ONCOMPASS™ REPORT

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Oncompass Report

powered by Realtime Oncology Molecular Treatment Calculator

ID	201005
NAME	Anonymous
RELEASE DATE	2018-10-19 09:43

PATIENT INFORMATION

Oncompass™ ID: 113981
Name: Anonymous
Year of birth: 1977

Primary Tumor Site: breast
Histology Type: invasive ductal carcinoma
Metastatic sites: Unknown

MEDICAL TEAM

Molecular Pharmacologist: István Peták MD PhD
Genetic Counselor: Júlia Déri MSc
Molecular Biologist: Edit Várkondi PhD
Clinical Oncologist: Csongor Lengyel MD
Case Coordinator: Petra Priger

PATHOLOGICAL AND MOLECULAR DIAGNOSTIC TESTS

Oncompass tumor molecular profiling was performed on a histology sample of the primary tumor of the patient.

NGS - 595 genes
FISH - FGFR1, MET, PIK3CA
IHC - PD-L1

Previous molecular test results:
ER positive, PR positive, HER2 negativ

SUMMARY

Oncompass tumor molecular profiling revealed amplification in the FGFR1 gene, which may cause resistance to certain hormonal therapies (like tamoxifen or letrozol), CDK inhibitors (like palbociclib and ribociclib). Anyhow, evidence about FGFR1 amplification causing resistance to hormone therapy is inconclusive. We would not recommend to completely eliminate hormone therapy from the patients treatment plan, but we advise to use combination therapy based on the molecular profile of the patient. FGFR1 amplification also has prognostic significance in ER pos breast cancer patients. FGFR1 inhibitors might be beneficial in the case of FGFR1 amplification. The patient may have the following adjuvant trial options: In Spain there is a window-of-opportunity clinical trial in Madrid (NCT02619162) with adjuvant NINTEDANIB-letrozol therapy. Other adjuvant option is the monarchE trial in Russia (NCT03155997) which compares the efficacy of adding abemaciclib to standard endocrine therapy with endocrine therapy in monotherapy.

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MOLECULAR TARGET ANALYSIS

MOLECULAR ALTERATIONS

ESR1 protein overexpression driver (AEL: 866.95, AF/TR: NA/70%),
FGFR1 amplification presence driver (AEL: 114.51, AF/TR: NA/70%),
ASXL1-G1397S driver (AEL: 10.00, AF/TR: 57.53%/70%),
PGR protein overexpression driver (AEL: 5.50, AF/TR: NA/70%),
CHEK2-K312E driver (AEL: 3.50, AF/TR: 43.19%/70%),
CHEK2-K355E driver (AEL: 3.50, AF/TR: 43.19%/70%),
CHEK2-K91E driver (AEL: 3.50, AF/TR: 43.19%/70%),
CHEK2-K245E driver (AEL: 3.50, AF/TR: 43.19%/70%),
KMT2C-A1685S driver (AEL: 1.81, AF/TR: 10.48%/70%),
KMT2C-D3420H driver (AEL: 1.78, AF/TR: 47.93%/70%),
LRP1B-T1043S driver (AEL: 0.28, AF/TR: 47.29%/70%),
KMT2D-A4496V driver (AEL: 0.22, AF/TR: 51.13%/70%),
JAK1-R506C driver (AEL: 0.21, AF/TR: 42.41%/70%),
JAK1-R505C driver (AEL: 0.21, AF/TR: 42.41%/70%),
AXIN1-V399L driver (AEL: 0.05, AF/TR: 54.76%/70%),
ZFHX3-S296P driver (AEL: 0.02, AF/TR: 45.53%/70%),
EPHA2-R822H driver (AEL: 0.01, AF/TR: 73.64%/70%),
ZNF217-M410V driver (AEL: 0.01, AF/TR: 36.19%/70%),
TMPRSS2-T112I driver (AEL: 0.01, AF/TR: 43.37%/70%),
TMPRSS2-T75I driver (AEL: 0.01, AF/TR: 43.37%/70%),
KRAS wild-type biomarker (AEL: 0.00),
PDL1 protein normal expression biomarker (AEL: 0.00),
TP53 wild-type biomarker (AEL: 0.00),
CYP2D6-K230DEL biomarker (AEL: 0.00, AF/TR: 53.02%/70%),
MUC16-H9993L non-confirmed driver (AEL: 0.00, AF/TR: 47.23%/70%),
IGF2R-D1681Y non-confirmed driver (AEL: 0.00, AF/TR: 51.97%/70%),
FAT3-A3354T non-confirmed driver (AEL: 0.00, AF/TR: 64.2%/70%),
CUBN-F2316L non-confirmed driver (AEL: 0.00, AF/TR: 7.35%/70%),
MAGI3-G1318D variant of unknown significance (AEL: 0.00, AF/TR: 37.79%/70%),
CCDC178-L49I variant of unknown significance (AEL: 0.00, AF/TR: 44.36%/70%),
CYP2D6-K281DEL variant of unknown significance (AEL: 0.00, AF/TR: 53.02%/70%),
IGSF10-I1311V variant of unknown significance (AEL: 0.00, AF/TR: 35.43%/70%),
KDM5A-R1133W variant of unknown significance (AEL: 0.00, AF/TR: 7.81%/70%),
MAGI2-I679T variant of unknown significance (AEL: 0.00, AF/TR: 7.87%/70%),
EPHA2-R876H non-driver (AEL: -0.99, AF/TR: 73.64%/70%),
EPHB1-V562I non-driver (AEL: -1.74, AF/TR: 62.91%/70%),
FLT1-M938V non-driver (AEL: -5.00, AF/TR: 49.46%/70%)

TARGET GENES

ESR1 wild-type (AEL: 1527.09),
- FGFR1 amplification presence driver (AEL: -114.52) ;
- ESR1 protein overexpression driver (AEL: 866.95)

mTOR wild-type (AEL: 885.20),
- EPHA2-R822H driver (AEL: 0.01) ;
- ESR1 protein overexpression driver (AEL: 866.95)

PIK3CA wild-type (AEL: 868.85),
- ESR1 protein overexpression driver (AEL: 866.95)

AKT1 wild-type (AEL: 868.17),
- ESR1 protein overexpression driver (AEL: 866.95)

CDK4 wild-type (AEL: 815.79),
- ESR1 protein overexpression driver (AEL: 866.95) ;
- FGFR1 amplification presence driver (AEL: -114.52)

CDK6 wild-type (AEL: 815.45),
- FGFR1 amplification presence driver (AEL: -114.52) ;
- ESR1 protein overexpression driver (AEL: 866.95)

FGFR1 wild-type (AEL: 201.78),
- FGFR1 amplification presence driver (AEL: 114.52)

BET wild-type (AEL: 16.68),
- KMT2C-A1685S driver (AEL: 1.81) ;
- ASXL1-G1397S driver (AEL: 10.00) ;
- KMT2C-D3420H driver (AEL: 1.79)

PARP1 wild-type (AEL: 16.57),
- CHEK2-K91E driver (AEL: 3.51) ;
- CHEK2-K355E driver (AEL: 3.51) ;
- CHEK2-K245E driver (AEL: 3.51) ;
- CHEK2-K312E driver (AEL: 3.51)

JAK1 wild-type (AEL: 15.76),
- JAK1-R505C driver (AEL: 0.21) ;
- JAK1-R506C driver (AEL: 0.21)

SOD1 wild-type (AEL: 15.18),
- CHEK2-K355E driver (AEL: 3.51) ;
- CHEK2-K312E driver (AEL: 3.51) ;
- CHEK2-K245E driver (AEL: 3.51) ;
- CHEK2-K91E driver (AEL: 3.51)

EGFR wild-type (AEL: 11.69),
MDM2 wild-type (AEL: 0.46)

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DRUGS POSITIVELY ASSOCIATED

DRUGS IN CLINICAL USE
10 selected from 66

PALBOCICLIB (breast - all [FDA]) (AEL: 6093.00)
- CDK4 wild-type target (AEL: 815.79) ;
- CDK6 wild-type target (AEL: 815.45) ;
- ESR1 protein overexpression driver (AEL: 866.95) ;
- FGFR1 amplification presence driver (AEL: -114.52)

LETROZOLE (breast - UNKNOWN [FDA]) (AEL: 4338.22)
- ESR1 protein overexpression driver (AEL: 866.95) ;
- ESR1 wild-type target (AEL: 1527.09)

EVEROLIMUS (rectum - neuroendocrine carcinoma [FDA+EMEA]; all - neuroendocrine carcinoma [FDA]; kidney - renal cell carcinoma [FDA+EMEA]; pancreas - all [FDA]; pancreas - neuroendocrine carcinoma [FDA+EMEA]; breast - all [FDA+EMEA]; colon - neuroendocrine carcinoma [FDA+EMEA]; lung - neuroendocrine carcinoma [FDA+EMEA]) (AEL: 4010.16)
- mTOR wild-type target (AEL: 885.20) ;
- ESR1 protein overexpression driver (AEL: 866.95) ;
- ESR1 wild-type target (AEL: 1527.09)

RIBOCICLIB (breast - all [FDA]) (AEL: 3391.92)
- ESR1 protein overexpression driver (AEL: 866.95) ;
- CDK4 wild-type target (AEL: 815.79) ;
- FGFR1 amplification presence driver (AEL: -114.52) ;
- CDK6 wild-type target (AEL: 815.45)

TAMOXIFEN (breast - carcinoma [FDA]) (AEL: 3058.24)
- FGFR1 amplification presence driver (AEL: -114.52) ;
- ESR1 protein overexpression driver (AEL: 866.95) ;
- ESR1 wild-type target (AEL: 1527.09)

ABEMACICLIB (breast - all [FDA]) (AEL: 3044.91)
- CDK6 wild-type target (AEL: 815.45) ;
- ESR1 protein overexpression driver (AEL: 866.95) ;
- CDK4 wild-type target (AEL: 815.79)

FULVESTRANT (AEL: 2912.35)
- ESR1 protein overexpression driver (AEL: 866.95) ;
- ESR1 wild-type target (AEL: 1527.09)

EXEMESTANE (AEL: 2424.52)
- ESR1 protein overexpression driver (AEL: 866.95) ;
- ESR1 wild-type target (AEL: 1527.09)

SIROLIMUS (AEL: 885.86)
- mTOR wild-type target (AEL: 885.20) ;
- EPHA2-R822H driver (AEL: 0.01)

TEMSIROLIMUS (kidney - renal cell carcinoma [FDA]) (AEL: 885.67)
- mTOR wild-type target (AEL: 885.20)

DRUGS NEGATIVELY ASSOCIATED

DRUGS IN CLINICAL USE
7 selected from 7

PERTUZUMAB (breast - all [FDA]) (AEL: -116.68)
- ERBB2 wild-type target (AEL: -116.68)

NERATINIB (breast - all [FDA]) (AEL: -104.83)
- ERBB2 wild-type target (AEL: -116.68) ;
- EGFR wild-type target (AEL: 11.69)

AFATINIB (lung - non-small cell carcinoma [FDA+EMEA]) (AEL: -104.81)
- EGFR wild-type target (AEL: 11.69) ;
- ERBB2 wild-type target (AEL: -116.68)

DACOMITINIB (lung - non-small cell carcinoma [FDA]) (AEL: -104.74)
- ERBB2 wild-type target (AEL: -116.68) ;
- EGFR wild-type target (AEL: 11.69)

GEFITINIB (lung - non-small cell carcinoma [FDA+EMEA]) (AEL: -13.51)
- EGFR wild-type target (AEL: -11.69)

CYTARABINE (AEL: -12.15)
- KMT2C-D3420H driver (AEL: -1.79) ;
- KMT2C-A1685S driver (AEL: -1.81)

DOXORUBICIN (ovary - carcinoma [FDA]; blood vessel - kaposi sarcoma [FDA]; breast - carcinoma [FDA]; bone marrow - multiple myeloma [FDA]) (AEL: -12.15)
- KMT2C-D3420H driver (AEL: -1.79) ;
- KMT2C-A1685S driver (AEL: -1.81)

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DRUGS POSITIVELY ASSOCIATED

DRUGS IN CLINICAL DEVELOPMENT
10 selected from 135

TASELISIB (AEL: 1790.20)
- PIK3CA wild-type target (AEL: 868.85) ;
- ESR1 protein overexpression driver (AEL: 866.95)

VOXTALISIB (AEL: 1754.24)
- mTOR wild-type target (AEL: 885.20) ;
- PIK3CA wild-type target (AEL: 868.85)

Dactolisib (AEL: 1754.23)
- mTOR wild-type target (AEL: 885.20) ;
- PIK3CA wild-type target (AEL: 868.85)

PWT33597 (AEL: 1754.05)
- PIK3CA wild-type target (AEL: 868.85) ;
- mTOR wild-type target (AEL: 885.20)

PI-103 (AEL: 1754.05)
- mTOR wild-type target (AEL: 885.20) ;
- PIK3CA wild-type target (AEL: 868.85)

VS-5584 (AEL: 1754.05)
- PIK3CA wild-type target (AEL: 868.85) ;
- mTOR wild-type target (AEL: 885.20)

PKI179 (AEL: 1754.05)
- PIK3CA wild-type target (AEL: 868.85) ;
- mTOR wild-type target (AEL: 885.20)

LY3023414 (AEL: 1754.05)
- mTOR wild-type target (AEL: 885.20) ;
- PIK3CA wild-type target (AEL: 868.85)

GSK2126458 (AEL: 1754.05)
- mTOR wild-type target (AEL: 885.20) ;
- PIK3CA wild-type target (AEL: 868.85)

SF1126 (AEL: 1754.05)
- mTOR wild-type target (AEL: 885.20) ;
- PIK3CA wild-type target (AEL: 868.85)

DRUGS NEGATIVELY ASSOCIATED

DRUGS IN CLINICAL DEVELOPMENT
13 selected from 19

TUCATINIB (AEL: -116.68)
- ERBB2 wild-type target (AEL: -116.68)

BMS-599626 (AEL: -116.68)
- ERBB2 wild-type target (AEL: -116.68)

CANERTINIB (AEL: -116.68)
- ERBB2 wild-type target (AEL: -116.68)

CP-724714 (AEL: -116.68)
- ERBB2 wild-type target (AEL: -116.68)

MARGETUXIMAB (AEL: -116.68)
- ERBB2 wild-type target (AEL: -116.68)

MUBRITINIB (AEL: -116.68)
- ERBB2 wild-type target (AEL: -116.68)

PYROTINIB (AEL: -116.68)
- ERBB2 wild-type target (AEL: -116.68)

MDX-210 (AEL: -116.68)
- ERBB2 wild-type target (AEL: -116.68)

ERTUMAXOMAB (AEL: -116.68)
- ERBB2 wild-type target (AEL: -116.68)

VARLITINIB (AEL: -116.68)
- ERBB2 wild-type target (AEL: -116.68)

MM-302 (AEL: -116.51)
- ERBB2 wild-type target (AEL: -116.68)

SYD985 (AEL: -116.41)
- ERBB2 wild-type target (AEL: -116.68)

ALLITINIB (AEL: -104.99)
- ERBB2 wild-type target (AEL: -116.68) ;
- EGFR wild-type target (AEL: 11.69)

Compound scores displayed represent aggregated evidence levels (AEL). AEL represents the number, scientific impact and clinical relevance of evidence relations in the system, connecting tumor types, molecular alterations, targets and compounds. Individual evidence relation scores are normalized and weighted according to the degree of similarity of the parameters to the parameters of the given patient case. Compound AELs are obtained by aggregating all relevant associations (and AELs) between the specific compound, tumor type, drivers and targets. Compounds are listed in descending order of their AELs.
(Abbreviations: AEL - aggregated evidence level, AF - allele frequency, TR: tumor ratio)

AVAILABLE CLINICAL TRIALS

Search Criteria

BIOMARKERS: AURKA, SYNE3, FANCM, NEK2, PRDM1, EP300, FLCN, RIT1, PIK3R1, CEBPA, ZNF226, KLC1, MAGI2-I679T, RUNX1T1, SF3A1, IKZF4, NKX3-1, BTK, PIK3CD, AR, ZBED4, FANCE, CYP2D6-K230DEL, CDH1, ERBB4, TCF7L2, MAP3K4, PAX7, RET, CARD11, EPCAM, CYP19A1, FGFR2, EPHA7, GRIN2A, FSTL5, KEAP1, SMC3, MAP3K1, CEP57, IL6, GNAQ, PIK3CG, CDKN1A, UBR3, SPOP, MITF, AKT1, RAC2, ZNF217-M410V, NTRK3, KIT, SF3B1, STAT3, MAGOH, ATM, PSMD2, CYLD, ABL2, HSPH1, CIC, mTOR, ABCC2, NTRK2, GATA3, FGF9, IGF1R, CD74, BRAF, IDH1, IGF2, WWP1, PTPN11, TRIO, QKI, GABRA6, FANCL, RXRA, SSTR1, OTOP1, JAK1-R505C, HRAS, PREX2, MAPK1, NCOR1, SHOC2, SEPT9, TP63, AKAP9, TMEM127, MIER3, BAZ2B, CDK4, AIP, TNFRSF14, CYP2D6-K281DEL, SH2B3, GLI1, PIK3CB, MSH2, PSMD1, AXIN1-V399L, FANCF, BMPR1A, TOP2A, GREM1, DDB2, ZNF595, GOPC, RPTOR, PAK3, RBM10, APC, RARG, EPHA3, GNA13, KMT2A, NTRK1, BARD1, TBX3, GATA2, SOCS1, NRG1, ZIC3, DICER1, POLE, SLC9A9, CBL, GSK3B, DNMT3A, KIF5B, IDH2, HNF1A, FZD3, RAF1, KNSTRN, FGF6, CYP2C19, IL6ST, LAMA2, STAG2, MET, FANCI, RXRG, AGTRAP, ABL, SDHA, CYP2A6, SNCAIP, KDM4B, KDM5C, ACVR1B, IRF4, WISP3, S1PR2, BRIP1, DAXX, PMS1, EPHA2-R876H, FGF8, TSHR, CHEK2-K245E, SLIT2, BIRC3, CTCF, TSC2, BCL2L1, PRKAR1A, SOX10, BCR, NFE2L2, SF1, MAGI3-G1318D, G6PD, CDKN2B, BRCA2, SUZ12, FANCA, CD79A, ALK, RARalpha, ROS1, GATA1, SMAD2, EPHB1-V562I, BCL6, TP53BP1, TACC3, SPEN, GAS6, GPR124, CD79B, RAF1, ECT2L, FBXO11, GPR78, POT1, PIK3CA, BRD4, KEL, MAP2K2, IKZF1, GATA6, MDM2, NKX2-8, FGF14, U2AF2, NF1, EZH2, CUBN-F2316L, KDM5A-R1133W, CDK8, FANCG, MAS1L, DCUN1D1, MCL1, WBSCR17, TP53, PLCG2, RICTOR, SLC45A3, DPYD, ARFRP1, BCL2L11, RAC1, FN1, RB1, CASP8, INPP4B, TNFAIP3, SCN11A, VHL, IL2RG, TYK2, KREMEN1, CDK6, RAD51D, TRRAP, KIAA1549, RAD51, ZFHX3-S296P, PRKDC, FAM46C, IL2RB, AMER1, PDCD1LG2, WNK2, NIPA2, FANCD2, LMO1, ETV6, SLCO1B1, GRM8, IFITM3, CUL3, EED, CDA, CRLF2, SOS1, RAD51B, FGF7, NF2, NOTCH2, PIK3C2B, CDC27, NRAS, DDX3X, RAD54L, PNP, MET, IL2RA, TBX20, MAP7, MYO18A, BLM, FGF1, STAT4, BRCA1, IL7R, USP16, MEN1, MYD88, SOX2, SETD2, WEE1, XPA, ATP11B, HSD3B1, CHEK2-K91E, TOP1, CCDC178-L49I, PBRM1, FGFR1, BUB1B, EZR, SOX9, BRD4, CASR, ARAF, SETBP1, RHBDF2, PPP2R1A, IRF2, WT1, RAD21, H3F3A, RHOA, TCERG1, BAP1, PPARG, RAD50, CDKN1B, IGSF10-I1311V, ZBTB2, FAM175A, CSF1R, FBXO32, ZNF703, FLT3, FOXL2, CHD2, DIS3L2, NRG1, CYP2C9, NOTCH1, FOXO1, LZTR1, MYCN, SDHD, FGF10, NELL2, MRE11A, ATRX, MUC16-H9993L, EPHA2-R822H, BIRC2, FGFR2, MYC, ATP6V0D2, NSD1, ERBB2, C11orf30, SDHAF2, MLH1, SYK, FGF4, PTGFR, PSMB5, MST1R, U2AF1, MUTYH, PTEN, PIK3R2, FGFR3, CCND1, FANCB, TIAF1, FGF19, PDGFRB, NFKBIA, VEGFA, SHH, GNAS, PAX3, GRM3, FOXA1, MEF2B, PRSS8, SMAD3, GNAI2, ATP4A, NKX2-1, CDK12, LYN, CDKN1C, NPM1, RET, TMPRSS2-T75I, YES1, CDC73, ALK, PSMB1, BCORL1, SLC34A2, MLLT3, ERCC4, RXRB, CHEK2-K312E, VCL, RAD51C, SBDS, CTNNA1, CYP2B6, CCND2, PPP2R2A, IFITM1, ERG, BAX, BCR, DDR1, CSMD3, RPS6KB1, RANBP2, NBN, CBLC, ERCC5, TSC1, FGFR1, MYCL1, PHOX2B, CDKN2A, BTG1, EPB41, SDHC, ENO1, USP25, CRKL, ESR2, PDK1, IRS2, KRAS, ZMYM3, EXOC2, ERBB3, PRPF40B, FH, PARK2, GNA11, CIT, DOT1L, MAX, FGF2, ABCB1, CHD1, JAK3, FLT4, EXT1, CHD4, PALB2, EPHA5, LPAR2, TACC3, CCND3, BCL2L2, RUNX1, FGFR4, BCL9, SMAD4, SDHB, NRCAM, SRC, FGF23, KMT2C-D3420H, CTNNB1, CHEK2-K355E, FOXP1, PDZRN3, PRKCI, SLC22A1, FGF5, CBLB, ZRSR2, WRN, ROS1, CHD7, MAP2K1, B2M, AXL, MED12, JAK1-R506C, MYO1B, FLT1-M938V, SMARCE1, NOTCH3, ERCC1, MAP2K4, ARID1A, BCOR, TPM3, CHIC2, PRF1, SMARCA4, MAP4K3, PSMB2, TACC1, LTK, XRCC2, ZNF473, SPTA1, CD74, CD274, MSH6, BRAF, ZNF2, ESRP1, SEC16A, MSH3, CCNE1, ESR1, SLC7A8, CSNK2A1, ITCH, IGF2R-D1681Y, CREBBP, NTRK1, PHF6, DSE, IRAK4, HGF, FAT3-A3354T, AXIN2, JUN, C2orf44, TAF1, CDKN2C, ELMO1, MDM4, PTPN12, GID4, OR5L1, BCL2, PCBP1, NCOA2, KIF5B, ACVRL1, SDC4, PCGF2, KDM6A, ERRFI1, AKT3, SPRED1, FUBP1, POLD1, EXT2, KLHL6, EGFR, UGT1A1, PAX5, YAP1, KMT2D-A4496V, JAK2, SAMD9L, LRP1B-T1043S, FBXW7, XPO1, FAT1, TAS2R38, DDR2, DMD, AKT2, SPEG, KLF6, CCDC6, APEX1, PTPRD, PPM1L, MPL, ATR, FAS, DCC, THSD7B, SMARCB1, RNF43, TMPRSS2-T112I, FGF3, TERT, AMPH, TPMT, GXYLT1, INHBA, GSTP1, AURKB, NUP93, TRAF5, PMS2, CHEK1, TFG, LCK, RECQL4, ERCC2, RHEB, TGFBR2, ARID1B, EGFR, ARID2, ASXL1-G1397S, MAPK3, KMT2C-A1685S, HOXB13, RARB, HIST1H3B, LRRK2, SLC31A1, NT5C2, ABL1, GNAT2, SLX4, ERCC3, GATA4, XPC, MED13, EML4, BAI3, KDR, FRS2, SMC1A, GPC3, KAT6A, SRSF2, SLC22A2, FGFR3, SUFU, CBFB, TET2, RARA, FANCC, PTCH1, TPM4, PDGFRA, SMO, GEN1, STK11, IKBKE, PDL1, ESR1, PGR, ERBB2, MET, FGFR1, PIK3CA

STATUS: Not yet recruiting,Active recruiting,Active (not recruiting)

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AVAILABLE CLINICAL TRIALS

MTC COMPOUNDS: DOVITINIB, GSK1059615, Apitolisib, PKI 166, ARQ 092, ZIV-AFLIBERCEPT, CC-115, MEDI-573, MLN1117, tiomolibdate diammonium, PONATINIB, RONICICLIB, AZD2014, P7170, RUXOLITINIB, SUNITINIB, PAZOPANIB, CETUXIMAB, INO-1001, debio 1347, Sonolisib, MEHD7945A, SSR128129E, AFURESERTIB, ERDAFITINIB, MLN0128, TAMOXIFEN, LUCITANIB, PF-04965842, OLARATUMAB, IMGATUZUMAB, PEMBROLIZUMAB, CGM097, CH 5132799, MOMELOTINIB, NIRAPARIB, REGORAFENIB, TRAMETINIB, DINUTUXIMAB, E7016, TALAZOPARIB, ABEMACICLIB, DS-3032B, RIBOCICLIB, ORANTINIB, Tesevatinib, JQ1, Recilisib, SAR405838, ERLOTINIB, PF-04691502, PALBOCICLIB, VISMODEGIB, NICLOSAMIDE, XL418, P1446A-05, OSI-027, Panulisib, Itacitinib, INIPARIB, PRT 2070, DANUSERTIB, AICAR, BRIGATINIB, SIMOTINIB, LETROZOLE, NAB-PACLITAXEL, MK-8242, MILCICLIB, TAS-102, BUPARLISIB, RUCAPARIB, SORAFENIB, ABT-414, Dactolisib, COPANLISIB, TEMSIROLIMUS, FOLFIRINOX, AZD6482, BORTEZOMIB, NINTEDANIB, EVEROLIMUS, PANITUMUMAB, CEP-9722, PWT33597, E7449, RIVICICLIB, JNJ-26483327, RO5045337, ETOPOSIDE, BAY1125976, NIVOLUMAB, BRIVANIB, MK-8284, ENTRECTINIB, Visusertib, AZD8055, OLAPARIB, AZD5363, NIMOTUZUMAB, SIROLIMUS, ALVOCIDIB, FULVESTRANT, METFORMIN, CEDIRANIB, ABT767, LY287445, MI-212, LAPATINIB, Filgotinib, JNJ-26854165, OSIMERTINIB, HDM201, IPILIMUMAB, P276-00, HM61713, RES 529, PICTILISIB, EXEMESTANE, RILUZOLE, SELUMETINIB, ATEZOLIZUMAB, TREBANANIB, BGT226, BIBX 1382, ALRN 6924, IDASANUTLIN, SONIDEGIB, LY3023414, IMATINIB, XL147, MK-2461, SAPITINIB, IPATASERTIB, SC-66, AEE788, CC-223, TASELISIB, S49076, GSK2126458, RGB-286638, AXITINIB, PI-103, TRICIRIBINE, BARICITINIB, MSC 2363318A, WX 037, ZSTK474, DENOSUMAB, PKI179, NUTLIN-3A, MATUZUMAB, RIDAFOROLIMUS, GDC 0084, VANDETANIB, GEDATOLISIB, CARBOPLATIN, GSK3052230, AT13148, CISPLATIN, AZD 2461, BMS-986158, APALUTAMIDE, LOBENGUANE, PD173074, VOXTALISIB, ENZALUTAMIDE, FLUZOPARIB, GSK2141795, GDC 0349, LCAR-B38M, AT13387, THELIATINIB, MIDOSTAURIN, NECITUMUMAB, VS-5584, ROCILETINIB, DS-7423, ALPELISIB, AZD4547, LENVATINIB, NILOTINIB, ZALUTUMUMAB, ABIRATERONE, RAMUCIRUMAB, BEVACIZUMAB, VELIPARIB, BGB-290, H 447, SR13668, ORTERONEL, FOLFOX, CABAZITAXEL, INCB047986, MK2206, AMG-232, OBINUTUZUMAB, PROPRANOLOL, SF1126, DASATINIB, GSK690693

CNS METASTATIC: Unknown | **ECOG:** 0 - 5 | **STAGE:** Unknown | **PATIENT'S COUNTRY:** Russian Federation

GENDER: Female | **TUMOR SET:** breast - invasive ductal carcinoma | **AGE:** 41

IDENTIFIER	DESCRIPTION
NCT02070549	A Phase I Trial of Single Agent Trametinib (GSK1120212) in Advanced Cancer Patients With Hepatic Dysfunction

Active recruiting

Line	Phase	Compounds
1-4	1a-1b	LY-2940680

Countries	Allocation	Masking
United States	N/A	Single Group Assignment

NCT02747004 — A Study of Abemaciclib (LY2835219) Plus Tamoxifen or Abemaciclib Alone in Women With Metastatic Breast Cancer (nextMONARCH 1)

Active recruiting

Line	Phase	Compounds
2-10	2	ABEMACICLIB, ABEMACICLIB, TAMOXIFEN

Countries	Allocation	Masking
Brazil, Taiwan, Province of China, Czech Republic, Italy, France, Turkey	Randomized	Open Label

Inclusive Biomarkers

ERBB2 amplification absence, ERBB2 protein normal expression, ERBB2 protein lack of expression, ESR1 protein overexpression, PGR protein overexpression

AVAILABLE CLINICAL TRIALS

NCT02264678 Ascending Doses of AZD6738 in Combination With Chemotherapy and/or Novel Anti Cancer Agents

Active recruiting

Line	Phase	Compounds
2-3	1-2	AZD6738, OLAPARIB

Countries	Allocation	Masking
Korea, Republic of, United Kingdom, France, United States	N/A	Single Group Assignment

Inclusive Biomarkers

ESR1 protein lack of expression, PGR protein lack of expression

Exclusive Biomarkers

BRCA1 ngs mutant, BRCA2 ngs mutant, ERBB2 amplification presence, ERBB2 protein overexpression

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Active recruiting

Line	Phase	Compounds
1-10	1-2	AZD6738, AZD6738, AZD6738, CARBOPLATIN, OLAPARIB

Countries	Allocation	Masking
Korea, Republic of, United Kingdom, France, United States	Non Randomized	Single Group Assignment

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Active recruiting

Line	Phase	Compounds
2	1-2	AZD6738, CARBOPLATIN

Countries	Allocation	Masking
Korea, Republic of, United Kingdom, France, United States	N/A	Single Group Assignment

Inclusive Biomarkers

ATM loss presence, ATM protein lack of expression

Active recruiting

Line	Phase	Compounds
2-3	1-2	AZD6738, OLAPARIB

Countries	Allocation	Masking
Korea, Republic of, United Kingdom, France, United States	N/A	Single Group Assignment

Inclusive Biomarkers

BRCA1 ngs mutant, BRCA2 ngs mutant

Exclusive Biomarkers

ERBB2 protein overexpression, ERBB2 amplification presence

Active recruiting

Line	Phase	Compounds
1-10	1-2	AZD6738, MEDI4736

Countries	Allocation	Masking
Korea, Republic of, United Kingdom, France, United States	N/A	Single Group Assignment

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Active recruiting

Line	Phase	Compounds
2	1-2	AZD6738, OLAPARIB

Countries	Allocation	Masking
Korea, Republic of, United Kingdom, France, United States	N/A	Single Group Assignment

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

AVAILABLE CLINICAL TRIALS

NCT01920061 — A Study Of PF-05212384 In Combination With Other Anti-Tumor Agents and in Combination With Cisplatin in Patients With Triple Negative Breast Cancer in an Expansion Arm (TNBC)

Active recruiting

Line	Phase	Compounds
1-3	1a-1b	CISPLATIN, GEDATOLISIB

Countries	Allocation	Masking
United Kingdom, Italy, Spain, Canada, United States	N/A	Single Group Assignment

Inclusive Biomarkers

ERBB2 amplification absence, ERBB2 protein normal expression, ERBB2 protein lack of expression, ESR1 protein normal expression, ESR1 protein lack of expression, PGR protein normal expression, PGR protein lack of expression

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Active recruiting

Line	Phase	Compounds
1-3	1a-1b	DACOMITINIB, GEDATOLISIB

Countries	Allocation	Masking
United Kingdom, Italy, Spain, Canada, United States	N/A	Single Group Assignment

Inclusive Biomarkers

ERBB2 amplification presence, ERBB2 protein overexpression

Active recruiting

Line	Phase	Compounds
1-3	1a-1b	DACOMITINIB, GEDATOLISIB

Countries	Allocation	Masking
United Kingdom, Italy, Spain, Canada, United States	N/A	Single Group Assignment

Inclusive Biomarkers

ERBB2 protein overexpression, ERBB2 amplification presence

Active recruiting

Line	Phase	Compounds
1-3	1a-1b	CISPLATIN, GEDATOLISIB

Countries	Allocation	Masking
United Kingdom, Italy, Spain, Canada, United States	N/A	Single Group Assignment

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NAME	Anonymous
RELEASE DATE	2018-10-19 09:43

AVAILABLE CLINICAL TRIALS

NCT03330405 Javelin Parp Medley: Avelumab Plus Talazoparib In Locally Advanced Or Metastatic Solid Tumors

Not yet recruiting

Line	Phase	Compounds
1-10	2	AVELUMAB, TALAZOPARIB

Countries	Allocation	Masking
Russian Federation, Hungary, United States	N/A	Single Group Assignment

Not yet recruiting

Line	Phase	Compounds
1-10	1b	AVELUMAB, TALAZOPARIB

Countries	Allocation	Masking
Russian Federation, Hungary, United States	N/A	Single Group Assignment

Not yet recruiting

Line	Phase	Compounds
1-10	1b	AVELUMAB, TALAZOPARIB

Countries	Allocation	Masking
Russian Federation, Hungary, United States	N/A	Single Group Assignment

Inclusive Biomarkers

ATM ngs mutant, BRCA1 ngs mutant, BRCA2 ngs mutant

This list of clinical trials has been generated by the Realtime Oncology Molecular Treatment Calculator by matching the clinical and molecular profile of the patient with inclusion and exclusion criteria of trials recorded in the system. Search criteria have been manually set to filter matching clinical trials but do not necessarily cover all screening parameters. Oncompass Medicine cannot take responsibility for the validity of the recorded clinical trial data concerning inclusion and exclusion criteria and status, and cannot guarantee that the patient is going to be enrolled in any of the trials included in the list provided.

DETAILED MOLECULAR PROFILE

MUTANT GENES

ASXL1-G1397S, AXIN1-V399L, CCDC178-L49I, CHEK2-K245E, CHEK2-K312E, CHEK2-K355E, CHEK2-K91E, CUBN-F2316L, CYP2D6-K230DEL, CYP2D6-K281DEL, EPHA2-R822H, EPHA2-R876H, EPHB1-V562I, FAT3-A3354T, FLT1-M938V, IGF2R-D1681Y, IGSF10-I1311V, JAK1-R505C, JAK1-R506C, KDM5A-R1133W, KMT2C-A1685S, KMT2C-D3420H, KMT2D-A4496V, LRP1B-T1043S, MAGI2-I679T, MAGI3-G1318D, MUC16-H9993L, TMPRSS2-T112I, TMPRSS2-T75I, ZFHX3-S296P, ZNF217-M410V

WILD TYPE GENES

ABCB1, ABCC2, ABL1, ABL2, ACVR1B, ACVRL1, AGTRAP, AIP, AKAP9, AKT1, AKT2, AKT3, ALK, AMER1, AMPH, APC, APEX1, AR, ARAF, ARFRP1, ARID1A, ARID1B, ARID2, ATM, ATP11B, ATP4A, ATP6V0D2, ATR, ATRX, AURKA, AURKB, AXIN2, AXL, B2M, BAI3, BAP1, BARD1, BAX, BAZ2B, BCL2, BCL2L1, BCL2L2, BCL6, BCL9, BCOR, BCORL1, BCR, BIM, BIRC2, BIRC3, BLM, BMPR1A, BRAF, BRCA1, BRCA2, BRD4, BRIP1, BTG1, BTK, BUB1B, CARD11, CASP8, CASR, CBFB, CBL, CBLB, CBLC, CCDC6, CCND1, CCND2, CCND3, CCNE1, CD74, CD79A, CD79B, CDA, CDC27, 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, CSMD3, CSNK2A1, CTCF, CTNNA1, CTNNB1, CUL3, CYLD, CYP19A1, CYP2A6, CYP2B6, CYP2C19, CYP2C9, DAXX, DCC, DCUN1D1, DDB2, DDR1, DDR2, DDX3X, DICER1, DIS3L2, DMD, DNMT3A, DOT1L, DPYD, DSE, ECT2L, EED, EGFR, ELMO1, EML4, EMSY, ENO1, EP300, EPB41, EPCAM, EPHA3, EPHA5, EPHA7, ERBB2, ERBB3, ERBB4, ERCC1, ERCC2, ERCC3, ERCC4, ERCC5, ERG, ERRFI1, ESR1, ESR2, ESRP1, ETV6, EXOC2, EXT1, EXT2, EZH2, EZR, FAM175A, FAM46C, FANCA, FANCB, FANCC, FANCD2, FANCE, FANCF, FANCG, FANCI, FANCL, FANCM, FAS, FAT1, FBXO11, FBXO32, FBXW7, FGF1, FGF10, FGF14, FGF19, FGF2, FGF23, FGF3, FGF4, FGF5, FGF6, FGF7, FGF8, FGF9, FGFR1, FGFR2, FGFR3, FGFR4, FH, FLCN, FLT3, FLT4, FN1, FOXA1, FOXL2, FOXO1, FOXP1, FRS2, FSTL5, FUBP1, FZD3, G6PD, GABRA6, GAS6, GATA1, GATA2, GATA3, GATA4, GATA6, GEN1, GID4, GLI1, GNA11, GNA13, GNAI2, GNAQ, GNAS, GNAT2, GOPC, GPC3, GPR124, GPR78, GREM1, GRIN2A, GRM3, GRM8, GSK3B, GSTP1, GXYLT1, H3F3A, HGF, HIST1H3B, HNF1A, HOXB13, HRAS, HSD3B1, HSPH1, IDH1, IDH2, IFITM1, IFITM3, IGF1R, IGF2, IKBKE, IKZF1, IKZF4, IL2RA, IL2RB, IL2RG, IL6, IL6ST, IL7R, INHBA, INPP4B, IRAK4, IRF2, IRF4, IRS2, ITCH, JAK2, JAK3, JUN, KAT6A, KDM4B, KDM5C, KDM6A, KDR, KEAP1, KEL, KIAA1549, KIF5B, KIT, KLC1, KLF6, KLHL6, KMT2A, KNSTRN, KRAS, KREMEN1, LAMA2, LCK, LMO1, LPAR2, LRRK2, LTK, LYN, LZTR1, MAGOH, MAP2K1, MAP2K2, MAP2K4, MAP3K1, MAP3K4, MAP4K3, MAP7, MAPK1, MAPK3, MAS1L, MAX, MCL1, MDM2, MDM4, MED12, MED13, MEF2B, MEN1, MET, MIER3, MITF, MLH1, MLLT3, MPL, MRE11, MSH2, MSH3, MSH6, MST1R, MTOR, MUTYH, MYC, MYCL1, MYCN, MYD88, MYO18A, MYO1B, NBN, NCOA2, NCOR1, NEK2, NELL2, NF1, NF2, NFE2L2, NFKBIA, NIPA2, NKX2-1, NKX2-8, NKX3-1, NOTCH1, NOTCH2, NOTCH3, NPM1, NRAS, NRCAM, NRG1, NSD1, NT5C2, NTRK1, NTRK2, NTRK3, NUP93, OR5L1, OTOP1, PAK3, PALB2, PARK2, PAX3, PAX5, PAX7, PBRM1, PCBP1, PCGF2, PDGFRA, PDGFRB, PDK1, PDL1, PDL2, PDZRN3, PHF6, PHOX2B, PIK3C2B, PIK3CA, PIK3CB, PIK3CD, PIK3CG, PIK3R1, PIK3R2, PLCG2, PMS1, PMS2, PNP, POLD1, POLE, POT1, PPARG, PPM1L, PPP2R1A, PPP2R2A, PRDM1, PREX2, PRF1, PRKAR1A, PRKCI, PRKDC, PRPF40B, PRSS8, PSMB1, PSMB2, PSMB5, PSMD1, PSMD2, PTCH1, PTEN, PTGFR, PTPN11, PTPN12, PTPRD, QKI, RAC1, RAC2, RAD21, RAD50, RAD51, RAD51B, RAD51C, RAD51D, RAD54L, RAF1, RANBP2, RARA, RARB, RARG, RB1, RBM10, RECQL4, 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, SEC16A, SEPT9, SETBP1, SETD2, SF1, SF3A1, SF3B1, SH2B3, SHH, SHOC2, SLC22A1, SLC22A2, SLC31A1, SLC34A2, SLC45A3, SLC7A8, SLC9A9, SLCO1B1, SLIT2, SLX4, SMAD2, SMAD3, SMAD4, SMARCA4, SMARCB1, SMARCE1, SMC1A, SMC3, SMO, SNCAIP, SOCS1, SOS1, SOX10, SOX2, SOX9, SPEG, SPEN, SPOP, SPRED1, SPTA1, SRC, SRSF2, SSTR1, STAG2, STAT3, STAT4, STK11, SUFU, SUZ12, SYK, SYNE3, TACC3, TAF1, TAS2R38, TBX20, TBX3, TCERG1, TCF7L2, TERT, TET2, TFG, TGFBR2, THSD7B, TIAF1, TMEM127, 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, WBSCR17, WDCP, WEE1, WISP3, WNK2, WRN, WT1, WWP1, XPA, XPC, XPO1, XRCC2, YAP1, YES1, ZBED4, ZBTB2, ZIC3, ZMYM3, ZNF2, ZNF226, ZNF473, ZNF595, ZNF703, ZRSR2

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ID	201005
NAME	Anonymous
RELEASE DATE	2018-10-19 09:43

DETAILED MOLECULAR PROFILE

FISH/CNA/IHC POSITIVE GENES

ESR1 PROTEIN OVEREXPRESSION, FGFR1 AMPLIFICATION PRESENCE, PGR PROTEIN OVEREXPRESSION

FISH/CNA/IHC NEGATIVE GENES

ABL1 TRANSLOCATION ABSENCE, ALK TRANSLOCATION ABSENCE, BCR TRANSLOCATION ABSENCE, BRAF TRANSLOCATION ABSENCE, BRD4 TRANSLOCATION ABSENCE, CD74 TRANSLOCATION ABSENCE, EGFR TRANSLOCATION ABSENCE, ERBB2 PROTEIN NORMAL EXPRESSION, FGFR1 TRANSLOCATION ABSENCE, FGFR2 TRANSLOCATION ABSENCE, FGFR3 TRANSLOCATION ABSENCE, KIF5B TRANSLOCATION ABSENCE, MET AMPLIFICATION ABSENCE, MET TRANSLOCATION ABSENCE, NRG1 TRANSLOCATION ABSENCE, NTRK1 TRANSLOCATION ABSENCE, PDL1 PROTEIN NORMAL EXPRESSION, PIK3CA AMPLIFICATION ABSENCE, RAF1 TRANSLOCATION ABSENCE, RARA TRANSLOCATION ABSENCE, RET TRANSLOCATION ABSENCE, ROS1 TRANSLOCATION ABSENCE, TACC1 TRANSLOCATION ABSENCE, TACC3 TRANSLOCATION ABSENCE

BIOINFORMATICAL AND FUNCTIONAL ANALYSIS

MOLECULAR ALTERATIONS

ESR1 protein overexpression driver (AEL: 866.95, AF/TR: NA/70%),
FGFR1 amplification presence driver (AEL: 114.51, AF/TR: NA/70%),
ASXL1-G1397S driver (AEL: 10.00, AF/TR: 57.53%/70%),
PGR protein overexpression driver (AEL: 5.50, AF/TR: NA/70%),
CHEK2-K312E driver (AEL: 3.50, AF/TR: 43.19%/70%),
CHEK2-K355E driver (AEL: 3.50, AF/TR: 43.19%/70%),
CHEK2-K91E driver (AEL: 3.50, AF/TR: 43.19%/70%),
CHEK2-K245E driver (AEL: 3.50, AF/TR: 43.19%/70%),
KMT2C-A1685S driver (AEL: 1.81, AF/TR: 10.48%/70%),
KMT2C-D3420H driver (AEL: 1.78, AF/TR: 47.93%/70%),
LRP1B-T1043S driver (AEL: 0.28, AF/TR: 47.29%/70%),
KMT2D-A4496V driver (AEL: 0.22, AF/TR: 51.13%/70%),
JAK1-R506C driver (AEL: 0.21, AF/TR: 42.41%/70%),
JAK1-R505C driver (AEL: 0.21, AF/TR: 42.41%/70%),
AXIN1-V399L driver (AEL: 0.05, AF/TR: 54.76%/70%),
ZFHX3-S296P driver (AEL: 0.02, AF/TR: 45.53%/70%),
EPHA2-R822H driver (AEL: 0.01, AF/TR: 73.64%/70%),
ZNF217-M410V driver (AEL: 0.01, AF/TR: 36.19%/70%),
TMPRSS2-T112I driver (AEL: 0.01, AF/TR: 43.37%/70%),
TMPRSS2-T75I driver (AEL: 0.01, AF/TR: 43.37%/70%),
KRAS wild-type biomarker (AEL: 0.00),
PDL1 protein normal expression biomarker (AEL: 0.00),
TP53 wild-type biomarker (AEL: 0.00),
CYP2D6-K230DEL biomarker (AEL: 0.00, AF/TR: 53.02%/70%),
MUC16-H9993L non-confirmed driver (AEL: 0.00, AF/TR: 47.23%/70%),
IGF2R-D1681Y non-confirmed driver (AEL: 0.00, AF/TR: 51.97%/70%),
FAT3-A3354T non-confirmed driver (AEL: 0.00, AF/TR: 64.2%/70%),
CUBN-F2316L non-confirmed driver (AEL: 0.00, AF/TR: 7.35%/70%),
MAGI3-G1318D variant of unknown significance (AEL: 0.00, AF/TR: 37.79%/70%),
CCDC178-L491 variant of unknown significance (AEL: 0.00, AF/TR: 44.36%/70%),
CYP2D6-K281DEL variant of unknown significance (AEL: 0.00, AF/TR: 53.02%/70%),
IGSF10-I1311V variant of unknown significance (AEL: 0.00, AF/TR: 35.43%/70%),
KDM5A-R1133W variant of unknown significance (AEL: 0.00, AF/TR: 7.81%/70%),
MAGI2-I679T variant of unknown significance (AEL: 0.00, AF/TR: 7.87%/70%),
EPHA2-R876H non-driver (AEL: -0.99, AF/TR: 73.64%/70%),
EPHB1-V562I non-driver (AEL: -1.74, AF/TR: 62.91%/70%),
FLT1-M938V non-driver (AEL: -5.00, AF/TR: 49.46%/70%)

TARGET GENES

ESR1 wild-type (AEL: 1527.09),
- FGFR1 amplification presence driver (AEL: -114.52) ;
- ESR1 protein overexpression driver (AEL: 866.95)

mTOR wild-type (AEL: 885.20),
- EPHA2-R822H driver (AEL: 0.01) ;
- ESR1 protein overexpression driver (AEL: 866.95)

PIK3CA wild-type (AEL: 868.85),
- ESR1 protein overexpression driver (AEL: 866.95)

AKT1 wild-type (AEL: 868.17),
- ESR1 protein overexpression driver (AEL: 866.95)

CDK4 wild-type (AEL: 815.79),
- ESR1 protein overexpression driver (AEL: 866.95) ;
- FGFR1 amplification presence driver (AEL: -114.52)

CDK6 wild-type (AEL: 815.45),
- FGFR1 amplification presence driver (AEL: -114.52) ;
- ESR1 protein overexpression driver (AEL: 866.95)

FGFR1 wild-type (AEL: 201.78),
- FGFR1 amplification presence driver (AEL: 114.52)

BET wild-type (AEL: 16.68),
- KMT2C-A1685S driver (AEL: 1.81) ;
- ASXL1-G1397S driver (AEL: 10.00) ;
- KMT2C-D3420H driver (AEL: 1.79)

PARP1 wild-type (AEL: 16.57),
- CHEK2-K91E driver (AEL: 3.51) ;
- CHEK2-K355E driver (AEL: 3.51) ;
- CHEK2-K245E driver (AEL: 3.51) ;
- CHEK2-K312E driver (AEL: 3.51)

JAK1 wild-type (AEL: 15.76),
- JAK1-R505C driver (AEL: 0.21) ;
- JAK1-R506C driver (AEL: 0.21)

SOD1 wild-type (AEL: 15.18),
- CHEK2-K355E driver (AEL: 3.51) ;
- CHEK2-K312E driver (AEL: 3.51) ;
- CHEK2-K245E driver (AEL: 3.51) ;
- CHEK2-K91E driver (AEL: 3.51)

EGFR wild-type (AEL: 11.69),
MDM2 wild-type (AEL: 0.46)

BIOINFORMATICAL AND FUNCTIONAL ANALYSIS

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

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IGF2R-D1681Y	Wellcome Trust Sanger Institute https://cancer.sanger.ac.uk/cosmic/search?q=IGF2R+S1194L
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DETAILED DESCRIPTION OF DRIVER AND TARGET GENES

DRIVER GENES

Name	Description
ASXL1	Probable Polycomb group (PcG) protein involved in transcriptional regulation mediated by ligand-bound nuclear hormone receptors, such as retinoic acid receptors (RARs) and peroxisome proliferator-activated receptor gamma (PPARG). Acts as coactivator of RARA and RXRA through association with NCOA1. Acts as corepressor through recruitment of KDM1A and CBX5 to target genes in a cell-type specific manner; the function seems to involve differential recruitment of methylated histone H3 to respective promoters. Acts as corepressor for PPARG and suppresses its adipocyte differentiation-inducing activity (By similarity). Non-catalytic component of the PR-DUB complex, a complex that specifically mediates deubiquitination of histone H2A monoubiquitinated at Lys-119 (H2AK119ub1).
AXIN1	Component of the beta-catenin destruction complex required for regulating CTNNB1 levels through phosphorylation and ubiquitination, and modulating Wnt-signaling. Controls dorsoventral patterning via two opposing effects; down-regulates CTNNB1 to inhibit the Wnt signaling pathway and ventralize embryos, but also dorsalizes embryos by activating a Wnt-independent JNK signaling pathway. In Wnt signaling, probably facilitates the phosphorylation of CTNNB1 and APC by GSK3B. Likely to function as a tumor suppressor. Facilitates the phosphorylation of TP53 by HIPK2 upon ultraviolet irradiation. Enhances TGF-beta signaling by recruiting the RNF111 E3 ubiquitin ligase and promoting the degradation of inhibitory SMAD7. Also component of the AXIN1-HIPK2-TP53 complex which controls cell growth, apoptosis and development.
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 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.
CUBN	Cotransporter which plays a role in lipoprotein, vitamin and iron metabolism, by facilitating their uptake. Binds to ALB, MB, Kappa and lambda-light chains, TF, hemoglobin, GC, SCGB1A1, APOA1, high density lipoprotein, and the GIF-cobalamin complex. The binding of all ligands requires calcium. Serves as important transporter in several absorptive epithelia, including intestine, renal proximal tubules and embryonic yolk sac. Interaction with LRP2 mediates its trafficking throughout vesicles and facilitates the uptake of specific ligands like GC, hemoglobin, ALB, TF and SCGB1A1. Interaction with AMN controls its trafficking to the plasma membrane and facilitates endocytosis of ligands. May play an important role in the development of the peri-implantation embryo through internalization of APOA1 and cholesterol. Binds to LGALS3 at the maternal-fetal interface.
CYP2D6	Responsible for the metabolism of many drugs and environmental chemicals that it oxidizes. It is involved in the metabolism of drugs such as antiarrhythmics, adrenoceptor antagonists, and tricyclic antidepressants.
EPHA2	Receptor tyrosine kinase which binds promiscuously membrane-bound ephrin-A family ligands residing on adjacent cells, leading to contact-dependent bidirectional signaling into neighboring cells. The signaling pathway downstream of the receptor is referred to as forward signaling while the signaling pathway downstream of the ephrin ligand is referred to as reverse signaling. Activated by the ligand ephrin-A1/EFNA1 regulates migration, integrin-mediated adhesion, proliferation and differentiation of cells. Regulates cell adhesion and differentiation through DSG1/desmoglein-1 and inhibition of the ERK1/ERK2 (MAPK3/MAPK1, respectively) signaling pathway. May also participate in UV radiation-induced apoptosis and have a ligand-independent stimulatory effect on chemotactic cell migration. During development, may function in distinctive aspects of pattern formation and subsequently in development of several fetal tissues. Involved for instance in angiogenesis, in early hindbrain development and epithelial proliferation and branching morphogenesis during mammary gland development. Engaged by the ligand ephrin-A5/EFNA5 may regulate lens fiber cells shape and interactions and be important for lens transparency development and maintenance. With ephrin-A2/EFNA2 may play a role in bone remodeling through regulation of osteoclastogenesis and osteoblastogenesis.

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DETAILED DESCRIPTION OF DRIVER AND TARGET GENES

DRIVER GENES

Name	Description
EPHB1	Receptor tyrosine kinase which binds promiscuously transmembrane ephrin-B 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. Cognate/functional ephrin ligands for this receptor include EFNB1, EFNB2 and EFNB3. During nervous system development, regulates retinal axon guidance redirecting ipsilaterally ventrotemporal retinal ganglion cells axons at the optic chiasm midline. This probably requires repulsive interaction with EFNB2. In the adult nervous system together with EFNB3, regulates chemotaxis, proliferation and polarity of the hippocampus neural progenitors. In addition to its role in axon guidance plays also an important redundant role with other ephrin-B receptors in development and maturation of dendritic spines and synapse formation. May also regulate angiogenesis. More generally, may play a role in targeted cell migration and adhesion. Upon activation by EFNB1 and probably other ephrin-B ligands activates the MAPK/ERK and the JNK signaling cascades to regulate cell migration and adhesion respectively.
ESR1	Nuclear hormone receptor. The steroid hormones and their receptors are involved in the regulation of eukaryotic gene expression and affect cellular proliferation and differentiation in target tissues. Ligand-dependent nuclear transactivation involves either direct homodimer binding to a palindromic estrogen response element (ERE) sequence or association with other DNA-binding transcription factors, such as AP-1/c-Jun, c-Fos, ATF-2, Sp1 and Sp3, to mediate ERE-independent signaling. Ligand binding induces a conformational change allowing subsequent or combinatorial association with multiprotein coactivator complexes through LXXLL motifs of their respective components. Mutual transrepression occurs between the estrogen receptor (ER) and NF-kappa-B in a cell-type specific manner. Decreases NF-kappa-B DNA-binding activity and inhibits NF-kappa-B-mediated transcription from the IL6 promoter and displace RELA/p65 and associated coregulators from the promoter. Recruited to the NF-kappa-B response element of the CCL2 and IL8 promoters and can displace CREBBP. Present with NF-kappa-B components RELA/p65 and NFKB1/p50 on ERE sequences. Can also act synergistically with NF-kappa-B to activate transcription involving respective recruitment adjacent response elements; the function involves CREBBP. Can activate the transcriptional activity of TFF1. Also mediates membrane-initiated estrogen signaling involving various kinase cascades. Isoform 3 is involved in activation of NOS3 and endothelial nitric oxide production. Isoforms lacking one or several functional domains are thought to modulate transcriptional activity by competitive ligand or DNA binding and/or heterodimerization with the full length receptor. Essential for MTA1-mediated transcriptional regulation of BRCA1 and BCAS3. Isoform 3 can bind to ERE and inhibit isoform 1.
FAT3	May play a role in the interactions between neurites derived from specific subsets of neurons during development.
FGFR1	Tyrosine-protein kinase that acts as cell-surface receptor for fibroblast growth factors and plays an essential role in the regulation of embryonic development, cell proliferation, differentiation and migration. Required for normal mesoderm patterning and correct axial organization during embryonic development, normal skeletogenesis and normal development of the gonadotropin-releasing hormone (GnRH) neuronal system. Phosphorylates PLCG1, FRS2, GAB1 and SHB. Ligand binding leads to the activation of several signaling cascades. Activation of PLCG1 leads to the production of the cellular signaling molecules diacylglycerol and inositol 1,4,5-trisphosphate. Phosphorylation of FRS2 triggers recruitment of GRB2, GAB1, PIK3R1 and SOS1, and mediates activation of RAS, MAPK1/ERK2, MAPK3/ERK1 and the MAP kinase signaling pathway, as well as of the AKT1 signaling pathway. Promotes phosphorylation of SHC1, STAT1 and PTPN11/SHP2. In the nucleus, enhances RPS6KA1 and CREB1 activity and contributes to the regulation of transcription. FGFR1 signaling is down-regulated by IL17RD/SEF, and by FGFR1 ubiquitination, internalization and degradation.
IGSF10	Involved in the control of early migration of neurons expressing gonadotropin-releasing hormone (GNRH neurons) (By similarity). May be involved in the maintenance of osteochondroprogenitor cells pool (By similarity).
JAK1	Tyrosine kinase of the non-receptor type, involved in the IFN-alpha/beta/gamma signal pathway. Kinase partner for the interleukin (IL)-2 receptor.
KDM5A	Histone demethylase that specifically demethylates Lys-4 of histone H3, thereby playing a central role in histone code. Does not demethylate histone H3 Lys-9, H3 Lys-27, H3 Lys-36, H3 Lys-79 or H4 Lys-20. Demethylates trimethylated and dimethylated but not monomethylated H3 Lys-4. May stimulate transcription mediated by nuclear receptors. May be involved in transcriptional regulation of Hox proteins during cell differentiation. May participate in transcriptional repression of cytokines such as CXCL12. Plays a role in the regulation of the circadian rhythm and in maintaining the normal periodicity of the circadian clock. In a histone demethylase-independent manner, acts as a coactivator of the CLOCK-ARNTL/BMAL1-mediated transcriptional activation of PER1/2 and other clock-controlled genes and increases histone acetylation at PER1/2 promoters by inhibiting the activity of HDAC1 (By similarity).
KMT2C	Histone methyltransferase. Methylates Lys-4 of histone H3. H3 Lys-4 methylation represents a specific tag for epigenetic transcriptional activation. Central component of the MLL2/3 complex, a coactivator complex of nuclear receptors, involved in transcriptional coactivation. KMT2C/MLL3 may be a catalytic subunit of this complex. May be involved in leukemogenesis and developmental disorder.
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.
LRP1B	Potential cell surface proteins that bind and internalize ligands in the process of receptor-mediated endocytosis
MAGI3	Acts as a scaffolding protein at cell-cell junctions, thereby regulating various cellular and signaling processes. Cooperates with PTEN to modulate the kinase activity of AKT1. Its interaction with PTPRB and tyrosine phosphorylated proteins suggests that it may link receptor tyrosine phosphatase with its substrates at the plasma membrane. In polarized epithelial cells, involved in efficient trafficking of TGFA to the cell surface. Regulates the ability of LPAR2 to activate ERK and RhoA pathways. Regulates the JNK signaling cascade via its interaction with FZD4 and VANGL2.
MUC16	Thought to provide a protective, lubricating barrier against particles and infectious agents at mucosal surfaces.

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DETAILED DESCRIPTION OF DRIVER AND TARGET GENES

DRIVER GENES

Name	Description
PDL1	Involved in the costimulatory signal, essential for T-cell proliferation and production of IL10 and IFNG, in an IL2-dependent and a PDCD1-independent manner. Interaction with PDCD1 inhibits T-cell proliferation and cytokine production.
TP53	Acts as a tumor suppressor in many tumor types; induces growth arrest or apoptosis depending on the physiological circumstances and cell type. Involved in cell cycle regulation as a trans-activator that acts to negatively regulate cell division by controlling a set of genes required for this process. One of the activated genes is an inhibitor of cyclin-dependent kinases. Apoptosis induction seems to be mediated either by stimulation of BAX and FAS antigen expression, or by repression of Bcl-2 expression. In cooperation with mitochondrial PPIF is involved in activating oxidative stress-induced necrosis; the function is largely independent of transcription. Induces the transcription of long intergenic non-coding RNA p21 (lincRNA-p21) and lincRNA-Mkln1. LincRNA-p21 participates in TP53-dependent transcriptional repression leading to apoptosis and seem to have to effect on cell-cycle regulation. Implicated in Notch signaling cross-over. Prevents CDK7 kinase activity when associated to CAK complex in response to DNA damage, thus stopping cell cycle progression. Isoform 2 enhances the transactivation activity of isoform 1 from some but not all TP53-inducible promoters. Isoform 4 suppresses transactivation activity and impairs growth suppression mediated by isoform 1. Isoform 7 inhibits isoform 1-mediated apoptosis. Regulates the circadian clock by repressing CLOCK-ARNTL/BMAL1-mediated transcriptional activation of PER2 (PubMed: 24051492).
ZNF217	Binds to the promoters of target genes and functions as repressor. Promotes cell proliferation and antagonizes cell death. Promotes phosphorylation of AKT1 at Ser-473.

DETAILED DESCRIPTION OF DRIVER AND TARGET GENES

TARGET GENES

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

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DETAILED DESCRIPTION OF DRIVER AND TARGET GENES

TARGET GENES

Name	Description
CDK6	Serine/threonine-protein kinase involved in the control of the cell cycle and differentiation; promotes G1/S transition. Phosphorylates pRB/RB1 and NPM1. Interacts with D-type G1 cyclins during interphase at G1 to form a pRB /RB1 kinase and controls the entrance into the cell cycle. Involved in initiation and maintenance of cell cycle exit during cell differentiation; prevents cell proliferation and regulates negatively cell differentiation, but is required for the proliferation of specific cell types (e.g. erythroid and hematopoietic cells). Essential for cell proliferation within the dentate gyrus of the hippocampus and the subventricular zone of the lateral ventricles. Required during thymocyte development. Promotes the production of newborn neurons, probably by modulating G1 length. Promotes, at least in astrocytes, changes in patterns of gene expression, changes in the actin cytoskeleton including loss of stress fibers, and enhanced motility during cell differentiation. Prevents myeloid differentiation by interfering with RUNX1 and reducing its transcription transactivation activity, but promotes proliferation of normal myeloid progenitors. Delays senescence. Promotes the proliferation of beta-cells in pancreatic islets of Langerhans. May play a role in the centrosome organization during the cell cycle phases (PubMed:23918663).
EGFR	Receptor tyrosine kinase binding ligands of the EGF family and activating several signaling cascades to convert extracellular cues into appropriate cellular responses. Known ligands include EGF, TGFA/TGF-alpha, amphiregulin, epigen/EPGN, BTC/betacellulin, epiregulin/EREG and HBEGF/heparin-binding EGF. Ligand binding triggers receptor homo- and/or heterodimerization and autophosphorylation on key cytoplasmic residues. The phosphorylated receptor recruits adapter proteins like GRB2 which in turn activates complex downstream signaling cascades. Activates at least 4 major downstream signaling cascades including the RAS-RAF-MEK-ERK, PI3 kinase-AKT, PLCgamma-PKC and STATs modules. May also activate the NF-kappa-B signaling cascade. Also directly phosphorylates other proteins like RGS16, activating its GTPase activity and probably coupling the EGF receptor signaling to the G protein-coupled receptor signaling. Also phosphorylates MUC1 and increases its interaction with SRC and CTNNB1/beta-catenin Isoform 2 may act as an antagonist of EGF action
ESR1	Nuclear hormone receptor. The steroid hormones and their receptors are involved in the regulation of eukaryotic gene expression and affect cellular proliferation and differentiation in target tissues. Ligand-dependent nuclear transactivation involves either direct homodimer binding to a palindromic estrogen response element (ERE) sequence or association with other DNA-binding transcription factors, such as AP-1/c-Jun, c-Fos, ATF-2, Sp1 and Sp3, to mediate ERE-independent signaling. Ligand binding induces a conformational change allowing subsequent or combinatorial association with multiprotein coactivator complexes through LXXLL motifs of their respective components. Mutual transrepression occurs between the estrogen receptor (ER) and NF-kappa-B in a cell-type specific manner. Decreases NF-kappa-B DNA-binding activity and inhibits NF-kappa-B-mediated transcription from the IL6 promoter and displace RELA/p65 and associated coregulators from the promoter. Recruited to the NF-kappa-B response element of the CCL2 and IL8 promoters and can displace CREBBP. Present with NF-kappa-B components RELA/p65 and NFKB1/p50 on ERE sequences. Can also act synergistically with NF-kappa-B to activate transcription involving respective recruitment adjacent response elements; the function involves CREBBP. Can activate the transcriptional activity of TFF1. Also mediates membrane-initiated estrogen signaling involving various kinase cascades. Isoform 3 is involved in activation of NOS3 and endothelial nitric oxide production. Isoforms lacking one or several functional domains are thought to modulate transcriptional activity by competitive ligand or DNA binding and/or heterodimerization with the full length receptor. Essential for MTA1-mediated transcriptional regulation of BRCA1 and BCAS3. Isoform 3 can bind to ERE and inhibit isoform 1.
FGFR1	Tyrosine-protein kinase that acts as cell-surface receptor for fibroblast growth factors and plays an essential role in the regulation of embryonic development, cell proliferation, differentiation and migration. Required for normal mesoderm patterning and correct axial organization during embryonic development, normal skeletogenesis and normal development of the gonadotropin-releasing hormone (GnRH) neuronal system. Phosphorylates PLCG1, FRS2, GAB1 and SHB. Ligand binding leads to the activation of several signaling cascades. Activation of PLCG1 leads to the production of the cellular signaling molecules diacylglycerol and inositol 1,4,5-trisphosphate. Phosphorylation of FRS2 triggers recruitment of GRB2, GAB1, PIK3R1 and SOS1, and mediates activation of RAS, MAPK1/ERK2, MAPK3/ERK1 and the MAP kinase signaling pathway, as well as of the AKT1 signaling pathway. Promotes phosphorylation of SHC1, STAT1 and PTPN11/SHP2. In the nucleus, enhances RPS6KA1 and CREB1 activity and contributes to the regulation of transcription. FGFR1 signaling is down-regulated by IL17RD/SEF, and by FGFR1 ubiquitination, internalization and degradation.
JAK1	Tyrosine kinase of the non-receptor type, involved in the IFN-alpha/beta/gamma signal pathway. Kinase partner for the interleukin (IL)-2 receptor.
MDM2	E3 ubiquitin-protein ligase that mediates ubiquitination of p53/TP53, leading to its degradation by the proteasome. Inhibits p53/TP53- and p73/TP73-mediated cell cycle arrest and apoptosis by binding its transcriptional activation domain. Also acts as a ubiquitin ligase E3 toward itself and ARRB1. Permits the nuclear export of p53/TP53. Promotes proteasome-dependent ubiquitin-independent degradation of retinoblastoma RB1 protein. Inhibits DAXX-mediated apoptosis by inducing its ubiquitination and degradation. Component of the TRIM28/KAP1-MDM2-p53 /TP53 complex involved in stabilizing p53/TP53. Also component of the TRIM28/KAP1-ERBB4-MDM2 complex which links growth factor and DNA damage response pathways. Mediates ubiquitination and subsequent proteasome degradation of DYRK2 in nucleus. Ubiquitinates IGF1R and SNAI1 and promotes them to proteasomal degradation.

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DETAILED DESCRIPTION OF DRIVER AND TARGET GENES

TARGET GENES

Name	Description
mTOR	Serine/threonine protein kinase which is a central regulator of cellular metabolism, growth and survival in response to hormones, growth factors, nutrients, energy and stress signals. MTOR directly or indirectly regulates the phosphorylation of at least 800 proteins. Functions as part of 2 structurally and functionally distinct signaling complexes mTORC1 and mTORC2 (mTOR complex 1 and 2). Activated mTORC1 up-regulates protein synthesis by phosphorylating key regulators of mRNA translation and ribosome synthesis. This includes phosphorylation of EIF4EBP1 and release of its inhibition toward the elongation initiation factor 4E (eiF4E). Moreover, phosphorylates and activates RPS6KB1 and RPS6KB2 that promote protein synthesis by modulating the activity of their downstream targets including ribosomal protein S6, eukaryotic translation initiation factor EIF4B, and the inhibitor of translation initiation PDCD4. Stimulates the pyrimidine biosynthesis pathway, both by acute regulation through RPS6KB1-mediated phosphorylation of the biosynthetic enzyme CAD, and delayed regulation, through transcriptional enhancement of the pentose phosphate pathway which produces 5-phosphoribosyl-1-pyrophosphate (PRPP), an allosteric activator of CAD at a later step in synthesis, this function is dependent on the mTORC1 complex. Regulates ribosome synthesis by activating RNA polymerase III-dependent transcription through phosphorylation and inhibition of MAF1 an RNA polymerase III-repressor. In parallel to protein synthesis, also regulates lipid synthesis through SREBF1/SREBP1 and LPIN1. To maintain energy homeostasis mTORC1 may also regulate mitochondrial biogenesis through regulation of PPARGC1A. mTORC1 also negatively regulates autophagy through phosphorylation of ULK1. Under nutrient sufficiency, phosphorylates ULK1 at Ser-758, disrupting the interaction with AMPK and preventing activation of ULK1. Also prevents autophagy through phosphorylation of the autophagy inhibitor DAP. mTORC1 exerts a feedback control on upstream growth factor signaling that includes phosphorylation and activation of GRB10 a INSR-dependent signaling suppressor. Among other potential targets mTORC1 may phosphorylate CLIP1 and regulate microtubules. As part of the mTORC2 complex MTOR may regulate other cellular processes including survival and organization of the cytoskeleton. Plays a critical role in the phosphorylation at Ser-473 of AKT1, a pro-survival effector of phosphoinositide 3-kinase, facilitating its activation by PDK1. mTORC2 may regulate the actin cytoskeleton, through phosphorylation of PRKCA, PXN and activation of the Rho-type guanine nucleotide exchange factors RHOA and RAC1A or RAC1B. mTORC2 also regulates the phosphorylation of SGK1 at Ser-422.
PARP1	Involved in the base excision repair (BER) pathway, by catalyzing the poly(ADP-ribosyl)ation of a limited number of acceptor proteins involved in chromatin architecture and in DNA metabolism. This modification follows DNA damages and appears as an obligatory step in a detection/signaling pathway leading to the reparation of DNA strand breaks. Mediates the poly(ADP-ribosyl)ation of APLF and CHFR. Positively regulates the transcription of MTUS1 and negatively regulates the transcription of MTUS2/TIP150. With EEF1A1 and TXK, forms a complex that acts as a T-helper 1 (Th1) cell-specific transcription factor and binds the promoter of IFN-gamma to directly regulate its transcription, and is thus involved importantly in Th1 cytokine production. Required for PARP9 and DTX3L recruitment to DNA damage sites. PARP1-dependent PARP9-DTX3L-mediated ubiquitination promotes the rapid and specific recruitment of 53BP1/TP53BP1, UIMC1/RAP80, and BRCA1 to DNA damage sites.
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.
SOD1	Destroys radicals which are normally produced within the cells and which are toxic to biological systems.

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ID	201005
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APPENDIX

TARGETED COMPOUNDS

DRUGS IN CLINICAL USE (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

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

Description of the genes is provided by UniProt (Universal Protein Resource).

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