CDK1 vad típus (AEL: 237,04),
- KRAS-Q61H driver (AEL: 236,74)

MAP2K1 vad típus (AEL: 178,91),
- PRKN-E309* driver (AEL: -1,55) ;
- PIK3CA-N345K driver (AEL: -69,80) ;
- KRAS-Q61H driver (AEL: 236,74)

MTOR vad típus (AEL: 119,10),
- PRKN-E309* driver (AEL: 1,55) ;
- PTEN-N323fs*2 driver (AEL: 24,48) ;
- PIK3CA-N345K driver (AEL: 69,80)

AKT1 vad típus (AEL: 101,70),
- PRKN-E309* driver (AEL: 1,55) ;
- PIK3CA-N345K driver (AEL: 69,80) ;
- PTEN-N323fs*2 driver (AEL: 24,48)

AKT2 vad típus (AEL: 70,90),
- PIK3CA-N345K driver (AEL: 69,80)

CTNNB1 vad típus (AEL: 70,23),
- PIK3CA-N345K driver (AEL: 69,80)

AKT3 vad típus (AEL: 70,16),
- PIK3CA-N345K driver (AEL: 69,80)

PIK3CB vad típus (AEL: 25,67),
- PTEN-N323fs*2 driver (AEL: 24,48)

ATM vad típus (AEL: 25,32),
- PTEN-N323fs*2 driver (AEL: 24,48)

PRKACA vad típus (AEL: 17,45),
- GNAS-R844C driver (AEL: 16,95)

COX2 vad típus (AEL: 15,50),
- APC-Q1328* driver (AEL: 6,04) ;
- APC-N741S driver (AEL: 5,99)

SOD1 vad típus (AEL: 2,89)
- CHEK2-Y159H driver (AEL: 1,52)

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DAGANAT MOLEKULÁRIS PROFILJÁVAL POZITÍV KAPCSOLATBAN ÁLLÓ HATÓANYAGOK

FORGALOMBAN LÉVŐ

10 listázott hatóanyag (összesen 84)

SELINEXOR (bármely tumor - multiple myeloma [FDA+EMA]; bármely tumor - diffuse large B-cell lymphoma [FDA]) (AEL: 503,72)
- KRAS-Q61H driver (AEL: 236,74) ;
- XPO1 vad típus target (AEL: 242,44)

TRAMETINIB (lung - adenocarcinoma [FDA+EMA]; thyroid - anaplastic carcinoma [FDA]; bármely tumor - malignant melanoma [FDA+EMA]) (AEL: 498,60)
- PRKN-E309* driver (AEL: -1,55) ;
- KRAS-Q61H driver (AEL: 236,74) ;
- MAP2K1 vad típus target (AEL: 178,91)

PALBOCICLIB (breast - bármely szövettan [FDA+EMA]) (AEL: 489,25)
- CDK4 vad típus target (AEL: 244,10) ;
- KRAS-Q61H driver (AEL: 236,74)

ABEMACICLIB (breast - bármely szövettan [FDA+EMA]) (AEL: 481,92)
- CDK4 vad típus target (AEL: 244,10) ;
- KRAS-Q61H driver (AEL: 236,74)

BINIMETINIB (skin - malignant melanoma [FDA+EMA]) (AEL: 436,72)
- KRAS-Q61H driver (AEL: 236,74) ;
- MAP2K1 vad típus target (AEL: 178,91)

METFORMIN (AEL: 430,88)
- KRAS-Q61H driver (AEL: 236,74) ;
- PIK3CA-N345K driver (AEL: 69,80) ;
- MTOR vad típus target (AEL: 119,10)

SELUMETINIB (bármely tumor - neurofibroma [FDA]; bármely tumor - plexiform neurofibroma [FDA]) (AEL: 424,15)
- KRAS-Q61H driver (AEL: 236,74) ;
- MAP2K1 vad típus target (AEL: 178,91)

COBIMETINIB (skin - malignant melanoma [FDA+EMA]) (AEL: 416,01)
- MAP2K1 vad típus target (AEL: 178,91) ;
- KRAS-Q61H driver (AEL: 236,74)

COPANLISIB (lymph node - follicular non-Hodgkin lymphoma [FDA]) (AEL: 366,40)
- PIK3CA vad típus target (AEL: 268,59) ;
- PIK3CA-N345K driver (AEL: 69,80) ;
- PIK3CB vad típus target (AEL: 25,67)

ATEZOLIZUMAB (lung - non-small cell carcinoma [FDA+EMA]; lung - small cell carcinoma [FDA+EMA]; breast - bármely szövettan [FDA+EMA]; liver - hepatocellular carcinoma [FDA+EMA]; bármely tumor - malignant melanoma [FDA]; bármely tumor - urothelial carcinoma [FDA+EMA]) (AEL: 252,93)
- KRAS-Q61H driver (AEL: 236,74)

KLINIKAI FEJLESZTÉS ALATT

10 listázott hatóanyag (összesen 150)

DACTOLISIB (AEL: 489,04)
- PIK3CA vad típus target (AEL: 268,59) ;
- PRKN-E309* driver (AEL: 1,55) ;
- MTOR vad típus target (AEL: 119,10) ;
- PIK3CA-N345K driver (AEL: 69,80) ;
- PIK3CB vad típus target (AEL: 25,67)

DAGANAT MOLEKULÁRIS PROFILJÁVAL NEGATÍV KAPCSOLATBAN ÁLLÓ HATÓANYAGOK

FORGALOMBAN LÉVŐ

10 listázott hatóanyag (összesen 40)

CETUXIMAB (rectum - bármely szövettan [FDA+EMA]; colon - bármely szövettan [FDA+EMA]; head-neck - squamous cell carcinoma [FDA+EMA]) (AEL: -1555,31)
- KRAS-Q61H driver (AEL: -236,74) ;
- PIK3CA-N345K driver (AEL: -69,80) ;
- EGFR vad típus target (AEL: -674,10) ;
- PTEN-N323fs*2 driver (AEL: -24,48)

PANITUMUMAB (colon - bármely szövettan [FDA+EMA]; rectum - bármely szövettan [FDA+EMA]) (AEL: -1383,01)
- KRAS-Q61H driver (AEL: -236,74) ;
- EGFR vad típus target (AEL: -674,10) ;
- PIK3CA-N345K driver (AEL: -69,80) ;
- PTEN-N323fs*2 driver (AEL: -24,48)

NERATINIB (breast - bármely szövettan [FDA+EMA]) (AEL: -1013,26)
- ERBB2 vad típus target (AEL: -339,17) ;
- EGFR vad típus target (AEL: -674,10)

AFATINIB (lung - squamous cell carcinoma [FDA+EMA]; lung - adenocarcinoma [FDA+EMA]; lung - non-small cell carcinoma [FDA+EMA]) (AEL: -1013,03)
- EGFR vad típus target (AEL: -674,10) ;
- ERBB2 vad típus target (AEL: -339,17)

LAPATINIB (breast - bármely szövettan [FDA+EMA]) (AEL: -1008,79)
- ERBB2 vad típus target (AEL: -339,17) ;
- EGFR vad típus target (AEL: -674,10) ;
- PIK3CA-N345K driver (AEL: -69,80) ;
- PTEN-N323fs*2 driver (AEL: -24,48) ;
- AKT1 vad típus target (AEL: 101,70)

ERLOTINIB (pancreas - bármely szövettan [FDA+EMA]; lung - adenocarcinoma [FDA+EMA]; lung - squamous cell carcinoma [FDA+EMA]; lung - non-small cell carcinoma [FDA+EMA]) (AEL: -1004,58)
- KRAS-Q61H driver (AEL: -236,74) ;
- EGFR vad típus target (AEL: -674,10) ;
- PIK3CA-N345K driver (AEL: -69,80)

GEFITINIB (lung - squamous cell carcinoma [FDA+EMA]; lung - adenocarcinoma [FDA+EMA]; lung - non-small cell carcinoma [FDA+EMA]) (AEL: -957,19)
- PTEN-N323fs*2 driver (AEL: -24,48) ;
- KRAS-Q61H driver (AEL: -236,74) ;
- EGFR vad típus target (AEL: -674,10)

TRASTUZUMAB (breast - bármely szövettan [FDA+EMA]; gastroesophageal junction - adenocarcinoma [FDA+EMA]; gastric - adenocarcinoma [FDA+EMA]) (AEL: -691,26)
- PIK3CA-N345K driver (AEL: -69,80) ;
- KRAS-Q61H driver (AEL: -236,74) ;
- PTEN-N323fs*2 driver (AEL: -24,48) ;
- ERBB2 vad típus target (AEL: -339,17)

OSIMERTINIB (lung - squamous cell carcinoma [FDA+EMA]; lung - non-small cell carcinoma [FDA+EMA]; lung - adenocarcinoma [FDA+EMA]) (AEL: -674,10)
- EGFR vad típus target (AEL: -674,10)

DACOMITINIB (lung - adenocarcinoma [FDA+EMA]; lung - non-small cell carcinoma [FDA+EMA]; lung - squamous cell carcinoma [FDA+EMA]) (AEL: -674,02)
- EGFR vad típus target (AEL: -674,10)

KLINIKAI FEJLESZTÉS ALATT

10 listázott hatóanyag (összesen 71)

ALLITINIB (AEL: -1013,26)
- EGFR vad típus target (AEL: -674,10) ;
- ERBB2 vad típus target (AEL: -339,17)

AV-412 (AEL: -1013,26)
- ERBB2 vad típus target (AEL: -339,17) ;
- EGFR vad típus target (AEL: -674,10)

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OMIPALISIB (AEL: 487,15)
- MTOR vad típus target (AEL: 119,10) ;
- PIK3CA vad típus target (AEL: 268,59) ;
- PIK3CA-N345K driver (AEL: 69,80) ;
- PIK3CB vad típus target (AEL: 25,67)

RIVICICLIB (AEL: 481,13)
- CDK1 vad típus target (AEL: 237,04) ;
- CDK4 vad típus target (AEL: 244,10)

RGB-286638 (AEL: 481,13)
- CDK4 vad típus target (AEL: 244,10) ;
- CDK1 vad típus target (AEL: 237,04)

ALVOCIDIB (AEL: 481,13)
- CDK1 vad típus target (AEL: 237,04) ;
- CDK4 vad típus target (AEL: 244,10)

MILCICLIB (AEL: 481,13)
- CDK4 vad típus target (AEL: 244,10) ;
- CDK1 vad típus target (AEL: 237,04)

RONICICLIB (AEL: 481,13)
- CDK4 vad típus target (AEL: 244,10) ;
- CDK1 vad típus target (AEL: 237,04)

Simurosertib (AEL: 479,31)
- CDC7 vad típus target (AEL: 237,91) ;
- KRAS-Q61H driver (AEL: 236,74)

ONVANSERTIB (AEL: 478,49)
- KRAS-Q61H driver (AEL: 236,74) ;
- PLK1 vad típus target (AEL: 237,74)

GANETESPIB (AEL: 476,28)
- KRAS-Q61H driver (AEL: 236,74) ;
- Hsp90 vad típus target (AEL: 237,49)

CUDC-101 (AEL: -1013,26)
- ERBB2 vad típus target (AEL: -339,17) ;
- EGFR vad típus target (AEL: -674,10)

PELITINIB (AEL: -1013,26)
- EGFR vad típus target (AEL: -674,10) ;
- ERBB2 vad típus target (AEL: -339,17)

TAK-285 (AEL: -1013,26)
- ERBB2 vad típus target (AEL: -339,17) ;
- EGFR vad típus target (AEL: -674,10)

EPERTINIB (AEL: -1013,26)
- ERBB2 vad típus target (AEL: -339,17) ;
- EGFR vad típus target (AEL: -674,10)

JNJ-26483327 (AEL: -1013,26)
- EGFR vad típus target (AEL: -674,10) ;
- ERBB2 vad típus target (AEL: -339,17)

AEE788 (AEL: -674,10)
- EGFR vad típus target (AEL: -674,10)

SAPITINIB (AEL: -674,10)
- EGFR vad típus target (AEL: -674,10)

MEHD7945A (AEL: -674,10)
- EGFR vad típus target (AEL: -674,10)

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

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Oncompass Report

A Realtime Oncology Molecular Treatment Calculator számításaival

AZONOSÍTÓ	430735
NÉV	Anonymous

KLINIKAI VIZSGÁLATOK

Keresési Kritériumok

ÁLLAPOT: Not yet recruiting,Active recruiting

AZONOSÍTÓ **LEÍRÁS**

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

RÉSZLETES MOLEKULÁRIS PROFIL

GENETIKAI VARIÁNSOK

APC-N741S, APC-Q1328*, BCL6-E164D, CHEK2-Y159H, CSMD3-E13D, EPHA3-C928F, GATA6-G540FS*5, GNAS-R844C, INPP4B-V594A, KMT2D-T2949A, KRAS-Q61H, MIER3-A529V, MYO18A-R2034Q, OTOP1-G407D, PIK3CA-N345K, PIK3CG-N522S, PRKN-E309*, PTEN-N323FS*2, RECQL5-S958R, SEC16A-G2247R, SEC16A-R1214C, SLIT2-S849T, SYNE3-P559T, TET2-M1701I, THSD7B-R353H, WNK2-V2107I

VAD TÍPUSÚ GÉNEK

ABCB1, ABCC2, ABL1, ABL2, ABRAXAS1, ACVR1B, ACVRL1, ADGRB3, AGTRAP, AIP, AKAP9, AKT1, AKT2, AKT3, ALK, AMER1, AMPH, APEX1, AR, ARAF, ARFRP1, ARID1A, ARID1B, ARID2, ASXL1, ATM, ATP11B, ATP4A, ATP6V0D2, ATR, ATRX, AURKA, AURKB, AXIN1, AXIN2, AXL, B2M, BAP1, BARD1, BAX, BAZ2B, BCL2, BCL2L1, BCL2L2, BCL9, BCOR, BCORL1, BCR, BIM, BIRC2, BIRC3, BLM, BMPR1A, BRAF, BRCA1, BRCA2, BRD4, BRIP1, BTG1, BTK, BUB1B, CARD11, CASP8, CASR, CBFB, CBL, CBLB, CBLC, CCDC178, CCDC6, CCND1, CCND2, CCND3, CCNE1, CD74, CD79A, CD79B, CDA, CDC27, CDC73, CDH1, CDK12, CDK4, CDK6, CDK8, CDKN1A, CDKN1B, CDKN1C, CDKN2A, CDKN2B, CDKN2C, CEBPA, CEP57, CHD1, CHD2, CHD4, CHD7, CHEK1, CHIC2, CIC, CIT, CREBBP, CRKL, CRLF2, CSF1R, CSNK2A1, CTCF, CTNNA1, CTNNB1, CUBN, CUL3, CYLD, CYP19A1, CYP2A6, CYP2B6, CYP2C19, CYP2C9, CYP2D6, DAXX, DCC, DCUN1D1, DDB2, DDR1, DDR2, DDX11, DDX3X, DICER1, DIS3L2, DMD, DNMT3A, DOT1L, DPH3, DPYD, DSE, ECT2L, EED, EGFR, ELMO1, EML4, EMSY, EP300, EPCAM, EPHA2, 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, FANCD2, FANCE, FANCF, FANCG, FANCI, FANCL, FANCM, FAS, FAT1, FAT3, FBXO11, FBXO32, FBXW7, FGF10, FGF14, FGF19, FGF23, FGF3, FGF4, FGF5, FGF6, FGF9, FGFR1, FGFR2, FGFR3, FGFR4, FH, FLCN, FLT1, FLT3, FLT4, FN1, FOXA1, FOXL2, FOXO1, FOXP1, FRS2, FSTL5, FUBP1, FZD3, G6PD, GABRA6, GALNT17, GAS6, GATA1, GATA2, GATA3, GATA4, GEN1, GID4, GLI1, GNA11, GNA13, GNAI2, GNAQ, GNAT2, GOPC, GPC3, GPR78, GREM1, GRIN2A, GRM3, GRM8, GSK3B, GSTP1, GXYLT1, H3-3A, H3C2, HGF, HNF1A, HOXB13, HRAS, HSD3B1, HSP90AA1, HSPH1, IDH1, IDH2, IFITM1, IFITM3, IGF1R, IGF2, IGF2R, IGSF10, IKBKE, IKZF1, IKZF4, IL2RA, IL2RB, IL2RG, IL6, IL6ST, IL7R, INHBA, IRAK4, IRF2, IRF4, IRS2, ITCH, JAK1, JAK2, JAK3, JUN, KAT6A, KDM4B, KDM5A, KDM5C, KDM6A, KDR, KEAP1, KEL, KIAA1549, KIF5B, KIT, KLF6, KLHL6, KMT2A, KMT2C, KNSTRN, KREMEN1, LAMA2, LCK, LMO1, LPAR2, LRP1B, LRRK2, LTK, LYN, LZTR1, MAGI2, MAGI3, MAGOH, MAP2K1, MAP2K2, MAP2K4, MAP3K1, MAP3K4, MAP4K3, MAP7, MAPK1, MAPK3, MAS1L, MAX, MCL1, MDM2, MDM4, MED12, MED13, MEF2B, MEN1, MET, MITF, MLH1, MLLT3, MPL, MRE11, MSH2, MSH3, MSH6, MST1R, MTOR, MUC16, MUTYH, MYC, MYCL1, MYCN, MYD88, MYO1B, NBN, NCOA2, NCOR1, NEK2, 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, PAK3, PALB2, PAX3, PAX5, PAX7, PBRM1, PCBP1, PCGF2, PD-L1, PDGFRA, PDGFRB, PDK1, PDL2, PDZRN3, PHF6, PHOX2B, PIK3C2B, PIK3CB, PIK3CD, PIK3R1, PIK3R2, PLCG2, PLEKHS1, PMS1, PMS2, PNP, POLD1, POLE, POT1, PPARG, PPM1L, PPP2R1A, PPP2R2A, PRDM1, PREX2, PRF1, PRKAR1A, PRKCI, PRKDC, PRPF40B, PRSS8, PSMB1, PSMB2, PSMB5, PSMD1, PSMD2, PTCH1, PTGFR, PTPN11, PTPN12, PTPRD, QKI, RAC1, RAC2, RAD21, RAD50, RAD51, RAD51B, RAD51C, RAD51D, RAD54L, RAF1, RANBP2, RARA, RARB, RARG, RB1, RBM10, RECQL4, RET, RHBDF2, RHEB, RHOA, RICTOR, RIT1, RNF43, ROS1, RPS6KB1, RPTOR, RUNX1, RUNX1T1, RXRA, RXRB, RXRG, S1PR2, SAMD9L, SBDS, SCN11A, SDC4, SDHA, SDHAF2, SDHB, SDHC, SDHD, SEPT9, SETBP1, SETD2, SF1, SF3A1, SF3B1, SH2B3, SHH, SHOC2, SLC22A1, SLC22A2, SLC31A1, SLC34A2, SLC45A3, SLC7A8, SLC9A9, SLCO1B1, SLX4, SMAD2, SMAD3, SMAD4, SMARCA4, SMARCB1, SMARCE1, SMC1A, SMC3, SMO, SNCAIP, SOCS1, SOS1, SOX10, SOX2, SOX9, SPEG, SPEN, SPOP, SPRED1, SPTA1, SRC, SRSF2, SSTR1, STAG2, STAT3, STAT4, STK11, SUFU, SUZ12, SYK, TACC3, TAF1, TAS2R38, TBX20, TBX3, TCERG1, TCF7L2, TENT5C, TERC, TERT, TFG, TGFBR2, 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, 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

FISH/CNA/IHC NEGATÍV GÉNEK

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

MOLEKULÁRIS BIOLÓGIAI INTERPRETÁCIÓ

MOLEKULÁRIS ALTERÁCIÓK

KRAS-Q61H driver (AEL: 236,74, AF/TR: 10.24%/50%),
PIK3CA-N345K driver (AEL: 69,80, AF/TR: 9.43%/50%),
PTEN-N323fs*2 driver (AEL: 24,48, AF/TR: 18.13%/50%),

INDIREKT CÉLPONT GÉNEK

PIK3CA vad típus (AEL: 268,59),

- PTEN-N323fs*2 driver (AEL: -24,48) ;
- PRKN-E309* driver (AEL: 1,55) ;

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RÉSZLETES MOLEKULÁRIS PROFIL

GNAS-R844C driver (AEL: 16,95, AF/TR: 7.99%/50%),
APC-Q1328* driver (AEL: 6,04, AF/TR: 18.05%/50%),
APC-N741S driver (AEL: 5,99, AF/TR: 59.78%/50%),
PRKN-E309* VUS, driver gén (AEL: 1,55, AF/TR: 8.16%/50%),
CHEK2-Y159H VUS, driver gén (AEL: 1,52, AF/TR: 47.08%/50%),
KMT2D-T2949A VUS, driver gén (AEL: 1,37, AF/TR: 50.34%/50%),
INPP4B-V594A driver (AEL: 0,41, AF/TR: 99.58%/50%),
EPHA3-C928F VUS, driver gén (AEL: 0,12, AF/TR: 50.09%/50%),
WNK2-V2107I VUS, driver gén (AEL: 0,11, AF/TR: 57.98%/50%),
RECQL5-S958R VUS, driver gén (AEL: 0,07, AF/TR: 47.42%/50%),
CSMD3-E13D VUS, driver gén (AEL: 0,03, AF/TR: 47.86%/50%),
PIK3CG-N522S driver (AEL: 0,03, AF/TR: 53.25%/50%),
SLIT2-S849T VUS, driver gén (AEL: 0,01, AF/TR: 10.53%/50%),
GATA6-G540fs*5 VUS, driver gén (AEL: 0,01, AF/TR: 9.87%/50%),
THSD7B-R353H ellentmondásos driver (AEL: 0,00, AF/TR: 47.07%/50%),
BCL6-E164D ellentmondásos driver (AEL: 0,00, AF/TR: 44.04%/50%),
MIER3-A529V ismeretlen jelentőségű variáns (AEL: 0,00, AF/TR: 45.13%/50%),
SEC16A-G2247R ismeretlen jelentőségű variáns (AEL: 0,00, AF/TR: 59.67%/50%),
SYNE3-P559T ismeretlen jelentőségű variáns (AEL: 0,00, AF/TR: 54.48%/50%),
OTOP1-G407D ismeretlen jelentőségű variáns (AEL: 0,00, AF/TR: 13.92%/50%),
MYO18A-R2034Q ismeretlen jelentőségű variáns (AEL: 0,00, AF/TR: 47.36%/50%),
SEC16A-R1214C nem driver (AEL: -0,03, AF/TR: 46.7%/50%),
TET2-M1701I nem driver (AEL: -24,90, AF/TR: 49.47%/50%)

- PIK3CA-N345K driver (AEL: 69,80)

CDK4 vad típus (AEL: 244,10),
- KRAS-Q61H driver (AEL: 236,74)

XPO1 vad típus (AEL: 242,44),
- KRAS-Q61H driver (AEL: 236,74)

RAF1 vad típus (AEL: 240,61),
- KRAS-Q61H driver (AEL: 236,74)

SOS1 vad típus (AEL: 238,58),
- KRAS-Q61H driver (AEL: 236,74)

MAPK3 vad típus (AEL: 238,19),
- KRAS-Q61H driver (AEL: 236,74)

MAPK1 vad típus (AEL: 238,19),
- KRAS-Q61H driver (AEL: 236,74)

CDC7 vad típus (AEL: 237,91),
- KRAS-Q61H driver (AEL: 236,74)

PLK1 vad típus (AEL: 237,74),
- KRAS-Q61H driver (AEL: 236,74)

CNKSR1 vad típus (AEL: 237,59),
- KRAS-Q61H driver (AEL: 236,74)

DNMT1 vad típus (AEL: 237,59),
- KRAS-Q61H driver (AEL: 236,74)

PTPN11 vad típus (AEL: 237,54),
- KRAS-Q61H driver (AEL: 236,74)

Hsp90 vad típus (AEL: 237,49),
- KRAS-Q61H driver (AEL: 236,74)

FAK vad típus (AEL: 237,24),
- KRAS-Q61H driver (AEL: 236,74)

CDK1 vad típus (AEL: 237,04),
- KRAS-Q61H driver (AEL: 236,74)

MAP2K1 vad típus (AEL: 178,91),
- PRKN-E309* driver (AEL: -1,55) ;
- PIK3CA-N345K driver (AEL: -69,80) ;
- KRAS-Q61H driver (AEL: 236,74)

MTOR vad típus (AEL: 119,10),
- PRKN-E309* driver (AEL: 1,55) ;
- PTEN-N323fs*2 driver (AEL: 24,48) ;
- PIK3CA-N345K driver (AEL: 69,80)

AKT1 vad típus (AEL: 101,70),
- PRKN-E309* driver (AEL: 1,55) ;
- PIK3CA-N345K driver (AEL: 69,80) ;
- PTEN-N323fs*2 driver (AEL: 24,48)

AKT2 vad típus (AEL: 70,90),
- PIK3CA-N345K driver (AEL: 69,80)

CTNNB1 vad típus (AEL: 70,23),
- PIK3CA-N345K driver (AEL: 69,80)

AKT3 vad típus (AEL: 70,16),
- PIK3CA-N345K driver (AEL: 69,80)

PIK3CB vad típus (AEL: 25,67),
- PTEN-N323fs*2 driver (AEL: 24,48)

ATM vad típus (AEL: 25,32),
- PTEN-N323fs*2 driver (AEL: 24,48)

PRKACA vad típus (AEL: 17,45),
- GNAS-R844C driver (AEL: 16,95)

COX2 vad típus (AEL: 15,50),

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RÉSZLETES MOLEKULÁRIS PROFIL

- APC-Q1328* driver (AEL: 6,04) ;
- APC-N741S driver (AEL: 5,99)

SOD1 vad típus (AEL: 2,89)

- CHEK2-Y159H driver (AEL: 1,52)

MOLEKULÁRIS BIOLÓGIAI INTERPRETÁCIÓ

A tumor mutational burden (TMB) vizsgálat eredménye

A vizsgált mintában a szekvencia analízis (NGS) során kapott 1 megabázisra vonatkozó mutációk száma (TMB) 1,02. Az adatbázisunkban lévő kalkulált TMB értékek (n=588) eloszlása alapján az eseteink 18%-ában kaptunk ennél alacsonyabb TMB értéket.

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

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).

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

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.

Daganatképződéssel összefüggésbe hozható gének, melyek feltehetően magasabb kópiaszámban vannak jelen (n<5), nem azonosítottunk a vizsgált mintában.

Daganatképződéssel összefüggésbe hozható gének, melyek feltehetően alacsonyabb kópiaszámban vannak jelen (n=**0**), nem azonosítottunk a vizsgált mintában.

Az újgenerációs szekvenálás (NGS) eredménye

591 gén NGS szekvenálása 5649 genetikai variánst mutatott ki a mintában. A molekuláris profilba feltöltött 27 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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MOLEKULÁRIS BIOLÓGIAI INTERPRETÁCIÓ

- 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.

KRAS-Q61H

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A szakirodalomban ismert onkogenikus variáns (1, 2), a COSMIC adatbázisban magas előfordulási értékkel szerepel. A ClinVar adatbázis szerint patogén variáns.
Egy KRAS-Q61H mutációt hordozó myeloma multiplexes betegnél trametinib kezeléssel a májléziók teljes regresszióját érték el (3).
Egy vizsgálatban a mutációt kimutatták egy colorectalis tumoros betegnél, akinél a cetuximab terápia ellenére progrediált a betegség (4).

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KRAS mutáns gén - célpontok

A KRAS a RAS géncsalád tagja, egy kis GTPáz típusú fehérjét kódol, a sejtproliferációt szabályozó jelátviteli utak része.
A KRAS onkogénben detektált mutáció miatt a daganat molekuláris profiljával pozitív asszociációban említhető célzott terápiás hatóanyagok a MEK (MAP2K1) (1), CDK (2, 3), HSP90 (4), PLK1 (5), CRAF (RAF1) (6, 7), ERK1/2 (MAPK3, MAPK1) (8), DNMT1 (9) és CNK1 (10) inhibitorok. KRAS mutációk esetén a BRAF gátlás tovább fokozhatja a tumorképződést (11), ezért a BRAF negatív célpontként szerepel a riportban. Preklinikai evidenciák alapján MEK vagy CDK inhibitor monoterápiánál hatásosabb lehet MEK + EGFR (1), MEK + CDK (12, 13), MEK + CRAF (14, 15) vagy MEK + mTOR (16, 17) gátló hatóanyagok kombinált alkalmazása. Forgalomban lévő, melanoma indikációban törzskönyvezett MEK gátló hatóanyagok a TRAMETINIB, a COBIMETINIB és a BINIMETINIB, valamint az FDA által 1-es típusú neurofibromatózisban elfogadott gyógyszer a SELUMETINIB. A CDK gátló PALBOCICLIB, RIBOCICLIB és ABEMACICLIB emlődaganat indikációjában törzskönyvezett hatóanyagok. Forgalomban lévő CRAF gátló hatással is rendelkező tirozin kináz gátlók a SORAFENIB és a REGORAFENIB. A DECITABINE forgalomban lévő DNMT1 gátló hatóanyag. CNK1 gátló hatóanyagok még nem állnak klinikai fejlesztés alatt.

A legújabb preklinikai eredmények a KRAS aktivált jelátvitel és a DNS károsodással összefüggő szabályozási mechanizmusok közötti kapcsolatokat tárták fel, aminek fontos terápiás vonatkozásai is lehetnek. KRAS aktiváció esetében a MEK gátlás kiegészítése PARP gátlással szinergisztikus hatást eredményezett számos sejtvonalban, a BRCA státusztól függetlenül (18). A tanulmány szerzői arra a következtetésre jutottak, hogy a PARPi és MEKi kölcsönösen blokkolják a másik hatóanyagra adott adaptív válaszokat, ami szintetikus letalitást eredményez. A kísérletek szerint a KRAS aktiváció rezisztenciát okozhat PARP gátló monoterápiára, de más modellrendszerekben végzett mérések ezt nem erősítették meg (19).
Egy másik közlemény szerint a CHK1 és MK2 együttes gátlása bizonyult hatékonynak KRAS mutáns sejtvonalakban (20). Hasonlóan, a homológ rekombinációs hibajavítás (HRR) és PARP együttes gátlása a KRAS mutáns sejtek szelektív elpusztulását eredményezte (21). Szintén szinergisztikus hatást figyeltek meg KRAS mutáns nem-kissejtes tüdőrák (NSCLC) sejtvonalak besugárzásra érzékenyítésében adavosertib (egy WEE1 inhibitor) és az olaparib együttes alkalmazásával (22).
A trametinib MEK inhibitor hatásossága korlátozott KRAS mutáns daganatok esetén, ugyanis a trametinib feedback aktivációt eredményez, ezzel rezisztenciát okozva a kezelésre. A legfrissebb preklinikai eredmények szerint azonban a trametinib zoledronsavval kombinálva kikerüli ezt a rezisztenciamechanizmust, és megnövekedett antitumor aktivitást mutat KRAS-mutáns tumorokban in vitro és in vivo (23). Ezt a kombinációt alkalmazva egy KRAS mutáns colorectalis tumoros betegnél, jelentős részleges választ és betegségstabilitást (11 hónap) értek el (24). A zoledronsav (nem daganatos indikációban törzskönyvezett hatóanyag) a RAS izoprenilációját gátolja, ezzel csökkentve aktivitását.
A BI 1701963 hatóanyag a SOS1 fehérjéhez kötődve megakadályozza annak KRAS aktiváló hatását. Ígéretes preklinikai eredmények alapján jelenleg egy KRAS mutáns szolid daganatos betegeket bevonó fázis I klinikai vizsgálatban tesztelik a hatóanyagot monoterápiaként, illetve trametinib MEK inhibitorral való kombinációs kezelésként (NCT04111458).
Az mRNA-5671 egy mRNS alapú tumorellenes vakcina mely a G12C, G12D, G12V, G13D KRAS mutációkat célozza. Egy folyamatban lévő, fázis I vizsgálatban (NCT03948763) az mRNA-5671 önmagában és pembrolizumabbal kombinációban tesztelik KRAS mutáns NSCLC, CRC vagy hasnyálmirigy adenocarciomában. A vizsgálat első felében minden HLA típust fogadnak, a második rész pedig specifikus HLA típusokra korlátozódik (25).
Klinikai adatok is megerősítik, hogy KRAS driver mutációk rezisztenciát okoznak EGFR-gátló hatóanyagokra (26), ezért az EGFR-gátlók a KRAS mutáns státusszal negatív asszociációban szerepelnek.
KRAS aktiváló mutációkat hordozó mCRC pácienseknél METFORMIN használata esetén az OS 37,8 hónappal volt hosszabb, mint azoknál, akik más hatóanyagokat szedtek diabétesz kezelésére. A medián PFS szintén hosszabbnak bizonyult 8,1 hónappal metformin mellett. Vad típusú KRAS-t hordozó pácienseknél a metformin használata nem eredményezett javulást sem OS-ben, sem PFS-ben. A metformin hatását előbbi

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mutációk esetén preklinikai kísérletekkel is alátámasztották (27). Egy másik vizsgálat során KRAS mutáns sejtek proliferációját a metformin szintén hatásosan gátolta, szemben a vad típust hordozókkal (28).

EVEROLIMUS kezelés egy fázis II vizsgálat alapján hatástalannak bizonyult, mCRC pácienseknél a KRAS mutációt hordozók körében rövidebb OS-t és DCR-t eredményezett, szemben a vad típusú KRAS-t hordozókkal (29). Ezt az eredményt egy másik preklinikai vizsgálat, valamint analízis is alátámasztotta, everolimus KRAS mutáns sejteknél nem fejtett ki gátló hatást, illetve 12-ből 11 KRAS mutáns betegnél progresszióhoz vezetett, míg vad típus mellett 31-ből 16 páciens nem részesült előnyben a kezelés hatására (30).

Egy esettanulmány szerint egy alacsony szintű MET amplifikációt hordozó tüdő adenocarcinomás páciensnél crizotinib kezelés tartós választ eredményezett. Progressziókor a MET amplifikáció elvesztését és KRAS mutációt detektáltak egy új lézióban, amelyek a szerzett rezisztenciáért lehetnek felelősek (31). MET exon 14-es alterációkat hordozó tüdődaganatos páciensnél MET-gátlók alkalmazása mutáns KRAS gén mellett rövid DC-vel (disease control) vagy progresszióval társult (32). Egy preklinikai vizsgálat során KRAS mutációk rezisztenciát okoztak MET-gátlásra, azonban MET+MEK inhibitorok együttes alkalmazása KRAS mutáció esetén is hatásosnak bizonyult (33).

Egy fázis III vizsgálat során medulláris pajzsmirigy daganatos páciensnél cabozantinib kezelés magasabb ORR-t eredményezett RAS-mutáns betegeknél, mint RET/RAS mutációt nem hordozóknál (31% vs 21%) (34).

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KRAS mutáns colorectalis daganat

A KRAS mutáció rezisztenciát okozhat a monoterápiában alkalmazott EGFR gátló hatóanyagokkal, így a colorectalis daganat (CRC, colorectal cancer) indikációban törzskönyvezett CETUXIMABBAL és PANITUMUMABBAL szemben is (1, 2).

A MEK (KRAS indirekt target) inhibitorok (AS703026 és selumetinib (AZD6244)) preklinikai evidenciák szerint gátolják cetuximab rezisztens CRC modellsejtek és tumor xenograftok növekedését (3). Fázis II vizsgálatokban a CI-1040 (MEK inhibitor) jól tolerálható volt, de nem mutatott antitumor hatást (4). A selumetinib (MEK1/2 inhibitor) a capecitabinhez hasonló hatékonyságot mutatott CRC betegekben (5).

Fázis II klinikai vizsgálatban 15 KRAS mutáns CRC beteget kezeltek palbociclibbel. Tumorválasz egyik betegnél sem volt megfigyelhető, de 5 betegnél stabil betegséget írtak le (6).

Egy fázis I/II vizsgálatban, metasztatikus, KRAS mutációt hordozó CRC betegekben második vagy későbbi vonalban alkalmazott SORAFENIB (multi-kináz inhibitor) és irinotecan kombinációs terápia 3,7 hónapos medián progressziómentes túlélést (progression-free survival, PFS) és 8,0 hónapos medián teljes túlélést (overall survival, OS) eredményezett (7).

A regorafenib hatékonyságát vizsgáló fázis III klinikai vizsgálatban vastagbél daganatos betegek egy csoportja monoterápiaként kapta a hatóanyagot, másik csoportjuk placebot kapott. A regorafenibet kapó csoportban a medián OS 6,4 hónap, a PFS 1,9 hónap volt, míg a placebo csoportban rendre 5,0 és 1,7 hónap. A PFS és OS is hosszabb volt a regorafenib csoportban a KRAS mutáns és a KRAS vad típusú alcsoportban is (8).

Egy fázis Ib/II vizsgálat (NCT03829410) előzetes eredményei alapján az onvansertib (PLK1 inhibitor) kombinációban BEVACIZUMAB és FOLFIRI terápiával ígéretes hatékonyságot mutatott KRAS mutáns metasztatikus CRC második vonalbeli kezelése esetén. Az ORR 36% (5/14), a DCR 86% (12/14) volt, a betegek 76%-ánál eredményezett tartós (6 hónapnál hosszabb) választ, a medián PFS nem került elérésre (9). Az FDA gyorsított eljárási rend besorolásban részesítette az onvansertib hatóanyagot KRAS mutáns CRC második vonalbeli kezelésére.

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PIK3CA-N345K

A variáns szerepel a COSMIC adatbázisban (n>290). A tudományos irodalom onkogenikus driver variánsként írja le (1, 2). A mutáció a p110 katalitikus alegység (PIK3CA) C2 doménjét érinti, feltételezhetően a membrán-kötő régiót befolyásolva járul hozzá a katalitikus alegység aktivitásának fokozásához (1, 3).

Egy szolid tumoros betegeket bevonó klinikai vizsgálatban egy emlődaganatos, PIK3CA-N345K mutáns betegnél részleges tumorválaszt írtak le temsirolimus (mTOR gátló) és trebananib (ANG1/2-Tie2 gátló) kombinációs kezelés hatására (4).

Egy PIK3CA-N345K mutációt hordozó emlődaganatos betegnél everolimus terápiával tumorregressziót értek el (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.

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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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PIK3CA mutáns colorectalis daganat

Azon colorectalis daganatos (colorectal cancer, CRC) betegeknél, akiknél PIK3CA mutációt detektáltak, az aszpirin használata megnövelte a daganat-specifikus túlélést (hazárd ráta (HR): 0,18) és a teljes túlélést (overall survival, OS) (HR: 0,54). A rendszeresen használt aszpirinhez hosszabb OS társult a PIK3CA mutáns, colorectalis daganatoknál, míg a vad típusú PIK3CA daganatoknál ez nem volt megfigyelhető. Ezek a megállapítások azt sugallják, hogy CRC-ben kimutatott PIK3CA mutáció prediktív biomarkere lehet az adjuváns aszpirin terápiának (1). Preklinikai eredmények is megerősítik, hogy az aszpirin PIK3CA-mutáns sejtekben jobb hatásfokkal csökkenti a sejtviabilitást, mint PIK3CA vad-típusú sejtekben (2).

Klinikai adatok szerint CRC betegek között az EGFR gátló cetuximab és panitumumab hatékonysága alacsonyabb PIK3CA driver mutáció jelenléte esetén (3-5). Preklinikai adatok szerint a cetuximab AKT vagy mTOR gátló gyógyszerrel kombinálva PIK3CA mutáció jelenléte esetén is hatékony (6).

35 CRC beteg vett részt a fázis I vizsgálatban, amelyben az alpelisib PIK3CA gátló hatóanyagot tesztelték PIK3CA mutáns vagy amplifikált szolid tumoros betegek körében. 2 CRC betegnél eredményezett a kezelés tumorválaszt, és 10 betegnél stabilizálódott a betegség (7).

PIK3CA mutációk hozzájárulhatnak az elsővonalas kemoterápiára mutatott rezisztenciához CRC esetén (8).

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KRAS és PIK3CA mutáció együttes jelenléte

A KRAS és a PIK3CA mutációk rezisztenciát okozhatnak egymás targetének gátlására. Preklinikai eredmények szerint, míg a PIK3CA mutáns sejtek érzékenyek voltak az mTOR gátló everolimusra, a KRAS és PIK3CA dupla mutáns sejtek nem reagáltak ugyanerre a kezelésre. Klinikai adatok is megerősítették, hogy azoknál a metasztatikus daganatos betegeknél, akiknél KRAS mutációt is detektáltak, nem tapasztaltak terápiás választ everolimus kezelésre (1).

Fordított esetben a PIK3CA mutáció jelenléte rezisztenciát okozott MEK gátlásra KRAS mutáns sejtekben. A dupla mutáns sejtek növekedésének gátlásához mindkét útvonal gátlására szükség volt (2). Mindezeken túl egy másik tanulmányban szinergisztikus hatást is megfigyeltek PI3K /mTOR és MEK inhibitor kombinálásával dupla mutáns NSCLC sejtvonalakon (3).

Referenciák:

(1) Di Nicolantonio F et al., Deregulation of the PI3K and KRAS signaling pathways in human cancer cells determines their response to everolimus. J Clin Invest. 2010 Aug;120(8):2858-66. Epub 2010 Jul 26. PMID: 20664172

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PTEN-N323fs*2

Ez az alteráció szerepel a COSMIC adatbázisban (n<100). A ClinVar adatbázisban patogén variánsként szerepel. Egy publikációban, mint patogén alteráció említik (1).

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

Referencia:

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PTEN mutáns gén - célpontok

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

A PTEN funkcióvesztéssel kapcsolatban említhető indirekt targetek a PI3K (1), az AKT (2) és az mTOR (2, 4-6), bár az mTOR gátlással kapcsolatos szakirodalmi adatok ellentmondásosak. Leírták továbbá, hogy PTEN-deficiens sejtek érzékenyek PARP (7) és ATM (8) inhibitorokra (a PTEN deficiencia és a paralel ATM/PARP gátlás szintetikus letális hatást okoz). A PTEN funkcióvesztéses alterációval pozitív asszociációban említhető, más indikációban törzskönyvezett hatóanyag az mTOR gátló EVEROLIMUS, TEMSIROLIMUS, METFORMIN és SIROLIMUS, a PARP gátló OLAPARIB, RUCAPARIB, NIRAPARIB és TALAZOPARIB, a PI3K delta inhibitor IDELALISIB, DUVELISIB (FDA).

A PTEN funkcióvesztése rezisztenciát okozhat EGFR gátló terápiákkal szemben (9, 10). Preklinikai eredmények szerint PTEN vesztés esetén a MEK + mTOR kombinált gátlás szinergisztikus hatású (11). A PTEN funkcióvesztése továbbá rezisztenciát okozhat PIK3CA gátlásra, és a PIK3CA gátló alpelisibre (12, 13), valamint a HER2 gátlásra is (14-16).

Több tanulmány eredményei alapján a PTEN génvesztés vagy mutáció csökkent T sejt infiltrációval, megváltozott tumor mikrokörnyezettel és anti-PD-1 terápiára való rezisztenciával asszociált (17, 18). Egér modellekben a szelektív PI3Kbeta inhibitor (GSK2636771) alkalmazása növelte az anti-PD-1 és anti-CTLA-4 ellenanyagok hatékonyságát (18).

Referenciák:

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GNAS-R844C

A mutáció magas frekvenciával szerepel a COSMIC adatbázisban (n>800), a ClinVar adatbázisban vélhetően patogén variánsként szerepel, a LOVD adatbázis szerint patogén elváltozás. Az R844C splicing variáns az XLas-1 izoforma esetén a GNAS-R201C alterációnak felel meg, amely a szakirodalomban leírt driver mutáció (1, 2). A GNAS fehérje GTP-kötő régiójában található alteráció a GNAS GTPáz aktivitásának csökkenését eredményezi és a downstream jelátviteli útvonal konstitutív aktivációjához vezet (1).

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GNAS mutáns gén - célpontok

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

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APC-Q1328*

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Ez a variáns szerepel a COSMIC adatbázisban (n>50). A ClinVar adatbázis szerint patogén mutáció. A mutáns génről egy csonka fehérjeváltozat képződik, ezért feltételezhető, hogy funkcióvesztéssel jár. A korai STOP kodon megjelenését eredményező mutáció (nonsense mutation) az APC gén nonsense-mediated decay (NMD) rezisztens pozícióját érinti, ezért nagy valószínűséggel az NMD folyamat nem vezet a mutáns mRNS lebomlásához (1). Így a mutáns génről egy kismértékben csonka fehérjeváltozat képződik, ezért lehetséges, hogy funkcióvesztéssel jár.

Referencia:

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APC-N741S

Az alteráció alacsony esetszámmal fordul elő a COSMIC (n<5) adatbázisban. A ClinVar adatbázis alapján ellentmondásos a funkcionális interpretációja, főként bizonytalan jelentőségű besorolással szerepel. A tudományos irodalomban nem érhető el egyéb adat funkcionális jelentőségéről.

APC mutáció az 1300-as aminosav közeli régióiban

Az 1300-as aminosav közeli régióiban (1194–1392) lokalizálódó mutációk instabilitást okoznak, viszonylag magas frekvenciával alakulnak ki spontán, és általában allélvesztéssel együtt járnak (1).

Referencia:

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APC mutáns gén - célpontok

Az APC fehérje a Wnt jelátviteli pálya része, azonban jelenleg nem állnak rendelkezésre olyan törzskönyvezett készítmények, amelyek a Wnt jelátviteli targeteket megbízhatóan gátolják (pl. beta-catenin inhibitorok) (1). APC mutáció esetén a COX2 gátlók említhetőek pozitív asszociációban a beteg molekuláris profiljával (2). Forgalomban lévő, COX2 gátló hatású nem-szteroid gyulladáscsökkentők a CELECOXIB, NEPAFENAC, MELOXICAM, NABUMETONE, MEFENAMINSAV és a NAPROXEN, illetve csak az FDA által jóváhagyott hatóanyag az ETODOLAC. Ezeket a készítményeket nem törzskönyvezték daganatos indikációban, azonban használatuk széleskörű a klinikumban gyulladáscsökkentés, fájdalomcsillapítás területén.
További törzskönyvezett, nem-szteroid gyulladáscsökkentő szerek, melyeknek COX1 és COX2 gátló hatásuk is van: acetilszalicilsav, ibuprofen, ketorolac, illetve a diclofenac.

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APC mutáns colorectalis daganat

Az APC funkcióvesztése fontos szerepet tölt be colorectalis daganatok (colorectal cancer, CRC) tumorigenezisében (1-4). CRC esetében az APC gén mutációi a leggyakoribbak, az esetek 80%-ában kimutathatóak (5). Egy újabb tanulmány szerint a vizsgált CRC estek 96%-ban voltak detektálhatóak a WNT jelpályát érintő mutációk (6), az APC gént érintő mutációk az újabb tanulmányok szerint is a leggyakoribb alterációk colorectalis daganatokban (6,7).
Egyes tanulmányok szerint vastagbéldaganatos betegekben a COX2 gátló hatással rendelkező acetilszalicilsav (Aspirin) szedése mellett alacsonyabb arányban újult ki a betegség, és kisebb volt a mortalitás (8), azonban az acetilszalicilsav daganatokban betöltött jelentőségéről ellentmondásosak az adatok (9, 10).

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PRKN-E309*

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

PRKN (PARK2) mutáns gén

A PRKN tumorszupresszor gén, melynek funkcióvesztése a PTEN inaktivációját eredményezi, így növeli a PI3K/AKT/mTOR jelátviteli út aktivitását és hozzájárul a tumorképződéshez (1, 2). A PRKN funkcióvesztése esetén hatékonyabbak a PI3K/AKT/mTOR jelátviteli útvonal gátlószerei, viszont a MEK gátló hatóanyagok hatékonysága csökken (3).

A PRKN gén germline funkcióvesztő mutációit több esetben detektálták Wilms tumorban, CNS daganatokban, neuroblastomában és osteosarcomában, de nem ismert, hogy a mutáció növeli-e ezeknek a daganatoknak a kockázatát (4). A germline PRKN mutációk bizonyos daganattípusok kialakulásának kockázatát növelik, más tumortípusokét viszont csökkentik (5).

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INPP4B-V594A

Az alteráció alacsony esetszámmal fordul elő a COSMIC (n<5) adatbázisban. A tudományos irodalomban nem érhető el adat funkcionális jelentőségéről.

PIK3CG-N522S

Ez a variáns szerepel a COSMIC adatbázisban (n>25). A PIK3CG p.N522S egy missense mutáció, de kívül esik a funkcionális alegységeket kódoló részen. A mutáció funkcionális hozadéka ismeretlen. Egy *in vitro* kísérlet szerint az ezzel a mutációval is rendelkező SW-1736-os sejtvonal (melynek egyéb ismert mutációi is vannak: BRAF V600E; MET E168D; PIK3R2 S313P és TP53 P72R) növekedése hatékonyabban gátolható CUDC-101-el, mint paclitaxellel, carboplatinnal, docetaxellel, sorafenibbel vagy doxorubicinnel (1).

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GATA6-G540fs*5

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A leolvasási kereteltolódást okozó mutáció (frameshift mutation) a/az GATA6 gén nonsense-mediated decay (NMD) rezisztens pozícióját érinti, ezért nagy valószínűséggel az NMD folyamat nem vezet a mutáns mRNS lebomlásához (1). Így a mutáns génről egy megváltozott C terminális szekvenciával rendelkező, kismértékben csonka fehérjeváltozat képződik, ezért lehetséges, hogy funkcióvesztéssel jár.

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Frameshift mutációk

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

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

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

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

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

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GATA6 mutáns gén

A GATA6 a GATA transzkripciós faktor család tagja, és tudődaganatokban onkogén vagy tumorszupresszor funkcióval is rendelkezhet (1, 2). GATA6 egyik legfőbb feladata, hogy szabályozza az ephitelial-mesenchymal átmenetet. Diszregulációja esetén a sejtek elveszíthetik sejt-sejt

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adhéziós képességüket, migrációs és invazív tulajdonságokat nyerve multipotens stromasejtté alakulhatnak (3). Tumorokban gyakran mutálódik, a sejtek differenciálódásának megváltozását eredményezve. Jelenleg nem ismert összefüggés a gén mutációi és célzott gyógyszerek hatékonysága között.

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TAS-102 colorectalis daganatban

A TAS-102 kódnevű hatóanyag (Lonsurf, trifluridine / tipiracil) törzskönyvezett más elérhető kezeléseken progrediált áttétes colorectalis daganatos (colorectal cancer, CRC) betegek részére. Randomizált vizsgálatban a TAS-102 kezelés 7,1 hónapos medián teljes túlélést (overall survival, OS) eredményezett, míg a placebo karban a medián OS 5,3 hónap volt. A túlélési előny a KRAS vad típusú és a KRAS mutáns alcsoportban is megfigyelhető volt (1).

Egy fázis II-es vizsgálatban a medián OS 9,0 hónap volt a TAS-102 kezelést kapó betegek körében, míg a placebo csoportban ez az érték 6,6 hónapnak adódott (2).

Egy fázis I/II vizsgálat során TAS-102 és BEVACIZUMAB kombinációjával történő kezelés hosszabb progressziómentes túlélést (progression-free survival, PFS) és magasabb 16 hetes PFS arányt eredményezett a TAS-102 monoterápiához képest (medián PFS: 3,7 hónap vs. 2,2 hónap, PFS arány 16 hét után: 46,6% vs. 33,9%) metasztatikus CRC páciensek esetében (3). Egy retrospektív vizsgálat szerint kombinált TAS-102 + BEVACIZUMAB terápia hosszabb medián OS-t eredményezett, mint a TAS-102 monoterápia (14,4 hónap vs. 4,5 hónap), metasztatikus CRC páciensek esetében (4).

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Molekuláris profiltól függetlenül törzskönyvezett célzott hatóanyagok colorectalis daganat indikációban

A beteg szövettanában törzskönyvezett, molekuláris profiltól független célzott hatóanyagok az érképződés-gátló BEVACIZUMAB, RAMUCIRUMAB és az AFLIBERCEPT, illetve a multi-tirozinkináz gátló REGORAFENIB. Továbbá az FDA gyorsított eljárásba sorolta a multi-VEGFR gátló FRUQUINTINIB hatóanyagot.

Egy randomizált fázis III vizsgálatban 1072 vastagbéltumoros betegben vizsgálták a ramucirumab hatékonyságát másodvonalas, FOLFIRI-vel kombinált terápiaként. A medián teljes túlélés (overall survival, OS) 13,3 hónap volt a ramucirumabot kapott betegekben a 11,7 hónaphoz képest, amit a placebo karban mértek (1).

Szintén fázis III vizsgálatban elemezték az aflibercept hatékonyságát FOLFIRI-vel kombinálva, másodvonalas terápiaként. A placebo karhoz képest az afliberceptet kapott betegek körében javult a teljes túlélési idő mediánja (12,06-ról 13,5 hónapra) és a progressziómentes túlélés (progression-free survival, PFS) mediánja (4,67-ről 6,9 hónapra) (2).

A regorafenib hatékonyságát vizsgáló fázis III klinikai vizsgálatban vastagbél daganatos betegek egy csoportja monoterápiaként kapta a hatóanyagot, másik csoportjuk placebot kapott. A regorafenibet kapó csoportban a medián OS 6,4 hónap, a PFS 1,9 hónap volt, míg a placebo csoportban rendre 5,0 és 1,7 hónap (3).

Fázis III klinikai vizsgálatban a fruquintinib (VEGFR1/2/3 inhibitor) növelte a PFS-t és OS-t a placebohoz képest (3,7 vs 1,8 hónap; valamint 9,3 vs 6,6 hónap) metasztatikus CRC betegek körében (4).

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Immunterápia mikroszatellita stabil (MSS) colorectalis daganatban

Korábbi tanulmányok azt mutatják, hogy az immuncheckpoint gátlószerek nem hatásosak MSS colorectalis daganatos (CRC) páciensek körében, bár ezen betegek körülbelül 10%-ánál jegyeztek fel válaszadást PD-1/PD-L1 gátló hatóanyagokra (1-3).

Egy fázis Ib klinikai vizsgálat szerint REGORAFENIB és NIVOLUMAB kombinációja tolerálható és tumorellenes aktivitást mutat korábban legalább két vonal kezelésben részesült kolorektális daganatos betegek körében. Az objektív válaszadási arány 33,3% volt a mikroszatellita stabil (MSS) betegek között (8/24 fő), a medián progressziómentes túlélés pedig 7,9 hónapnak bizonyult a 24 MSS és egy mikroszatellita instabil beteget vizsgáló csoportban (4).

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Sztatinok colorectalis daganatban

A sztatinok koleszterincsökkentő szerek, amik a 3-hidroxi-3-metil-glutaril-koenzim-A-reduktáz (HMGCR) gátlása, mely a mevalonát-útvonal egy sebességmeghatározó lépését katalizálja. A lipidcsökkentés mellett, a sztatinok tumorképződésre és progresszióra gyakorolt gátlóhatásáról számos tanulmány beszámolt. Azonban az antitumor aktivitás hátterében áll molekuláris mechanizmus egyelőre nem tisztázott. Több retrospektív analízis alapján, a sztatinok használata csökkent mortalitással asszociált colorectalis daganatos betegekben (1, 2). Egy meta-analízis eredményei alapján a sztatinok használata 20%-os colorectalis daganat kockázattal volt asszociált nem-IBD-s páciensek esetén (3).

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DRIVER ÉS TARGET GÉNEK LEÍRÁSA

DRIVER GÉNEK

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APC	Tumor suppressor. Promotes rapid degradation of CTNNB1 and participates in Wnt signaling as a negative regulator. APC activity is correlated with its phosphorylation state. Activates the GEF activity of SPATA13 and ARHGEF4. Plays a role in hepatocyte growth factor (HGF)-induced cell migration. Required for MMP9 up-regulation via the JNK signaling pathway in colorectal tumor cells. Acts as a mediator of ERBB2-dependent stabilization of microtubules at the cell cortex. It is required for the localization of MACF1 to the cell membrane and this localization of MACF1 is critical for its function in microtubule stabilization.
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.
CHEK2	Serine/threonine-protein kinase which is required for checkpoint-mediated cell cycle arrest, activation of DNA repair and apoptosis in response to the presence of DNA double-strand breaks. May also negatively regulate cell cycle progression during unperturbed cell cycles. Following activation, phosphorylates numerous effectors preferentially at the consensus sequence [L-X-R-X-X-S/T]. Regulates cell cycle checkpoint arrest through

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	phosphorylation of CDC25A, CDC25B and CDC25C, inhibiting their activity. Inhibition of CDC25 phosphatase activity leads to increased inhibitory tyrosine phosphorylation of CDK-cyclin complexes and blocks cell cycle progression. May also phosphorylate NEK6 which is involved in G2/M cell cycle arrest. Regulates DNA repair through phosphorylation of BRCA2, enhancing the association of RAD51 with chromatin which promotes DNA repair by homologous recombination. Also stimulates the transcription of genes involved in DNA repair (including BRCA2) through the phosphorylation and activation of the transcription factor FOXM1. Regulates apoptosis through the phosphorylation of p53/TP53, MDM4 and PML. Phosphorylation of p53/TP53 at Ser-20 by CHEK2 may alleviate inhibition by MDM2, leading to accumulation of active p53/TP53. Phosphorylation of MDM4 may also reduce degradation of p53/TP53. Also controls the transcription of pro-apoptotic genes through phosphorylation of the transcription factor E2F1. Tumor suppressor, it may also have a DNA damage-independent function in mitotic spindle assembly by phosphorylating BRCA1. Its absence may be a cause of the chromosomal instability observed in some cancer cells.
CSMD3	Involved in dendrite development.
EPHA3	Receptor tyrosine kinase which binds promiscuously membrane-bound ephrin family ligands residing on adjacent cells, leading to contact-dependent bidirectional signaling into neighboring cells. The signaling pathway downstream of the receptor is referred to as forward signaling while the signaling pathway downstream of the ephrin ligand is referred to as reverse signaling. Highly promiscuous for ephrin-A ligands it binds preferentially EFNA5. Upon activation by EFNA5 regulates cell-cell adhesion, cytoskeletal organization and cell migration. Plays a role in cardiac cells migration and differentiation and regulates the formation of the atrioventricular canal and septum during development probably through activation by EFNA1. Involved in the retinotectal mapping of neurons. May also control the segregation but not the guidance of motor and sensory axons during neuromuscular circuit development.
GNAS	May inhibit the adenylyl cyclase-stimulating activity of guanine nucleotide-binding protein G(s) subunit alpha which is produced from the same locus in a different open reading frame. Guanine nucleotide-binding proteins (G proteins) are involved as modulators or transducers in various transmembrane signaling systems. The G(s) protein is involved in hormonal regulation of adenylate cyclase: it activates the cyclase in response to beta-adrenergic stimuli. XLas isoforms interact with the same set of receptors as Gnas isoforms (By similarity). Guanine nucleotide-binding proteins (G proteins) are involved as modulators or transducers in various transmembrane signaling systems. The G(s) protein is involved in hormonal regulation of adenylate cyclase: it activates the cyclase in response to beta-adrenergic stimuli. Stimulates the Ras signaling pathway via RAPGEF2.
INPP4B	Catalyzes the hydrolysis of the 4-position phosphate of phosphatidylinositol 3,4-bisphosphate, inositol 1,3,4-trisphosphate and inositol 1,4-bisphosphate
KRAS	Ras proteins bind GDP/GTP and possess intrinsic GTPase activity. Plays an important role in the regulation of cell proliferation (PubMed:23698361, PubMed:22711838). Plays a role in promoting oncogenic events by inducing transcriptional silencing of tumor suppressor genes (TSGs) in colorectal cancer (CRC) cells in a ZNF304-dependent manner (PubMed:24623306). Enzyme regulation : Alternates between an inactive form bound to GDP and an active form bound to GTP. Activated by a guanine nucleotide-exchange factor (GEF) and inactivated by a GTPase-activating protein (GAP). Interaction with SOS1 promotes exchange of bound GDP by GTP.
MIER3	Transcriptional repressor.
MYO18A	May link Golgi membranes to the cytoskeleton and participate in the tensile force required for vesicle budding from the Golgi. Thereby, may play a role in Golgi membrane trafficking and could indirectly give its flattened shape to the Golgi apparatus. Alternatively, in concert with LURAP1 and CDC42BPA/CDC42BPB, has been involved in modulating lamellar actomyosin retrograde flow that is crucial to cell protrusion and migration. May be involved in the maintenance of the stromal cell architectures required for cell to cell contact.
OTOP1	Required for normal formation of otoconia in the inner ear. Inhibits P2Y purinoceptors. Modulates calcium homeostasis and influx of calcium in response to extracellular ATP (By similarity).
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.
PIK3CG	Phosphoinositide-3-kinase (PI3K) that phosphorylates PtdIns(4,5)P2 (Phosphatidylinositol 4,5-bisphosphate) to generate phosphatidylinositol 3,4,5-trisphosphate (PIP3). PIP3 plays a key role by recruiting PH domain-containing proteins to the membrane, including AKT1 and PDPK1, activating signaling cascades involved in cell growth, survival, proliferation, motility and morphology. Links G-protein coupled receptor activation to PIP3 production. Involved in immune, inflammatory and allergic responses. Modulates leukocyte chemotaxis to inflammatory sites and in response to chemoattractant agents. May control leukocyte polarization and migration by regulating the spatial accumulation of PIP3 and by regulating the organization of F-actin formation and integrin-based adhesion at the leading edge. Controls motility of dendritic cells. Together with PIK3CD is involved in natural killer (NK) cell development and migration towards the sites of inflammation. Participates in T-lymphocyte migration. Regulates T-lymphocyte proliferation and cytokine production. Together with PIK3CD participates in T-lymphocyte development. Required for B-lymphocyte development and signaling. Together with PIK3CD participates in neutrophil respiratory burst. Together with PIK3CD is involved in neutrophil chemotaxis and extravasation. Together with PIK3CB promotes platelet aggregation and thrombosis. Regulates alpha-IIb/beta-3 integrins (ITGA2B/

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	ITGB3) adhesive function in platelets downstream of P2Y12 through a lipid kinase activity-independent mechanism. May have also a lipid kinase activity-dependent function in platelet aggregation. Involved in endothelial progenitor cell migration. Negative regulator of cardiac contractility. Modulates cardiac contractility by anchoring protein kinase A (PKA) and PDE3B activation, reducing cAMP levels. Regulates cardiac contractility also by promoting beta-adrenergic receptor internalization by binding to ADRBK1 and by non-muscle tropomyosin phosphorylation. Also has serine/threonine protein kinase activity: both lipid and protein kinase activities are required for beta-adrenergic receptor endocytosis. May also have a scaffolding role in modulating cardiac contractility. Contributes to cardiac hypertrophy under pathological stress. Through simultaneous binding of PDE3B to RAPGEF3 and PIK3R6 is assembled in a signaling complex in which the PI3K gamma complex is activated by RAPGEF3 and which is involved in angiogenesis.
PTEN	Tumor suppressor. Acts as a dual-specificity protein phosphatase, dephosphorylating tyrosine-, serine- and threonine-phosphorylated proteins. Also acts as a lipid phosphatase, removing the phosphate in the D3 position of the inositol ring from phosphatidylinositol 3,4,5-trisphosphate, phosphatidylinositol 3,4-diphosphate, phosphatidylinositol 3-phosphate and inositol 1,3,4,5-tetrakisphosphate with order of substrate preference in vitro PtdIns(3,4,5)P3 > PtdIns(3,4)P2 > PtdIns3P > Ins(1,3,4,5)P4. The lipid phosphatase activity is critical for its tumor suppressor function. Antagonizes the PI3K-AKT/PKB signaling pathway by dephosphorylating phosphoinositides and thereby modulating cell cycle progression and cell survival. The unphosphorylated form cooperates with AIP1 to suppress AKT1 activation. Dephosphorylates tyrosine-phosphorylated focal adhesion kinase and inhibits cell migration and integrin-mediated cell spreading and focal adhesion formation. Plays a role as a key modulator of the AKT-mTOR signaling pathway controlling the tempo of the process of newborn neurons integration during adult neurogenesis, including correct neuron positioning, dendritic development and synapse formation. May be a negative regulator of insulin signaling and glucose metabolism in adipose tissue. The nuclear monoubiquitinated form possesses greater apoptotic potential, whereas the cytoplasmic nonubiquitinated form induces less tumor suppressive ability. In motile cells, suppresses the formation of lateral pseudopods and thereby promotes cell polarization and directed movement Isoform alpha: Functional kinase, like isoform 1 it antagonizes the PI3K-AKT /PKB signaling pathway. Plays a role in mitochondrial energetic metabolism by promoting COX activity and ATP production, via collaboration with isoform 1 in increasing protein levels of PINK1
RECQL5	Isoform beta is a DNA helicase that plays an important role in DNA replication, transcription and repair. Inhibits elongation of stalled transcripts at DNA damage sites by binding to the RNA polymerase II subunit POLR2A and blocking the TCEA1 binding site. Required for mitotic chromosome separation after cross-over events and cell cycle progress. Required for efficient DNA repair, including repair of inter-strand cross-links. Stimulates DNA decatenation mediated by TOP2A. Prevents sister chromatid exchange and homologous recombination.
SEC16A	Defines endoplasmic reticulum exit sites (ERES) and is required for secretory cargo traffic from the endoplasmic reticulum to the Golgi apparatus. SAR1A-GTP-dependent assembly of SEC16A on the ER membrane forms an organized scaffold defining an ERES. Required for normal transitional endoplasmic reticulum (tER) organization.
SYNE3	As a component of the LINC (LInker of Nucleoskeleton and Cytoskeleton) complex involved in the connection between the nuclear lamina and the cytoskeleton. The nucleocytoplasmic interactions established by the LINC complex play an important role in the transmission of mechanical forces across the nuclear envelope and in nuclear movement and positioning. Probable anchoring protein which tethers the nucleus to the cytoskeleton by binding PLEC which can associate with the intermediate filament system. Plays a role in the regulation of aortic epithelial cell morphology, and is required for flow-induced centrosome polarization and directional migration in aortic endothelial cells.
TET2	Dioxygenase that catalyzes the conversion of the modified genomic base 5-methylcytosine (5mC) into 5-hydroxymethylcytosine (5hmC) and plays a key role in active DNA demethylation. Has a preference for 5-hydroxymethylcytosine in CpG motifs. Also mediates subsequent conversion of 5hmC into 5-formylcytosine (5fC), and conversion of 5fC to 5-carboxylcytosine (5caC). Conversion of 5mC into 5hmC, 5fC and 5caC probably constitutes the first step in cytosine demethylation. Methylation at the C5 position of cytosine bases is an epigenetic modification of the mammalian genome which plays an important role in transcriptional regulation. In addition to its role in DNA demethylation, also involved in the recruitment of the O-GlcNAc transferase OGT to CpG-rich transcription start sites of active genes, thereby promoting histone H2B GlcNAcylation by OGT.
WNK2	Serine/threonine kinase which plays an important role in the regulation of electrolyte homeostasis, cell signaling, survival, and proliferation. Acts as an activator and inhibitor of sodium-coupled chloride cotransporters and potassium-coupled chloride cotransporters respectively. Activates SLC12A2, SCNN1A, SCNN1B, SCNN1D and SGK1 and inhibits SLC12A5. Negatively regulates the EGF-induced activation of the ERK/MAPK-pathway and the downstream cell cycle progression. Affects MAPK3/MAPK1 activity by modulating the activity of MAP2K1 and this modulation depends on phosphorylation of MAP2K1 by PAK1. WNK2 acts by interfering with the activity of PAK1 by controlling the balance of the activity of upstream regulators of PAK1 activity, RHOA and RAC1, which display reciprocal activity.

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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

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	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
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.
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	Serine/threonine protein kinase which activates checkpoint signaling upon double strand breaks (DSBs), apoptosis and genotoxic stresses such as ionizing ultraviolet A light (UVA), thereby acting as a DNA damage sensor. Recognizes the substrate consensus sequence [ST]-Q. Phosphorylates Ser-139 of histone variant H2AX/H2AFX at double strand breaks (DSBs), thereby regulating DNA damage response mechanism. Also plays a role in pre-B cell allelic exclusion, a process leading to expression of a single immunoglobulin heavy chain allele to enforce clonality and monospecific recognition by the B-cell antigen receptor (BCR) expressed on individual B-lymphocytes. After the introduction of DNA breaks by the RAG complex on one immunoglobulin allele, acts by mediating a repositioning of the second allele to pericentromeric heterochromatin, preventing accessibility to the RAG complex and recombination of the second allele. Also involved in signal transduction and cell cycle control. May function as a tumor suppressor. Necessary for activation of ABL1 and SAPK. Phosphorylates DYRK2, CHEK2, p53/TP53, FANCD2, NFKBIA, BRCA1, CTIP, nibrin (NBN), TERF1, RAD9 and DCLRE1C. May play a role in vesicle and/or protein transport. Could play a role in T-cell development, gonad and neurological function. Plays a role in replication-dependent histone mRNA degradation. Binds DNA ends. Phosphorylation of DYRK2 in nucleus in response to genotoxic stress prevents its MDM2-mediated ubiquitination and subsequent proteasome degradation. Phosphorylates ATF2 which stimulates its function in DNA damage response.
CDK1	Plays a key role in the control of the eukaryotic cell cycle by modulating the centrosome cycle as well as mitotic onset; promotes G2-M transition, and regulates G1 progress and G1-S transition via association with multiple interphase cyclins. Required in higher cells for entry into S-phase and mitosis. Phosphorylates PARVA/actopaxin, APC, AMPH, APC, BARD1, Bcl-xL/BCL2L1, BRCA2, CALD1, CASP8, CDC7, CDC20, CDC25A, CDC25C, CC2D1A, CSNK2 proteins/CKII, FZR1/CDH1, CDK7, CEBPB, CHAMP1, DMD/dystrophin, EEF1 proteins/EF-1, EZH2, KIF11/EG5, EGFR, FANCG, FOS, GFAP, GOLGA2/GM130, GRASP1, UBE2A/hHR6A, HIST1H1 proteins/histone H1, HMGA1, HIVEP3/KRC, LMNA, LMNB, LMNC, LBR, LATS1, MAP1B, MAP4, MARCKS, MCM2, MCM4, MKLP1, MYB, NEFH, NFIC, NPC/nuclear pore complex, PITPNM1/NIR2, NPM1, NCL, NUCKS1, NPM1/numatrin, ORC1, PRKAR2A, EEF1E1/p18, EIF3F/p47, p53/TP53, NONO/p54NRB, PAPOLA, PLEC/plectin, RB1, UL40/R2, RAB4A, RAP1GAP, RCC1, RPS6KB1 /S6K1, KHDRBS1/SAM68, ESPL1, SKI, BIRC5/survivin, STIP1, TEX14, beta-tubulins, MAPT/TAU, NEDD1, VIM/vimentin, TK1, FOXO1, RUNX1/AML1, SIRT2 and RUNX2. CDK1/CDC2-cyclin-B controls pronuclear union in interphase fertilized eggs. Essential for early stages of embryonic development. During G2 and early mitosis, CDC25A/B/C-mediated dephosphorylation activates CDK1/cyclin complexes which phosphorylate several substrates that trigger at least centrosome separation, Golgi dynamics, nuclear envelope breakdown and chromosome condensation. Once chromosomes are condensed and aligned at the metaphase plate, CDK1 activity is switched off by WEE1- and PKMYT1-mediated phosphorylation to allow sister chromatid separation, chromosome decondensation, reformation of the nuclear envelope and cytokinesis. Inactivated by PKR/EIF2AK2- and WEE1-mediated phosphorylation upon DNA damage to stop cell cycle and genome replication at the G2 checkpoint thus facilitating DNA repair. Reactivated after successful DNA repair through WIP1-dependent signaling leading to CDC25A/B/C-mediated dephosphorylation and restoring cell cycle progression. In proliferating cells, CDK1-mediated FOXO1 phosphorylation at the G2-M phase represses FOXO1 interaction with 14-3-3 proteins and thereby promotes FOXO1 nuclear accumulation and transcription factor activity, leading to cell death of postmitotic neurons. The phosphorylation of beta-tubulins regulates microtubule dynamics during mitosis. NEDD1 phosphorylation promotes PLK1-mediated NEDD1 phosphorylation and subsequent targeting of the gamma-tubulin ring complex (gTuRC) to the centrosome, an important step for spindle formation. In addition, CC2D1A phosphorylation regulates CC2D1A spindle pole localization and association with SCC1/RAD21 and centriole cohesion during mitosis. The phosphorylation of Bcl-xL/BCL2L1 after prolongated G2 arrest upon DNA damage triggers apoptosis. In contrast, CASP8 phosphorylation during mitosis prevents its activation by proteolysis and subsequent apoptosis. This phosphorylation occurs in cancer cell lines, as well as in primary breast tissues and lymphocytes. EZH2 phosphorylation promotes H3K27me3 maintenance and epigenetic gene silencing. CALD1 phosphorylation promotes Schwann cell migration during peripheral nerve regeneration.
CDK4	Ser/Thr-kinase component of cyclin D-CDK4 (DC) complexes that phosphorylate and inhibit members of the retinoblastoma (RB) protein family including RB1 and regulate the cell-cycle during G(1)/S transition. Phosphorylation of RB1 allows dissociation of the transcription factor E2F from the RB/E2F complexes and the subsequent transcription of E2F target genes which are responsible for the progression through the G(1) phase. Hypophosphorylates RB1 in early G(1) phase. Cyclin D-CDK4 complexes are major integrators of various mitogenenic and antimitogenic signals. Also phosphorylates SMAD3 in a cell-cycle-dependent manner and represses its transcriptional activity. Component of the ternary complex, cyclin D/CDK4/CDKN1B, required for nuclear translocation and activity of the cyclin D-CDK4 complex.
CNKSR1	connector enhancer of kinase suppressor of Ras 1
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).
DNMT1	Methylates CpG residues. Preferentially methylates hemimethylated DNA. Associates with DNA replication sites in S phase maintaining the methylation pattern in the newly synthesized strand, that is essential for epigenetic inheritance. Associates with chromatin during G2 and M phases to maintain DNA methylation independently of replication. It is responsible for maintaining methylation patterns established in development. DNA methylation is coordinated with methylation of histones. Mediates transcriptional repression by direct binding to HDAC2. In association with DNMT3B and via the recruitment of CTCFL/BORIS, involved in activation of BAG1 gene expression by modulating dimethylation of promoter histone H3 at H3K4 and H3K9.
MAP2K1	Dual specificity protein kinase which acts as an essential component of the MAP kinase signal transduction pathway. Binding of extracellular ligands such as growth factors, cytokines and hormones to their cell-surface

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	receptors activates RAS and this initiates RAF1 activation. RAF1 then further activates the dual-specificity protein kinases MAP2K1/MEK1 and MAP2K2/MEK2. Both MAP2K1/MEK1 and MAP2K2/MEK2 function specifically in the MAPK/ERK cascade, and catalyze the concomitant phosphorylation of a threonine and a tyrosine residue in a Thr-Glu-Tyr sequence located in the extracellular signal-regulated kinases MAPK3/ERK1 and MAPK1/ERK2, leading to their activation and further transduction of the signal within the MAPK/ERK cascade. Depending on the cellular context, this pathway mediates diverse biological functions such as cell growth, adhesion, survival and differentiation, predominantly through the regulation of transcription, metabolism and cytoskeletal rearrangements. One target of the MAPK/ERK cascade is peroxisome proliferator-activated receptor gamma (PPARG), a nuclear receptor that promotes differentiation and apoptosis. MAP2K1/MEK1 has been shown to export PPARG from the nucleus. The MAPK/ERK cascade is also involved in the regulation of endosomal dynamics, including lysosome processing and endosome cycling through the perinuclear recycling compartment (PNRC), as well as in the fragmentation of the Golgi apparatus during mitosis.
MAPK1	Serine/threonine kinase which acts as an essential component of the MAP kinase signal transduction pathway. MAPK1/ERK2 and MAPK3/ERK1 are the 2 MAPKs which play an important role in the MAPK/ERK cascade. They participate also in a signaling cascade initiated by activated KIT and KITLG/SCF. Depending on the cellular context, the MAPK/ERK cascade mediates diverse biological functions such as cell growth, adhesion, survival and differentiation through the regulation of transcription, translation, cytoskeletal rearrangements. The MAPK/ERK cascade plays also a role in initiation and regulation of meiosis, mitosis, and postmitotic functions in differentiated cells by phosphorylating a number of transcription factors. About 160 substrates have already been discovered for ERKs. Many of these substrates are localized in the nucleus, and seem to participate in the regulation of transcription upon stimulation. However, other substrates are found in the cytosol as well as in other cellular organelles, and those are responsible for processes such as translation, mitosis and apoptosis. Moreover, the MAPK/ERK cascade is also involved in the regulation of the endosomal dynamics, including lysosome processing and endosome cycling through the perinuclear recycling compartment (PNRC); as well as in the fragmentation of the Golgi apparatus during mitosis. The substrates include transcription factors (such as ATF2, BCL6, ELK1, ERF, FOS, HSF4 or SPZ1), cytoskeletal elements (such as CANX, CTTN, GJA1, MAP2, MAPT, PXN, SORBS3 or STMN1), regulators of apoptosis (such as BAD, BTG2, CASP9, DAPK1, IER3, MCL1 or PPARG), regulators of translation (such as EIF4EBP1) and a variety of other signaling-related molecules (like ARHGEF2, DCC, FRS2 or GRB10). Protein kinases (such as RAF1, RPS6KA1/RSK1, RPS6KA3/RSK2, RPS6KA2/RSK3, RPS6KA6/RSK4, SYK, MKNK1/MNK1, MKNK2/MNK2, RPS6KA5/MSK1, RPS6KA4/MSK2, MAPKAPK3 or MAPKAPK5) and phosphatases (such as DUSP1, DUSP4, DUSP6 or DUSP16) are other substrates which enable the propagation the MAPK/ERK signal to additional cytosolic and nuclear targets, thereby extending the specificity of the cascade. Mediates phosphorylation of TPR in respons to EGF stimulation. May play a role in the spindle assembly checkpoint. Phosphorylates PML and promotes its interaction with PIN1, leading to PML degradation Acts as a transcriptional repressor. Binds to a [GC]AAA[GC] consensus sequence. Repress the expression of interferon gamma-induced genes. Seems to bind to the promoter of CCL5, DMP1, IFIH1, IFITM1, IRF7, IRF9, LAMP3, OAS1, OAS2, OAS3 and STAT1. Transcriptional activity is independent of kinase activity
MAPK3	Serine/threonine kinase which acts as an essential component of the MAP kinase signal transduction pathway. MAPK1/ERK2 and MAPK3/ERK1 are the 2 MAPKs which play an important role in the MAPK/ERK cascade. They participate also in a signaling cascade initiated by activated KIT and KITLG/SCF. Depending on the cellular context, the MAPK/ERK cascade mediates diverse biological functions such as cell growth, adhesion, survival and differentiation through the regulation of transcription, translation, cytoskeletal rearrangements. The MAPK/ERK cascade plays also a role in initiation and regulation of meiosis, mitosis, and postmitotic functions in differentiated cells by phosphorylating a number of transcription factors. About 160 substrates have already been discovered for ERKs. Many of these substrates are localized in the nucleus, and seem to participate in the regulation of transcription upon stimulation. However, other substrates are found in the cytosol as well as in other cellular organelles, and those are responsible for processes such as translation, mitosis and apoptosis. Moreover, the MAPK/ERK cascade is also involved in the regulation of the endosomal dynamics, including lysosome processing and endosome cycling through the perinuclear recycling compartment (PNRC); as well as in the fragmentation of the Golgi apparatus during mitosis. The substrates include transcription factors (such as ATF2, BCL6, ELK1, ERF, FOS, HSF4 or SPZ1), cytoskeletal elements (such as CANX, CTTN, GJA1, MAP2, MAPT, PXN, SORBS3 or STMN1), regulators of apoptosis (such as BAD, BTG2, CASP9, DAPK1, IER3, MCL1 or PPARG), regulators of translation (such as EIF4EBP1) and a variety of other signaling-related molecules (like ARHGEF2, FRS2 or GRB10). Protein kinases (such as RAF1, RPS6KA1/RSK1, RPS6KA3/RSK2, RPS6KA2/RSK3, RPS6KA6/RSK4, SYK, MKNK1/MNK1, MKNK2/MNK2, RPS6KA5/MSK1, RPS6KA4/MSK2, MAPKAPK3 or MAPKAPK5) and phosphatases (such as DUSP1, DUSP4, DUSP6 or DUSP16) are other substrates which enable the propagation the MAPK/ERK signal to additional cytosolic and nuclear targets, thereby extending the specificity of the cascade.
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

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	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.
PIK3CA	Phosphoinositide-3-kinase (PI3K) that phosphorylates PtdIns (Phosphatidylinositol), PtdIns4P (Phosphatidylinositol 4-phosphate) and PtdIns(4,5)P2 (Phosphatidylinositol 4,5-bisphosphate) to generate phosphatidylinositol 3,4,5-trisphosphate (PIP3). PIP3 plays a key role by recruiting PH domain-containing proteins to the membrane, including AKT1 and PDPK1, activating signaling cascades involved in cell growth, survival, proliferation, motility and morphology. Participates in cellular signaling in response to various growth factors. Involved in the activation of AKT1 upon stimulation by receptor tyrosine kinases ligands such as EGF, insulin, IGF1, VEGFA and PDGF. Involved in signaling via insulin-receptor substrate (IRS) proteins. Essential in endothelial cell migration during vascular development through VEGFA signaling, possibly by regulating RhoA activity. Required for lymphatic vasculature development, possibly by binding to RAS and by activation by EGF and FGF2, but not by PDGF. Regulates invadopodia formation in breast cancer cells through the PDPK1-AKT1 pathway. Participates in cardiomyogenesis in embryonic stem cells through a AKT1 pathway. Participates in vasculogenesis in embryonic stem cells through PDK1 and protein kinase C pathway. Has also serine-protein kinase activity: phosphorylates PIK3R1 (p85alpha regulatory subunit), EIF4EBP1 and HRAS.
PIK3CB	Phosphoinositide-3-kinase (PI3K) that phosphorylates PtdIns (Phosphatidylinositol), PtdIns4P (Phosphatidylinositol 4-phosphate) and PtdIns(4,5)P2 (Phosphatidylinositol 4,5-bisphosphate) to generate phosphatidylinositol 3,4,5-trisphosphate (PIP3). PIP3 plays a key role by recruiting PH domain-containing proteins to the membrane, including AKT1 and PDPK1, activating signaling cascades involved in cell growth, survival, proliferation, motility and morphology. Involved in the activation of AKT1 upon stimulation by G-protein coupled receptors (GPCRs) ligands such as CXCL12, sphingosine 1-phosphate, and lysophosphatidic acid. May also act downstream receptor tyrosine kinases. Required in different signaling pathways for stable platelet adhesion and aggregation. Plays a role in platelet activation signaling triggered by GPCRs, alpha-IIb/beta-3 integrins (ITGA2B/ ITGB3) and ITAM (immunoreceptor tyrosine-based activation motif)-bearing receptors such as GP6. Regulates the strength of adhesion of ITGA2B/ ITGB3 activated receptors necessary for the cellular transmission of contractile forces. Required for platelet aggregation induced by F2 (thrombin) and thromboxane A2 (TXA2). Has a role in cell survival. May have a role in cell migration. Involved in the early stage of autophagosome formation. Modulates the intracellular level of PtdIns3P (Phosphatidylinositol 3-phosphate) and activates PIK3C3 kinase activity. May act as a scaffold, independently of its lipid kinase activity to positively regulate autophagy. May have a role in insulin signaling as scaffolding protein in which the lipid kinase activity is not required. May have a kinase-independent function in regulating cell proliferation and in clathrin-mediated endocytosis. Mediator of oncogenic signal in cell lines lacking PTEN. The lipid kinase activity is necessary for its role in oncogenic transformation. Required for the growth of ERBB2 and RAS driven tumors
PLK1	Serine/threonine-protein kinase that performs several important functions throughout M phase of the cell cycle, including the regulation of centrosome maturation and spindle assembly, the removal of cohesins from chromosome arms, the inactivation of anaphase-promoting complex/cyclosome (APC/C) inhibitors, and the regulation of mitotic exit and cytokinesis. Polo-like kinase proteins acts by binding and phosphorylating proteins are that already phosphorylated on a specific motif recognized by the POLO box domains. Phosphorylates BORA, BUB1B/BUBR1, CCNB1, CDC25C, CEP55, ECT2, ERCC6L, FBXO5/EMI1, FOXM1, KIF20A/MKLP2, CENPU, NEDD1, NINL, NPM1, NUDC, PKMYT1/MYT1, KIZ, PPP1R12A/MYPT1, PRC1, RACGAP1/CYK4, SGOL1, STAG2/SA2, TEX14, TOPORS, p73/TP73, TPT1 and WEE1. Plays a key role in centrosome functions and the assembly of bipolar spindles by phosphorylating KIZ, NEDD1 and NINL. NEDD1 phosphorylation promotes subsequent targeting of the gamma-tubulin ring complex (gTuRC) to the centrosome, an important step for spindle formation. Phosphorylation of NINL component of the centrosome leads to NINL dissociation from other centrosomal proteins. Involved in mitosis exit and cytokinesis by phosphorylating CEP55, ECT2, KIF20A/MKLP2, CENPU, PRC1 and RACGAP1. Recruited at the central spindle by phosphorylating and docking PRC1 and KIF20A/MKLP2; creates its own docking sites on PRC1 and KIF20A/MKLP2 by mediating phosphorylation of sites subsequently recognized by the POLO box domains. Phosphorylates RACGAP1, thereby creating a docking site for the Rho GTP exchange factor ECT2 that is essential for the cleavage furrow formation. Promotes the central spindle recruitment of ECT2. Plays a central role in G2/M transition of mitotic cell cycle by phosphorylating CCNB1, CDC25C, FOXM1, CENPU, PKMYT1/MYT1, PPP1R12A /MYPT1 and WEE1. Part of a regulatory circuit that promotes the activation of CDK1 by phosphorylating the positive regulator CDC25C and inhibiting the negative regulators WEE1 and PKMYT1/MYT1. Also acts by mediating phosphorylation of cyclin-B1 (CCNB1) on centrosomes in prophase. Phosphorylates FOXM1, a key mitotic transcription regulator, leading to enhance FOXM1 transcriptional activity. Involved in kinetochore functions and sister chromatid cohesion by phosphorylating BUB1B/BUBR1, FBXO5/EMI1 and STAG2/SA2. PLK1 is high on non-attached kinetochores suggesting a role of PLK1 in kinetochore attachment or in spindle assembly checkpoint (SAC) regulation. Required for kinetochore localization of BUB1B. Regulates the dissociation of cohesin from chromosomes by phosphorylating cohesin subunits such as STAG2/SA2. Phosphorylates SGOL1: required for spindle pole localization of isoform 3 of SGOL1 and plays a role in regulating its centriole cohesion function. Mediates phosphorylation of FBXO5/EMI1, a negative regulator of the APC/C complex during prophase, leading to FBXO5/EMI1 ubiquitination and degradation by the proteasome. Acts as a negative regulator of p53 family members: phosphorylates TOPORS, leading to inhibit the sumoylation of p53/TP53 and simultaneously enhance the ubiquitination and subsequent degradation of p53/TP53. Phosphorylates the transactivation domain of the transcription factor p73/TP73, leading to inhibit p73/TP73-mediated transcriptional activation and pro-apoptotic functions. Phosphorylates BORA, and thereby promotes the degradation of BORA. Contributes to the regulation of AURKA function. Also required for recovery after DNA damage checkpoint and entry into mitosis. Phosphorylates MISP, leading to stabilization of cortical and astral microtubule attachments required for proper spindle positioning (PubMed:8991084, PubMed:11202906, PubMed:12207013, PubMed:12447691, PubMed:12524548, PubMed:12738781, PubMed:12852856, PubMed:12939256, PubMed:14532005, PubMed:14734534, PubMed:15070733,

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	PubMed:15148369, PubMed:15469984, PubMed:16198290, PubMed:16247472, PubMed:16980960, PubMed:17081991, PubMed:17351640, PubMed:17376779, PubMed:17617734, PubMed:18174154, PubMed:18331714, PubMed:18418051, PubMed:18477460, PubMed:18521620, PubMed:1
PRKACA	Phosphorylates a large number of substrates in the cytoplasm and the nucleus. Regulates the abundance of compartmentalized pools of its regulatory subunits through phosphorylation of PJA2 which binds and ubiquitinates these subunits, leading to their subsequent proteolysis. Phosphorylates CDC25B, ABL1, NFKB1, CLDN3, PSMC5 /RPT6, PJA2, RYR2, RORA and VASP. RORA is activated by phosphorylation. Required for glucose-mediated adipogenic differentiation increase and osteogenic differentiation inhibition from osteoblasts. Involved in the regulation of platelets in response to thrombin and collagen; maintains circulating platelets in a resting state by phosphorylating proteins in numerous platelet inhibitory pathways when in complex with NF-kappa-B (NFKB1 and NFKB2) and I-kappa-B-alpha (NFKBIA), but thrombin and collagen disrupt these complexes and free active PRKACA stimulates platelets and leads to platelet aggregation by phosphorylating VASP. Prevents the antiproliferative and anti-invasive effects of alpha-difluoromethylornithine in breast cancer cells when activated. RYR2 channel activity is potentiated by phosphorylation in presence of luminal Ca2+, leading to reduced amplitude and increased frequency of store overload-induced Ca2+ release (SOICR) characterized by an increased rate of Ca2+ release and propagation velocity of spontaneous Ca2+ waves, despite reduced wave amplitude and resting cytosolic Ca2+. PSMC5/RPT6 activation by phosphorylation stimulates proteasome. Negatively regulates tight junctions (TJs) in ovarian cancer cells via CLDN3 phosphorylation. NFKB1 phosphorylation promotes NF-kappa-B p50-p50 DNA binding. Involved in embryonic development by down-regulating the Hedgehog (Hh) signaling pathway that determines embryo pattern formation and morphogenesis. Prevents meiosis resumption in prophase-arrested oocytes via CDC25B inactivation by phosphorylation. May also regulate rapid eye movement (REM) sleep in the pedunculopontine tegmental (PPT). Phosphorylates APOBEC3G and AICDA. Isoform 2 phosphorylates and activates ABL1 in sperm flagellum to promote spermatozoa capacitation. Phosphorylates HSF1; this phosphorylation promotes HSF1 nuclear localization and transcriptional activity upon heat shock (PubMed:21085490).
PTPN11	Acts downstream of various receptor and cytoplasmic protein tyrosine kinases to participate in the signal transduction from the cell surface to the nucleus. Dephosphorylates ROCK2 at Tyr-722 resulting in stimulatation of its RhoA binding activity.
RAF1	Serine/threonine-protein kinase that acts as a regulatory link between the membrane-associated Ras GTPases and the MAPK/ERK cascade, and this critical regulatory link functions as a switch determining cell fate decisions including proliferation, differentiation, apoptosis, survival and oncogenic transformation. RAF1 activation initiates a mitogen-activated protein kinase (MAPK) cascade that comprises a sequential phosphorylation of the dual-specific MAPK kinases (MAP2K1/MEK1 and MAP2K2/MEK2) and the extracellular signal-regulated kinases (MAPK3/ERK1 and MAPK1/ERK2). The phosphorylated form of RAF1 (on residues Ser-338 and Ser-339, by PAK1) phosphorylates BAD /Bcl2-antagonist of cell death at Ser-75. Phosphorylates adenylyl cyclases: ADCY2, ADCY5 and ADCY6, resulting in their activation. Phosphorylates PPP1R12A resulting in inhibition of the phosphatase activity. Phosphorylates TNNT2 /cardiac muscle troponin T. Can promote NF-kB activation and inhibit signal transducers involved in motility (ROCK2), apoptosis (MAP3K5/ASK1 and STK3/MST2), proliferation and angiogenesis (RB1). Can protect cells from apoptosis also by translocating to the mitochondria where it binds BCL2 and displaces BAD/Bcl2-antagonist of cell death. Regulates Rho signaling and migration, and is required for normal wound healing. Plays a role in the oncogenic transformation of epithelial cells via repression of the TJ protein, occludin (OCLN) by inducing the up-regulation of a transcriptional repressor SNAI2/SLUG, which induces down-regulation of OCLN. Restricts caspase activation in response to selected stimuli, notably Fas stimulation, pathogen-mediated macrophage apoptosis, and erythroid differentiation.
SOD1	Destroys radicals which are normally produced within the cells and which are toxic to biological systems.
SOS1	Promotes the exchange of Ras-bound GDP by GTP (PubMed:8493579). Probably by promoting Ras activation, regulates phosphorylation of MAP kinase MAPK3 in response to EGF (PubMed:17339331). Catalytic component of a trimeric complex that participates in transduction of signals from Ras to Rac by promoting the Rac-specific guanine nucleotide exchange factor (GEF) activity (By similarity).
XPO1	Mediates the nuclear export of cellular proteins (cargos) bearing a leucine-rich nuclear export signal (NES) and of RNAs. In the nucleus, in association with RANBP3, binds cooperatively to the NES on its target protein and to the GTPase RAN in its active GTP-bound form (Ran-GTP). Docking of this complex to the nuclear pore complex (NPC) is mediated through binding to nucleoporins. Upon transit of a nuclear export complex into the cytoplasm, disassembling of the complex and hydrolysis of Ran-GTP to Ran-GDP (induced by RANBP1 and RANGAP1, respectively) cause release of the cargo from the export receptor. The directionality of nuclear export is thought to be conferred by an asymmetric distribution of the GTP- and GDP-bound forms of Ran between the cytoplasm and nucleus. Involved in U3 snoRNA transport from Cajal bodies to nucleoli. Binds to late precursor U3 snoRNA bearing a TMG cap. Several viruses, among them HIV-1, HTLV-1 and influenza A use it to export their unspliced or incompletely spliced RNAs out of the nucleus. Interacts with, and mediates the nuclear export of HIV-1 Rev and HTLV-1 Rex proteins. Involved in HTLV-1 Rex multimerization.

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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

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

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