ONCOMPASS™ REPORT

POWERED BY

Realtime Oncology
Molecular Treatment Calculator™

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Oncompass Report

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PATIENT INFORMATION

Oncompass™ ID: [redacted]
Name: [redacted]
Year of birth: 1955

Primary Tumor Site: ovary
Histology Type: serous adenocarcinoma
Metastatic sites: peritoneum, lymph node

MEDICAL TEAM

Treating Physician: [redacted]
Case Coordinator: [redacted]
Case Manager: [redacted]
Molecular Pharmacologist: [redacted]
Genetic Counselor: [redacted]
Molecular Biologist: [redacted]
Consulting Physician: [redacted]
Info-bionics Engineer: [redacted]
Molecular Biologist: [redacted]

PATHOLOGICAL AND MOLECULAR DIAGNOSTIC TESTS

Sample ID: 2219B1933 B
Sample source: Metastasis (lymph node)
Tumor cell rate: N/A
Sampling type: Biopsy
Tumor type: ovary serous adenocarcinoma

Tests performed:

NGS - FoundationOne test - (2219B1933 B)
MSI test (NGS-based) - MSS (microsatellite stable) - (2219B1933 B)
TMB - LOW - (2219B1933 B)

PREVIOUS THERAPIES

Line: 1 - CARBOPLATIN + PACLITAXEL - 4 cycles - (15/08/2019 - 15/11/2019)
Line: 2 - TRAMETINIB - (15/01/2020 - 15/04/2021)

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SUMMARY

Oncompass Report of Marziye Ulusoy, diagnosed with ovarian serous adenocarcinoma, has been completed for digital drug assignment and interpretation purposes using Realtime Oncology Treatment Calculator. Reinterpretation of FMI Report was based on sample 2219B1933 B.

Tumor-agnostic/immunotherapy biomarkers:

The tumor is MSS and TMB-Low, which do not support involving immunotherapy. Additionally, the detected MYC amplification may also cause resistance to IT.

NTRK fusions were not detected based on the FMI report.

Tumor-specific on-label biomarkers:

OLAPARIB, NIRAPARIB, and RUCAPARIB are PARP inhibitors approved as a maintenance treatment of patients with platinum-sensitive ovarian cancer. In case of BRCA mutation, these compounds are indicated in further treatment lines. No BRCA pathogenic mutations were identified in the tested sample. In the same histology, the combination of BEVACIZUMAB and OLAPARIB is also approved as a first-line maintenance treatment for homologous repair deficient (HRD) patients who responded to platinum-based chemotherapy. No mutations were identified that would cause HRD.

Also, MYC amplification may cause resistance to anti-estrogens, although clinical results are controversial, which sometimes is used in low-grade ovarian carcinoma.

Histology based on-label therapies: BEVACIZUMAB is an approved VEGFR inhibitor for epithelial, fallopian tube, or primary peritoneal ovarian cancer patients.

Based on the NGS, the following results could be relevant for off-label treatments:

NF1 loss presence driver (AEL: 71.36, AF/TR: NA/NA), MYC amplification presence driver (AEL: 64.70, AF/TR: NA/NA), TP53-560-2A>T driver (AEL: 27.77, AF/TR: NA/NA)

NF1 copy number loss: NF1 gene is a tumor suppressor encoding neurofibromin, a RAS GTPase-activating protein that inhibits RAS activity and the MAPK pathway. Loss of NF1 was found to be associated with RAS activation and MEK dependence. Based on preclinical evidence, the mTOR inhibitor rapamycin (sirolimus) and the MEK inhibitor trametinib efficiently inhibited the growth of NF1-deficient cells. In a case study, a melanoma patient with NF1 mutation responded to trametinib treatment. The MEK1/2 inhibitor SELUMETINIB is approved by the FDA for pediatric patients (aged 2 years (FDA) or 3 years (EMA) and above) with neurofibromatosis type 1 (caused by germline NF1 mutation) associated symptomatic, inoperable plexiform neurofibromas. mTOR inhibitors (including the registered EVEROLIMUS, TEMSIROLIMUS, SIROLIMUS and METFORMIN) and MEK inhibitors (including the registered TRAMETINIB, COBIMETINIB, BINIMETINIB, and the FDA-approved SELUMETINIB), and CABOZANTINIB can be mentioned in positive association with the molecular profile.

The detected TP53-560-2A>T is a loss of function mutation, in which case CDK inhibitors are in positive association with the profile.

In a phase II study, palbociclib was well tolerated and resulted in 30% progression-free survival (PFS) rate at 6 months among recurrent, previously treated ovarian cancer patients. Ribociclib + letrozole combinational therapy resulted in 50% progression-free survival rate at 12 weeks in ER-positive ovarian cancer patients in a phase II study.

The patient was previously successfully treated with MEK inhibitor, Trametinib.

Taking into consideration the previous therapies, and molecular results, the following could be recommended if the patient is still treatable:

Since the patient was previously on long-lasting targeted therapy, molecular profiling from a new tissue sample could be more informative in order to identify potential mechanisms of resistance and new targets.

Based on the existing results, Selumetinib, MEK inhibitor, registered in NF1 related plexiform neurofibroma, could be considered. Adding, mTOR inhibitors, such as metformin, would cover more pathways that NF1 is involved in. Bevacizumab is still an on-label treatment option.

MOLECULAR TARGET ANALYSIS

MOLECULAR ALTERATIONS

NF1 loss presence driver (AEL: 71.36, AF/TR: NA/NA),
MYC amplification presence driver (AEL: 64.70, AF/TR: NA/NA),
TP53-560-2A>T driver (AEL: 27.77, AF/TR: NA/NA),
PIM1 amplification presence driver (AEL: 9.96, AF/TR: NA/NA),
APC-R854K VUS in a driver gene (AEL: 4.74, AF/TR: NA/NA),
CDH1-R124C VUS in a driver gene (AEL: 3.13, AF/TR: NA/NA),
TNFRSF14-P167L VUS in a driver gene (AEL: 0.16, AF/TR: NA/NA),

TARGET GENES

CDK1 wild-type (AEL: 99.23),
- MYC amplification presence driver (AEL: 64.70) ;
- TP53-560-2A>T driver (AEL: 27.77) ;
- CDH1-R124C VUS in a driver (AEL: 3.13)

CHEK1 wild-type (AEL: 95.10),
- TP53-560-2A>T driver (AEL: 27.77) ;

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MOLECULAR TARGET ANALYSIS

KLHL6-L258F VUS in a driver gene (AEL: 0.05, AF/TR: NA/NA),
NOTCH2-R1332L VUS in a driver gene (AEL: 0.03, AF/TR: NA/NA),
MERTK-R557W variant of unknown significance (AEL: 0.00, AF/TR: NA/NA),
INPP4B amplification presence variant of unknown significance (AEL: 0.00, AF/TR: NA/NA),
DDR1 amplification presence variant of unknown significance (AEL: 0.00, AF/TR: NA/NA),
MERTK-T795M variant of unknown significance (AEL: 0.00, AF/TR: NA/NA),
DAXX amplification presence variant of unknown significance (AEL: 0.00, AF/TR: NA/NA),
CDKN1A amplification presence variant of unknown significance (AEL: 0.00, AF/TR: NA/NA),
KDR-G671E non-driver (AEL: -5.00, AF/TR: NA/NA)

- MYC amplification presence driver (AEL: 64.70)

MAP2K1 wild-type (AEL: 74.71),
- NF1 loss presence driver (AEL: 71.36)

BRD4 wild-type (AEL: 67.65),
- MYC amplification presence driver (AEL: 64.70)

CDK12 wild-type (AEL: 64.97),
- MYC amplification presence driver (AEL: 64.70)

PIM1 wild-type (AEL: 34.86),
- PIM1 amplification presence driver (AEL: 9.96)

AURKB wild-type (AEL: 32.23),
- TP53-560-2A>T driver (AEL: 27.77) ;
- CDH1-R124C VUS in a driver (AEL: 3.13)

CDK2 wild-type (AEL: 31.73),
- CDH1-R124C VUS in a driver (AEL: 3.13) ;
- TP53-560-2A>T driver (AEL: 27.77)

WEE1 wild-type (AEL: 31.57),
- TP53-560-2A>T driver (AEL: 27.77)

ATR wild-type (AEL: 29.10),
- TP53-560-2A>T driver (AEL: 27.77)

CDK4 wild-type (AEL: 28.75),
- TP53-560-2A>T driver (AEL: 27.77)

RARG wild-type (AEL: 28.66),
- TP53-560-2A>T driver (AEL: 27.77)

PLK1 wild-type (AEL: 28.24),
- TP53-560-2A>T driver (AEL: 27.77)

PRKDC wild-type (AEL: 28.16),
- TP53-560-2A>T driver (AEL: 27.77)

CDK9 wild-type (AEL: 28.09),
- TP53-560-2A>T driver (AEL: 27.77)

MTOR wild-type (AEL: 11.26),
- MYC amplification presence driver (AEL: -64.70) ;
- NF1 loss presence driver (AEL: 71.36) ;
- CDH1-R124C VUS in a driver (AEL: 3.13)

COX2 wild-type (AEL: 8.21),
- APC-R854K VUS in a driver (AEL: 4.74)

ROS1 wild-type (AEL: 5.63),
- CDH1-R124C VUS in a driver (AEL: 3.13)

PIK3CB wild-type (AEL: 4.18),
- CDH1-R124C VUS in a driver (AEL: 3.13)

ALK wild-type (AEL: 4.18),
- CDH1-R124C VUS in a driver (AEL: 3.13)

PIK3CD wild-type (AEL: 4.18),
- CDH1-R124C VUS in a driver (AEL: 3.13)

AURKA wild-type (AEL: 4.18),
- CDH1-R124C VUS in a driver (AEL: 3.13)

PIK3CG wild-type (AEL: 4.18),
- CDH1-R124C VUS in a driver (AEL: 3.13)

AURKC wild-type (AEL: 4.18),
- CDH1-R124C VUS in a driver (AEL: 3.13)

FGFR1 wild-type (AEL: 3.64),
- CDH1-R124C VUS in a driver (AEL: 3.13)

SRC wild-type (AEL: 3.64),
- CDH1-R124C VUS in a driver (AEL: 3.13)

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MOLECULAR TARGET ANALYSIS	
	JAK3 wild-type (AEL: 3.64), • CDH1-R124C VUS in a driver (AEL: 3.13) NPY5R wild-type (AEL: 3.64), • CDH1-R124C VUS in a driver (AEL: 3.13) RET wild-type (AEL: 3.64), • CDH1-R124C VUS in a driver (AEL: 3.13) JAK2 wild-type (AEL: 3.64), • CDH1-R124C VUS in a driver (AEL: 3.13) NTRK1 wild-type (AEL: 3.64), • CDH1-R124C VUS in a driver (AEL: 3.13) BCL2 wild-type (AEL: 3.64), • CDH1-R124C VUS in a driver (AEL: 3.13) PDGFRA wild-type (AEL: 3.64), • CDH1-R124C VUS in a driver (AEL: 3.13) PDGFRB wild-type (AEL: 3.64), • CDH1-R124C VUS in a driver (AEL: 3.13) JAK1 wild-type (AEL: 3.64), • CDH1-R124C VUS in a driver (AEL: 3.13) ABL1 wild-type (AEL: 3.64), • CDH1-R124C VUS in a driver (AEL: 3.13) GBF1 wild-type (AEL: 3.64), • CDH1-R124C VUS in a driver (AEL: 3.13) HMGCR wild-type (AEL: 3.63) • CDH1-R124C VUS in a driver (AEL: 3.13)

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DRUGS POSITIVELY ASSOCIATED

DRUGS IN CLINICAL USE
10 selected from 91

SELUMETINIB (all - neurofibroma [FDA+EMA]; all - plexiform neurofibroma [FDA+EMA]) (AEL: 331.47)
- NF1 loss presence driver (AEL: 71.36) ;
- MAP2K1 wild-type target (AEL: 74.71)

TRAMETINIB (thyroid - anaplastic carcinoma [FDA]; all - malignant melanoma [FDA+EMA]; lung - adenocarcinoma [FDA+EMA]) (AEL: 186.07)
- NF1 loss presence driver (AEL: 71.36) ;
- MAP2K1 wild-type target (AEL: 74.71)

SIROLIMUS (AEL: 130.72)
- MTOR wild-type target (AEL: 11.26) ;
- NF1 loss presence driver (AEL: 71.36)

DASATINIB (bone marrow - acute lymphoblastic leukemia [FDA+EMA]; bone marrow - chronic myeloid leukemia [FDA+EMA]) (AEL: 90.12)
- SRC wild-type target (AEL: 3.64) ;
- MYC amplification presence driver (AEL: 64.70) ;
- ABL1 wild-type target (AEL: 3.64) ;
- PDGFRB wild-type target (AEL: 3.64)

BINIMETINIB (skin - malignant melanoma [FDA+EMA]) (AEL: 75.13)
- MAP2K1 wild-type target (AEL: 74.71)

PAZOPANIB (soft tissue - sarcoma [FDA+EMA]; kidney - renal cell carcinoma [FDA+EMA]) (AEL: 48.63)
- TP53-560-2A>T driver (AEL: 27.77) ;
- PDGFRB wild-type target (AEL: 3.64) ;
- FGFR1 wild-type target (AEL: 3.64) ;
- PDGFRA wild-type target (AEL: 3.64)

BEVACIZUMAB (cervix - all [FDA+EMA]; rectum - all [FDA+EMA]; kidney - renal cell carcinoma [FDA+EMA]; fallopian tube - all [FDA+EMA]; ovary - epithelial carcinoma [FDA+EMA]; brain - glioblastoma multiforme [FDA]; liver - hepatocellular carcinoma [FDA]; lung - non-small cell carcinoma [FDA+EMA]; breast - all [FDA+EMA]; colon - all [FDA+EMA]; peritoneum - all [FDA+EMA]) (AEL: 44.10)
- TP53-560-2A>T driver (AEL: 27.77)

ABEMACICLIB (breast - all [FDA+EMA]) (AEL: 29.42)
- CDK4 wild-type target (AEL: 28.75)

PALBOCICLIB (breast - all [FDA+EMA]) (AEL: 29.35)
- CDK4 wild-type target (AEL: 28.75)

RIBOCICLIB (breast - all [FDA+EMA]) (AEL: 29.00)
- CDK4 wild-type target (AEL: 28.75)

DRUGS NEGATIVELY ASSOCIATED

DRUGS IN CLINICAL USE
10 selected from 36

FULVESTRANT (breast - all [FDA+EMA]) (AEL: -374.41)
- NF1 loss presence driver (AEL: -71.36) ;
- ESR1 wild-type target (AEL: -139.54) ;
- MYC amplification presence driver (AEL: -64.70)

ERLOTINIB (lung - adenocarcinoma [FDA+EMA]; lung - squamous cell carcinoma [FDA+EMA]; pancreas - all [FDA+EMA]; lung - non-small cell carcinoma [FDA+EMA]) (AEL: -266.55)
- NF1 loss presence driver (AEL: -71.36) ;
- EGFR wild-type target (AEL: -79.19)

TRETINOIN (AEL: -189.16)
- NF1 loss presence driver (AEL: -71.36)

CRIZOTINIB (lung - non-small cell carcinoma [FDA+EMA]; all - anaplastic large cell lymphoma [FDA]) (AEL: -165.78)
- MET wild-type target (AEL: -68.52) ;
- ALK wild-type target (AEL: 4.18) ;
- NF1 loss presence driver (AEL: -71.36) ;
- ROS1 wild-type target (AEL: 5.63) ;
- TP53-560-2A>T driver (AEL: -27.77)

AMIVANTAMAB (lung - non-small cell carcinoma [FDA]; lung - adenocarcinoma [FDA]) (AEL: -147.70)
- EGFR wild-type target (AEL: -79.19) ;
- MET wild-type target (AEL: -68.52)

LAPATINIB (breast - all [FDA+EMA]) (AEL: -141.80)
- EGFR wild-type target (AEL: -79.19) ;
- AKT1 wild-type target (AEL: -62.51)

BAZEDOXIFENE (AEL: -139.38)
- ESR1 wild-type target (AEL: -139.54)

EVEROLIMUS (breast - all [FDA+EMA]; lung - neuroendocrine carcinoma [FDA+EMA]; rectum - neuroendocrine carcinoma [FDA+EMA]; pancreas - neuroendocrine carcinoma [FDA+EMA]; pancreas - all [FDA]; all - neuroendocrine carcinoma [FDA]; brain - subependymal giant cell astrocytoma (SEGA) [FDA+EMA]; colon - neuroendocrine carcinoma [FDA+EMA]; kidney - renal cell carcinoma [FDA+EMA]) (AEL: -90.46)
- MYC amplification presence driver (AEL: -64.70) ;
- MTOR wild-type target (AEL: -11.26)

TEPOTINIB (lung - non-small cell carcinoma [FDA]) (AEL: -68.51)
- MET wild-type target (AEL: -68.52)

CEMIPLIMAB (skin - squamous cell carcinoma [FDA+EMA]; skin - basal cell carcinoma [FDA+EMA]; lung - squamous cell carcinoma [FDA+EMA]; lung - non-small cell carcinoma [FDA+EMA]; lung - adenocarcinoma [FDA+EMA]) (AEL: -64.99)
- PDCD1 wild-type target (AEL: -65.09)

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DRUGS POSITIVELY ASSOCIATED

DRUGS IN CLINICAL DEVELOPMENT
10 selected from 166

JQ1 (AEL: 258.95)
- MYC amplification presence driver (AEL: 64.70) ;
- BRD4 wild-type target (AEL: 67.65)

RIVICICLIB (AEL: 187.81)
- CDK1 wild-type target (AEL: 99.23) ;
- CDK2 wild-type target (AEL: 31.73) ;
- CDK4 wild-type target (AEL: 28.75) ;
- CDK9 wild-type target (AEL: 28.09)

RGB-286638 (AEL: 187.81)
- CDK1 wild-type target (AEL: 99.23) ;
- CDK4 wild-type target (AEL: 28.75) ;
- CDK9 wild-type target (AEL: 28.09) ;
- CDK2 wild-type target (AEL: 31.73)

RONICICLIB (AEL: 187.81)
- CDK9 wild-type target (AEL: 28.09) ;
- CDK4 wild-type target (AEL: 28.75) ;
- CDK2 wild-type target (AEL: 31.73) ;
- CDK1 wild-type target (AEL: 99.23)

MIRDAMETINIB (AEL: 177.47)
- NF1 loss presence driver (AEL: 71.36) ;
- MAP2K1 wild-type target (AEL: 74.71)

AZD1208 (AEL: 144.42)
- PIM1 amplification presence driver (AEL: 9.96) ;
- PIM1 wild-type target (AEL: 34.86)

MK-8776 (AEL: 125.19)
- TP53-560-2A>T driver (AEL: 27.77) ;
- CHEK1 wild-type target (AEL: 95.10)

PREXASERTIB (AEL: 96.90)
- CHEK1 wild-type target (AEL: 95.10)

SCH 900776 (AEL: 95.10)
- CHEK1 wild-type target (AEL: 95.10)

BI-847325 (AEL: 78.89)
- AURKA wild-type target (AEL: 4.18) ;
- MAP2K1 wild-type target (AEL: 74.71)

DRUGS NEGATIVELY ASSOCIATED

DRUGS IN CLINICAL DEVELOPMENT
10 selected from 94

AZD9496 (AEL: -139.54)
- ESR1 wild-type target (AEL: -139.54)

SRN-927 (AEL: -139.54)
- ESR1 wild-type target (AEL: -139.54)

ELACESTRANT (AEL: -139.38)
- ESR1 wild-type target (AEL: -139.54)

AEE788 (AEL: -79.19)
- EGFR wild-type target (AEL: -79.19)

ALLITINIB (AEL: -79.19)
- EGFR wild-type target (AEL: -79.19)

AV-412 (AEL: -79.19)
- EGFR wild-type target (AEL: -79.19)

CI-1040 (AEL: -78.06)
- MAP2K1 wild-type target (AEL: -74.71)

RILOTUMUMAB (AEL: -68.51)
- MET wild-type target (AEL: -68.52)

AMG 208 (AEL: -68.51)
- MET wild-type target (AEL: -68.52)

AMG 337 (AEL: -68.51)
- MET wild-type target (AEL: -68.52)

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)

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

APC-R854K, CDH1-R124C, KDR-G671E, KLHL6-L258F, MERTK-R557W, MERTK-T795M, NOTCH2-R1332L, TNFRSF14-P167L, TP53-560-2A>T

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DETAILED MOLECULAR PROFILE

WILD TYPE GENES

ABL1, ACVR1B, AKT1, AKT2, AKT3, ALK, ALOX12B, AMER1, AR, ARAF, ARFRP1, ARID1A, ASXL1, ATM, ATR, ATRX, AURKA, AURKB, AXIN1, AXL, BAP1, BARD1, BCL2, BCL2L1, BCL2L2, BCL6, BCOR, BCORL1, BRAF, BRCA1, BRCA2, BRD4, BRIP1, BTG1, BTG2, BTK, CALR, CARD11, CASP8, CBFB, CBL, CCND1, CCND2, CCND3, CCNE1, CD22, CD274, CD70, CD79A, CD79B, CDC73, CDK12, CDK4, CDK6, CDK8, CDKN1A, CDKN1B, CDKN2A, CDKN2B, CDKN2C, CEBPA, CHEK1, CHEK2, CIC, CREBBP, CRKL, CSF1R, CSF3R, CTCF, CTNNA1, CTNNB1, CUL3, CUL4A, CXCR4, CYP17A1, DAXX, DDR1, DDR2, DIS3, DNMT3A, DOT1L, EED, EGFR, EMSY, EP300, EPHA3, EPHB1, EPHB4, ERBB2, ERBB3, ERBB4, ERCC4, ERG, ERRFI1, ESR1, EZH2, FAM46C, FANCA, FANCC, FANCG, FANCL, FAS, FBXW7, FGF10, FGF12, FGF14, FGF19, FGF23, FGF3, FGF4, FGF6, FGFR1, FGFR2, FGFR3, FGFR4, FH, FLCN, FLT1, FLT3, FOXL2, FUBP1, GABRA6, GATA3, GATA4, GATA6, GID4, GNA11, GNA13, GNAQ, GNAS, GRM3, GSK3B, H3F3A, HDAC1, HGF, HNF1A, HRAS, HSD3B1, ID3, IDH1, IDH2, IGF1R, IKBKE, IKZF1, INPP4B, IRF2, IRF4, IRS2, JAK1, JAK2, JAK3, JUN, KDM5A, KDM5C, KDM6A, KEAP1, KEL, KIT, KMT2A, KMT2D, KRAS, LTK, LYN, MAF, MAP2K1, MAP2K2, MAP2K4, MAP3K1, MAP3K13, MAPK1, MCL1, MDM2, MDM4, MED12, MEF2B, MEN1, MET, MITF, MKNK1, MLH1, MPL, MRE11A, MSH2, MSH3, MSH6, MST1R, MTAP, MTOR, MUTYH, MYC, MYCL, MYCN, MYD88, NBN, NF1, NF2, NFE2L2, NFKBIA, NKX2-1, NOTCH1, NOTCH3, NPM1, NRAS, NSD3, NT5C2, NTRK1, NTRK2, NTRK3, P2RY8, PALB2, PARK2, PARP1, PARP2, PARP3, PAX5, PBRM1, PDCD1, PDCD1LG2, PDGFRA, PDGFRB, PDK1, PIK3C2B, PIK3C2G, PIK3CA, PIK3CB, PIK3R1, PIM1, PMS2, POLD1, POLE, PPARG, PPP2R1A, PPP2R2A, PRDM1, PRKAR1A, PRKCI, PTCH1, PTEN, PTPN11, PTPRO, QKI, RAC1, RAD21, RAD51, RAD51B, RAD51C, RAD51D, RAD52, RAD54L, RAF1, RARA, RB1, RBM10, REL, RET, RICTOR, RNF43, ROS1, RPTOR, SDHA, SDHB, SDHC, SDHD, SETD2, SF3B1, SGK1, SMAD2, SMAD4, SMARCA4, SMARCB1, SMO, SNCAIP, SOCS1, SOX2, SOX9, SPEN, SPOP, SRC, STAG2, STAT3, STK11, SUFU, SYK, TBX3, TEK, TET2, TGFBR2, TIPARP, TNFAIP3, TSC1, TSC2, TYRO3, U2AF1, VEGFA, VHL, WHSC1, WT1, XPO1, XRCC2, ZNF217, ZNF703

FISH/CNA/IHC POSITIVE GENES

CDKN1A AMPLIFICATION PRESENCE, DAXX AMPLIFICATION PRESENCE, DDR1 AMPLIFICATION PRESENCE, INPP4B AMPLIFICATION PRESENCE, MYC AMPLIFICATION PRESENCE, NF1 LOSS PRESENCE, PIM1 AMPLIFICATION PRESENCE

FISH/CNA/IHC NEGATIVE GENES

ALK TRANSLOCATION ABSENCE, BCL2 TRANSLOCATION ABSENCE, BCR TRANSLOCATION ABSENCE, BRAF TRANSLOCATION ABSENCE, BRCA1 TRANSLOCATION ABSENCE, BRCA2 TRANSLOCATION ABSENCE, CD74 TRANSLOCATION ABSENCE, EGFR TRANSLOCATION ABSENCE, ETV4 TRANSLOCATION ABSENCE, ETV5 TRANSLOCATION ABSENCE, ETV6 TRANSLOCATION ABSENCE, EWSR1 TRANSLOCATION ABSENCE, EZR TRANSLOCATION ABSENCE, FGFR1 TRANSLOCATION ABSENCE, FGFR2 TRANSLOCATION ABSENCE, FGFR3 TRANSLOCATION ABSENCE, KIT TRANSLOCATION ABSENCE, KMT2A TRANSLOCATION ABSENCE, MSH2 TRANSLOCATION ABSENCE, MYB TRANSLOCATION ABSENCE, MYC TRANSLOCATION ABSENCE, NOTCH2 TRANSLOCATION ABSENCE, NTRK1 TRANSLOCATION ABSENCE, NTRK2 TRANSLOCATION ABSENCE, NUTM1 TRANSLOCATION ABSENCE, PDGFRA TRANSLOCATION ABSENCE, RAF1 TRANSLOCATION ABSENCE, RARA TRANSLOCATION ABSENCE, RET TRANSLOCATION ABSENCE, ROS1 TRANSLOCATION ABSENCE, RSPO2 TRANSLOCATION ABSENCE, SDC4 TRANSLOCATION ABSENCE, SLC34A2 TRANSLOCATION ABSENCE, TERC TRANSLOCATION ABSENCE, TERT TRANSLOCATION ABSENCE, TMPRSS2 TRANSLOCATION ABSENCE

MICROSATELLITE INSTABILITY

MSS

BIOMEDICAL INTERPRETATION

MOLECULAR ALTERATIONS

NF1 loss presence driver (AEL: 71.36, AF/TR: NA/NA),
MYC amplification presence driver (AEL: 64.70, AF/TR: NA/NA),
TP53-560-2A>T driver (AEL: 27.77, AF/TR: NA/NA),
PIM1 amplification presence driver (AEL: 9.96, AF/TR: NA/NA),
APC-R854K VUS in a driver gene (AEL: 4.74, AF/TR: NA/NA),
CDH1-R124C VUS in a driver gene (AEL: 3.13, AF/TR: NA/NA),
TNFRSF14-P167L VUS in a driver gene (AEL: 0.16, AF/TR: NA/NA),
KLHL6-L258F VUS in a driver gene (AEL: 0.05, AF/TR: NA/NA),
NOTCH2-R1332L VUS in a driver gene (AEL: 0.03, AF/TR: NA/NA),
MERTK-R557W variant of unknown significance (AEL: 0.00, AF/TR: NA /NA),
INPP4B amplification presence variant of unknown significance (AEL: 0.00, AF/TR: NA/NA),
DDR1 amplification presence variant of unknown significance (AEL: 0.00, AF/TR: NA/NA),
MERTK-T795M variant of unknown significance (AEL: 0.00, AF/TR: NA /NA),
DAXX amplification presence variant of unknown significance (AEL: 0.00, AF/TR: NA/NA),
CDKN1A amplification presence variant of unknown significance (AEL: 0.00, AF/TR: NA/NA),
KDR-G671E non-driver (AEL: -5.00, AF/TR: NA/NA)

TARGET GENES

CDK1 wild-type (AEL: 99.23),
- MYC amplification presence driver (AEL: 64.70) ;
- TP53-560-2A>T driver (AEL: 27.77) ;
- CDH1-R124C VUS in a driver (AEL: 3.13)

CHEK1 wild-type (AEL: 95.10),
- TP53-560-2A>T driver (AEL: 27.77) ;
- MYC amplification presence driver (AEL: 64.70)

MAP2K1 wild-type (AEL: 74.71),
- NF1 loss presence driver (AEL: 71.36)

BRD4 wild-type (AEL: 67.65),
- MYC amplification presence driver (AEL: 64.70)

CDK12 wild-type (AEL: 64.97),
- MYC amplification presence driver (AEL: 64.70)

PIM1 wild-type (AEL: 34.86),
- PIM1 amplification presence driver (AEL: 9.96)

AURKB wild-type (AEL: 32.23),
- TP53-560-2A>T driver (AEL: 27.77) ;
- CDH1-R124C VUS in a driver (AEL: 3.13)

CDK2 wild-type (AEL: 31.73),
- CDH1-R124C VUS in a driver (AEL: 3.13) ;
- TP53-560-2A>T driver (AEL: 27.77)

WEE1 wild-type (AEL: 31.57),
- TP53-560-2A>T driver (AEL: 27.77)

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DETAILED MOLECULAR PROFILE

ATR wild-type (AEL: 29.10),
- TP53-560-2A>T driver (AEL: 27.77)

CDK4 wild-type (AEL: 28.75),
- TP53-560-2A>T driver (AEL: 27.77)

RARG wild-type (AEL: 28.66),
- TP53-560-2A>T driver (AEL: 27.77)

PLK1 wild-type (AEL: 28.24),
- TP53-560-2A>T driver (AEL: 27.77)

PRKDC wild-type (AEL: 28.16),
- TP53-560-2A>T driver (AEL: 27.77)

CDK9 wild-type (AEL: 28.09),
- TP53-560-2A>T driver (AEL: 27.77)

MTOR wild-type (AEL: 11.26),
- MYC amplification presence driver (AEL: -64.70) ;
- NF1 loss presence driver (AEL: 71.36) ;
- CDH1-R124C VUS in a driver (AEL: 3.13)

COX2 wild-type (AEL: 8.21),
- APC-R854K VUS in a driver (AEL: 4.74)

ROS1 wild-type (AEL: 5.63),
- CDH1-R124C VUS in a driver (AEL: 3.13)

PIK3CB wild-type (AEL: 4.18),
- CDH1-R124C VUS in a driver (AEL: 3.13)

ALK wild-type (AEL: 4.18),
- CDH1-R124C VUS in a driver (AEL: 3.13)

PIK3CD wild-type (AEL: 4.18),
- CDH1-R124C VUS in a driver (AEL: 3.13)

AURKA wild-type (AEL: 4.18),
- CDH1-R124C VUS in a driver (AEL: 3.13)

PIK3CG wild-type (AEL: 4.18),
- CDH1-R124C VUS in a driver (AEL: 3.13)

AURKC wild-type (AEL: 4.18),
- CDH1-R124C VUS in a driver (AEL: 3.13)

FGFR1 wild-type (AEL: 3.64),
- CDH1-R124C VUS in a driver (AEL: 3.13)

SRC wild-type (AEL: 3.64),
- CDH1-R124C VUS in a driver (AEL: 3.13)

JAK3 wild-type (AEL: 3.64),
- CDH1-R124C VUS in a driver (AEL: 3.13)

NPY5R wild-type (AEL: 3.64),
- CDH1-R124C VUS in a driver (AEL: 3.13)

RET wild-type (AEL: 3.64),
- CDH1-R124C VUS in a driver (AEL: 3.13)

JAK2 wild-type (AEL: 3.64),
- CDH1-R124C VUS in a driver (AEL: 3.13)

NTRK1 wild-type (AEL: 3.64),
- CDH1-R124C VUS in a driver (AEL: 3.13)

BCL2 wild-type (AEL: 3.64),
- CDH1-R124C VUS in a driver (AEL: 3.13)

PDGFRA wild-type (AEL: 3.64),
- CDH1-R124C VUS in a driver (AEL: 3.13)

PDGFRB wild-type (AEL: 3.64),
- CDH1-R124C VUS in a driver (AEL: 3.13)

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DETAILED MOLECULAR PROFILE

	JAK1 wild-type (AEL: 3.64), • CDH1-R124C VUS in a driver (AEL: 3.13) ABL1 wild-type (AEL: 3.64), • CDH1-R124C VUS in a driver (AEL: 3.13) GBF1 wild-type (AEL: 3.64), • CDH1-R124C VUS in a driver (AEL: 3.13) HMGCR wild-type (AEL: 3.63) • CDH1-R124C VUS in a driver (AEL: 3.13)

BIOMEDICAL INTERPRETATION

Functional interpretation of the detected alterations:

The detected genetic alterations were classified into the following categories by the Molecular Treatment Calculator (MTC), based on their functional consequences and their contribution to tumor formation (gains selective growth advantage compared to healthy cells): driver, variant of unknown significance in a driver gene (VUS, driver gene), non-confirmed driver, biomarker, variant of unknown significance (VUS), non-driver.

The algorithm calculates with positive score, in case of scientific evidence describing that a mutation or a gene contributes to cancer formation. It calculates with negative score, in case of scientific evidence describing that a mutation or a gene does not contribute to cancer formation.
The classification of a given variant is based on evidence describing the given alteration, the mutant gene or other specific mutations of the same gene as driver alterations. The algorithm summarizes and biases the related evidence and calculates the aggregated evidence level (AEL).

Driver: The algorithm classifies variants as drivers if there is available matching evidence in the database (describing the detected alteration) and it has a positive AEL.

Variant of unknown significance in a driver gene (VUS in a driver gene): In case of these variants there is no available matching evidence. The classification is based on evidence describing the mutant gene or other specific mutations of the same gene as drivers.

VUS (variant of unknown significance): There is no available evidence regarding the given alteration, the mutant gene or other specific mutations of the same gene.

Biomarker: These alterations are associated with the efficacy of a targeted drug based on matching scientific evidence (describing the detected alteration), but it does not fulfill the criteria to be a driver.

Conflicting driver: In case of these variants the number and level of the available matching evidence describing the detected alteration as a driver is limited.

Non-driver: The AEL values of these variants are negative.

NF1 copy number loss

The NF1 gene is a tumor suppressor encoding neurofibromin, a RAS GTPase-activating protein that inhibits RAS activity and the MAPK pathway. Loss of NF1 was found to be associated with RAS activation and MEK dependence.
Based on preclinical evidence, the mTOR inhibitor rapamycin (sirolimus) (1, 2) and the MEK inhibitor trametinib (3) efficiently inhibited the growth of NF1-deficient cells. In a case study, a melanoma patient with NF1 mutation responded to trametinib treatment (4).
The MEK1/2 inhibitor SELUMETINIB is approved by the FDA for pediatric patients (aged 2 years (FDA) or 3 years (EMA) and above) with neurofibromatosis type 1 (caused by germline NF1 mutation) associated symptomatic, inoperable plexiform neurofibromas.

MTOR inhibitors (including the registered EVEROLIMUS, TEMSIROLIMUS, SIROLIMUS and METFORMIN) and MEK inhibitors (including the registered TRAMETINIB, COBIMETINIB, BINIMETINIB, and the FDA-approved SELUMETINIB), and CABOZANTINIB can be mentioned in positive association with the molecular profile (5-9).
According to clinical evidence, NF1 deficiency can lead to resistance to EGFR inhibitors (10, 11).

References:

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BIOMEDICAL INTERPRETATION

(1) Johannessen CM et al., TORC1 is essential for NF1-associated malignancies. Curr Biol. 2008 Jan 8;18(1):56-62. PMID: 18164202

(2) Johannessen CM et al., The NF1 tumor suppressor critically regulates TSC2 and mTOR. Proc Natl Acad Sci U S A. 2005 Jun 14;102(25):8573-8. Epub 2005 Jun 3. Erratum in: Proc Natl Acad Sci U S A. 2005 Nov 1;102(44):16119. PMID: 15937108

(3) Nissan MH et al., Loss of NF1 in cutaneous melanoma is associated with RAS activation and MEK dependence. Cancer Res. 2014 Apr 15;74(8):2340-50. Epub 2014 Feb 27. PMID: 24576830

(4) Py C et al., Response of NF1-Mutated Melanoma to an MEK Inhibitor, JCO Precision Oncology 2018 :2, 1-11

(5) Nissan MH et al., Loss of NF1 in cutaneous melanoma is associated with RAS activation and MEK dependence. Cancer Res. 2014 Apr 15;74(8):2340-50. Epub 2014 Feb 27. PMID: 24576830

(6) Gross AM et al., SPRINT: Phase II study of the MEK 1/2 inhibitor selumetinib (AZD6244, ARRY-142886) in children with neurofibromatosis type 1 (NF1) and inoperable plexiform neurofibromas (PN). Journal of Clinical Oncology. May 2018;36(15_suppl):10503-10503. doi: 10.1200/JCO.2018.36.15_suppl.10503

(7) O'Sullivan Coyne GH et al., Phase II trial of the MEK 1/2 inhibitor selumetinib (AZD6244, ARRY-142886 Hydrogen Sulfate) in adults with neurofibromatosis type 1 (NF1) and inoperable plexiform neurofibromas (PN). Journal of Clinical Oncology. 2020;38(15_suppl):3612-3612. doi: 10.1200/JCO.2020.38.15_suppl.3612.

(8) Fisher MJ et al., Cabozantinib for neurofibromatosis type 1-related plexiform neurofibromas: a phase 2 trial. Nat Med. 2021 Jan;27(1):165-173. Epub 2021 Jan 13. PMID: 33442015

(9) Jessen WJ et al., MEK inhibition exhibits efficacy in human and mouse neurofibromatosis tumors. J Clin Invest. 2013 Jan;123(1):340-7. Epub 2012 Dec 10. PMID: 23221341

(10) Mei Z et al., SMAD4 and NF1 mutations as potential biomarkers for poor prognosis to cetuximab-based therapy in Chinese metastatic colorectal cancer patients. BMC Cancer. 2018 Apr 27;18(1):479. PMID: 29703253

(11) de Bruin EC et al., Reduced NF1 expression confers resistance to EGFR inhibition in lung cancer. Cancer Discov. 2014 May;4(5):606-19. Epub 2014 Feb 17. PMID: 24535670

MYC amplification

Amplification of the oncogene MYC (1-3), which most frequently occurs in different tumor types, can contribute to tumorigenesis (4).

Targets in positive association include CDK1 (5), CDK12 (6), CHEK1 (7) and BET (8). MYC amplification can cause resistance to anti-estrogens, although clinical results are controversial (9, 10).

MYC activation sensitizes cells to dasatinib treatment and causes resistance to PI3K/AKT/mTOR pathway inhibitors (11). According to a study amplification of the MYC gene plays role in the primary resistance to ALK inhibitors in non-small cell lung cancer (12).

In a preclinical study, MYC overexpression increased the expression of glycolytic enzymes in glioblastoma cells. Small-molecule inhibitors of glycolysis, like NAMPT inhibitors, were selectively cytotoxic to MYC/MYCN-amplified patient-derived glioblastoma models (13).

MYC amplification might contribute to resistance to PD-1/PD-L1-targeted immunotherapy (14).

References:

(1) Nesbit CE et al., MYC oncogenes and human neoplastic disease. Oncogene. 1999 May 13;18(19):3004-16. Review. PubMed PMID: 10378696

(2) Meyer N & Penn LZ. Reflecting on 25 years with MYC. Nat Rev Cancer. 2008 Dec;8(12):976-90. PMID: 19029958

(3) Dang CV. MYC on the path to cancer. Cell. 2012 Mar 30;149(1):22-35. PMID: 22464321

(4) Beroukhim R et al., The landscape of somatic copy-number alteration across human cancers. Nature. 2010 Feb 18;463(7283):899-905. PMID: 20164920

(5) Goga A et al., Inhibition of CDK1 as a potential therapy for tumors over-expressing MYC. Nat Med. 2007 Jul;13(7):820-7. PubMed PMID: 17589519

(6) Lui GYL et al., CDK12: an emerging therapeutic target for cancer. J Clin Pathol. 2018 Nov;71(11):957-962. Review. PubMed PMID: 30104286

(7) Sen T et al., CHK1 Inhibition in Small-Cell Lung Cancer Produces Single-Agent Activity in Biomarker-Defined Disease Subsets and Combination Activity with Cisplatin or Olaparib. Cancer Res. 2017 Jul 15;77(14):3870-3884. PubMed PMID: 28490518

(8) Mertz JA et al., Targeting MYC dependence in cancer by inhibiting BET bromodomains. Proc Natl Acad Sci U S A. 2011 Oct 4;108(40):16669-74. PubMed PMID: 21949397

(9) Green AR et al., MYC functions are specific in biological subtypes of breast cancer and confers resistance to endocrine therapy in luminal tumours. Br J Cancer. 2016 Apr 12;114(8):917-28. Epub 2016 Mar 8. PubMed PMID: 26954716

(10) Butt AJ et al., Downstream targets of growth factor and oestrogen signalling and endocrine resistance: the potential roles of c-Myc, cyclin D1 and cyclin E. Endocr Relat Cancer. 2005 Jul;12 Suppl 1:S47-59. Review. PubMed PMID: 16113099

(11) Martins MM et al., Linking tumor mutations to drug responses via a quantitative chemical-genetic interaction map. Cancer Discov. 2015 Feb;5(2):154-67. PMID: 25501949

(12) Rihawi K et al., MYC Amplification as a Potential Mechanism of Primary Resistance to Crizotinib in ALK-Rearranged Non-Small Cell Lung Cancer: A Brief Report. Transl Oncol. 2019 Jan;12(1):116-121. Epub 2018 Oct 2. PMID: 30290287

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BIOMEDICAL INTERPRETATION

(13) Tateishi K,et al. Myc-Driven Glycolysis Is a Therapeutic Target in Glioblastoma. Clin Cancer Res. 2016 Sep 1;22(17):4452-65. doi: 10.1158/1078-0432.CCR-15-2274. PMID: 27076630.

(14) Forschner A et al., MDM2, MDM4 and EGFR Amplifications and Hyperprogression in Metastatic Acral and Mucosal Melanoma. Cancers (Basel). 2020 Feb 26;12(3) PubMed PMID: 32110946.

TP53-560-2A>T

TP53-560-2A>T is a loss of function mutation according to the scientific literature.

References:

(1) Pollock NC, et al. --Differences in Somatic TP53 Mutation Type in Breast Tumors by Race and Receptor Status. null. doi: 10.21203/rs.3.rs-268719/v2

TP53 loss-of-function mutation - targets

The p53 tumor suppressor encoded by the TP53 gene functions to block the cell cycle or to initiate apoptosis in response to cellular stress (e.g. genomic damage).

In the presence of loss of function TP53 alterations CHEK1 (1-3), ATR (4), PLK1 (5), WEE1 (6) and CDK (7, 8) inhibitors can be mentioned in positive association with the molecular profile. The CDK inhibitors PALBOCICLIB, RIBOCICLIB, and ABEMACICLIB are approved in breast cancer indication.

In addition, in the presence of non-functional p53 protein, the small molecule eprenetapopt (APR-246) can also be mentioned as a potential therapeutic agent with anti-tumor activity (9). The MQ (methylene quinuclidinone) prodrug APR-246 is a methylated structural analog of PRIMA-1 (p53 reactivation and induction of massive apoptosis). By binding to the cysteine residues of the mutant p53 protein, MQ induces its destabilization, thereby reconstituting endogenous p53 activity. In addition, APR-246 also might have chemoradiotherapy sensitizing effect in tumor cells, through restoring p53 activity and induction of oxidative stress (9, 10). APR-246 is currently tested in phase I/II trials in hematologic and solid malignancies. The FDA granted fast track designation to eprenetapopt in TP53-mutant acute myeloid leukemia (AML) or myelodysplastic syndromes (MDS) indications.

According to preclinical data, certain TP53 mutations (e.g. R175H, R248G, R273H, and C135F), may cause resistance to the chemotherapeutic drugs cisplatin, doxorubicin, paclitaxel, etoposide, and carboplatin.

In a study, the combination of ramucirumab plus paclitaxel achieved better overall survival in gastric cancer patients with loss of function TP53 mutations, compared with chemotherapy (11).

In patients with different types of TP53 mutant advanced cancer median PFS on standard systemic therapy was significantly longer with bevacizumab-containing regimens as compared to non-bevacizumab containing regimen (11.0 vs. 4.0 months), whereas no difference was seen in TP53 wild-type cases (12).

In a study, TP53 mutations were associated with improved PFS and OS in endometrial cancer patients who received chemotherapy combined with bevacizumab as compared to chemotherapy plus temsirolimus (PFS: HR 0.48; OS: HR 0.61) (13).

References:

(1) Dai Y et al., The novel Chk1 inhibitor MK-8776 sensitizes human leukemia cells to HDAC inhibitors by targeting the intra-S checkpoint and DNA replication and repair. Mol Cancer Ther. 2013 Jun;12(6):878-89. PubMed PMID: 23536721

(2) Chen Z et al., Selective Chk1 inhibitors differentially sensitize p53-deficient cancer cells to cancer therapeutics. Int J Cancer. 2006 Dec 15;119 (12):2784-94. PubMed PMID: 17019715

(3) Koniaras K et al., Inhibition of Chk1-dependent G2 DNA damage checkpoint radiosensitizes p53 mutant human cells. Oncogene. 2001 Nov 8; 20(51):7453-63. PubMed PMID: 11709716

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

(5) Degenhardt Y et al., Sensitivity of cancer cells to Plk1 inhibitor GSK461364A is associated with loss of p53 function and chromosome instability. Mol Cancer Ther. 2010 Jul;9(7):2079-89. PubMed PMID: 20571075

(6) Hirai H et al., Small-molecule inhibition of Wee1 kinase by MK-1775 selectively sensitizes p53-deficient tumor cells to DNA-damaging agents. Mol Cancer Ther. 2009 Nov;8(11):2992-3000. PubMed PMID: 19887545

(7) Bhattacharya S et al., Cyclin-dependent kinases regulate apoptosis of intestinal epithelial cells. Apoptosis. 2014 Mar;19(3):451-66. PubMed PMID: 24242917

(8) Zou X et al., Cdk4 disruption renders primary mouse cells resistant to oncogenic transformation, leading to Arf/p53-independent senescence. Genes Dev. 2002 Nov 15;16(22):2923-34. PubMed PMID: 12435633

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BIOMEDICAL INTERPRETATION

(9) Green JA, Von Euler M, Abrahmsen LB. Restoration of conformation of mutant p53. Ann Oncol. 2018 May 1;29(5):1325-1328. doi: 10.1093 /annonc/mdy057. PMID: 29462239
(10) Lambert JM et al., PRIMA-1 reactivates mutant p53 by covalent binding to the core domain. Cancer Cell. 2009 May 5;15(5):376-88. doi: 10.1016/j.ccr.2009.03.003. PMID: 19411067
(11) Graziano F et al. TP53 Mutation Analysis in Gastric Cancer and Clinical Outcomes of Patients with Metastatic Disease Treated with Ramucirumab/Paclitaxel or Standard Chemotherapy. Cancers (Basel). 2020 Jul 24;12(8): PubMed PMID: 32722340
(12) Said R et al. P53 mutations in advanced cancers: clinical characteristics, outcomes, and correlation between progression-free survival and bevacizumab-containing therapy. Oncotarget. 2013 May;4(5):705-14. PubMed PMID: 23670029
(13) Leslie KK et al. Mutated p53 portends improvement in outcomes when bevacizumab is combined with chemotherapy in advanced/recurrent endometrial cancer: An NRG Oncology study. Gynecol Oncol. 2021 Apr;161(1):113-121. PubMed PMID: 33541735

TP53 mutant ovarian cancer

In a preclinical study the compound APR-246 sensitized TP53 mutated platinum resistant ovarian cancer cells to cisplatin (1). In a phase Ib study, APR-246 in combination with carboplatin and pegylated liposomal doxorubicin showed efficacy in platinum sensitive relapsed high grade serous ovarian cancer (HGSOC). Overall response rate was 17/23 (74%) in the total cohort, and 11/16 (69%) in the partially platinum sensitive group (2).
In a phase II study palbociclib was well tolerated and resulted in 30% progression-free survival (PFS) rate at 6 months among recurrent, previously treated ovarian cancer patients (3). Ribociclib + letrozole combinational therapy resulted in 50% progression-free survival rate at 12 weeks in ER positive ovarian cancer patients in a phase II study (4).
Olaparib maintenance treatment resulted in increased overall survival time in BRCA mutant and TP53 mutant patients, but not in the BRCA and TP53 wild-type group (5).

References:

(1) Fransson A et al., Strong synergy with APR-246 and DNA-damaging drugs in primary cancer cells from patients with TP53 mutant High-Grade Serous ovarian cancer. J Ovarian Res. 2016 May 14;9(1):27. PubMed PMID: 27179933
(2) Gourley C et al., PISARRO: A EUTROC phase Ib study of APR-246 in combination with carboplatin (C) and pegylated liposomal doxorubicin (PLD) in platinum sensitive relapsed high grade serous ovarian cancer (HGSOC). Journal of Clinical Oncology. 2016;34(15_suppl)5571-5571. doi: 10.1200/JCO.2016.34.15_suppl.5571.
(3) Konecny GE et al., A multicenter open-label phase II study of the efficacy and safety of palbociclib a cyclin-dependent kinases 4 and 6 inhibitor in patients with recurrent ovarian cancer. Journal of Clinical Oncology. 2016 May;34(15_suppl):5557-5557. doi: 10.1200/JCO.2016.34.15 _suppl.5557.
(4) Colon-Otero G et al., Results of a phase 2 trial of ribociclib and letrozole in patients with either relapsed estrogen receptor (ER)-positive ovarian cancers or relapsed ER-positive endometrial cancers. Journal of Clinical Oncology. 2019;37(15_suppl):5510-5510. doi: 10.1200/JCO. 2019.37.15_suppl.5510.
(5) BUENO, A. Martinez, et al. Disruptive mutations in TP53 associate with survival benefit in a PARPi trial in ovarian cancer. Annals of Oncology, 2017, 28: v626.

PIM1 amplification

The PIM1 proto-oncogene is a serine/threonine kinase, which is a member of the constitutively active PIM kinase family (1).
In a study K00135 (PIM1-specific small molecular inhibitor) impaired the survival of gastric cancer cell lines with high PIM1 expression levels (2).
According to a study, glioblastoma multiforme (GBM) patients with short overall survival showed a significantly higher PIM1 expression compared with GBM patients who lived longer than the median (3).
The PIM inhibitor SGI-1776 induced apoptosis and reduced proliferation of several types of cancer cell in preclinical studies (4-6).

References:

(1) Linowes BA et al. Pim1 permits generation and survival of CD4+ T cells in the absence of c cytokine receptor signaling. Eur J Immunol. 2013 Sep;43(9):2283-94. doi: 10.1002/eji.201242686. Epub 2013 Jan 21. PubMed PMID: 23712827
(2) Yan B et al. Clinical and therapeutic relevance of PIM1 kinase in gastric cancer. Gastric Cancer. 2012 Apr;15(2):188-97. doi: 10.1007/s10120-011-0097-2. Epub 2011 Jan 13. PubMed PMID: 21993851.
(3) Herzog S et al. Pim1 kinase is upregulated in glioblastoma multiforme and mediates tumor cell survival. Neuro Oncol. 2015 Feb;17(2):223-42. doi: 10.1093/neuonc/nou216. Epub 2014 Jan 25. PubMed PMID: 25155357
(4) Leung MS et al. Anti-tumour effects of PIM kinase inhibition on progression and chemoresistance of hepatocellular carcinoma. J Pathol. 2020 Sep;252(1):65-76. doi: 10.1002/path.5492. Epub 2020 Jan 31. PubMed PMID: 32558942.
(5) Chen LS et al. Pim kinase inhibitor, SGI-1776, induces apoptosis in chronic lymphocytic leukemia cells. Blood. 2009 Nov 05;114(19):4150-7. doi: 10.1182/blood-2009-03-212852. Epub 2009 Jan 04. PubMed PMID: 19734450

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BIOMEDICAL INTERPRETATION

(6) Xie J, Bai J. SGI-1776, an imidazo pyridazine compound, inhibits the proliferation of ovarian cancer cells by inactivating Pim-1. Zhong Nan Da Xue Xue Bao Yi Xue Ban. 2014 Jul;39(7):649-57. doi: 10.11817/j.issn.1672-7347.2014.07.001. PubMed PMID: 25080901.

INPP4B amplification

INPP4B is one of the enzymes involved in phosphatidylinositol signaling pathways. It is a dual cancer driver with tumor suppressor function in several tumor types and oncogenic role in others (1). Its activation has been shown to contribute to tumorigenesis in colorectal cancer, gall bladder cancer, and pancreatic cancer (2-4). INPP4B amplification is not known to be associated with the efficacy of targeted compounds.

References:

(1) Hamila SA, et al. The INPP4B paradox: Like PTEN, but different. Adv Biol Regul. 2021 Jun 16;82:100817. doi: 10.1016/j.jbior.2021.100817. Epub ahead of print. PMID: 34216856.

(2) Wu Y, et al. Expression and functional characterization of INPP4B in gallbladder cancer patients and gallbladder cancer cells. BMC Cancer. 2021 Apr 20;21(1):433. doi: 10.1186/s12885-021-08143-6. PMID: 33879096.

(3) Zhai S, et al. INPP4B As A Prognostic And Diagnostic Marker Regulates Cell Growth Of Pancreatic Cancer Via Activating AKT. Onco Targets Ther. 2019 Oct 9;12:8287-8299. doi: 10.2147/OTT.S223221. PMID: 31632078.

(4) Guo ST, et al. INPP4B is an oncogenic regulator in human colon cancer. Oncogene. 2016 Jun 9;35(23):3049-61. doi: 10.1038/onc.2015.361. Epub 2015 Sep 28. PMID: 26411369.

DDR1 amplification

DDR1 (Discoidin Domain Receptor Tyrosine Kinase 1) is a collagen-activated tyrosine kinase receptor. It regulates cell attachment to the extracellular matrix, remodeling of the extracellular matrix, cell migration, differentiation, survival and cell proliferation. It activates ERK pathway (1). DDR1 mutations and overexpression were reported to be associated with multiple tumor types (2). DDR1 has a complex role in breast cancer. Although a number of studies have reported that DDR1 promotes apoptosis and inhibits migration in breast carcinoma, it has also been reported to be associated with tumor cell survival, chemoresistance to genotoxic drugs and the facilitation of invasion (3).

IMATINIB, NILOTINIB, and DASATINIB are kinase inhibitors with DDR1 inhibitory capacity. They have not been tested specifically in DDR1 amplified tumor yet.

References:

(1) El Azreq et al. Discoidin domain receptor 1 promotes Th17 cell migration by activating the RhoA/ROCK/MAPK/ERK signaling pathway. Oncotarget. 2016 Jul 19;7(29):44975-44990. doi: 10.18632/oncotarget.10455. PubMed PMID: 27391444.

(2) Ford CE, et al. Expression and mutation analysis of the discoidin domain receptors 1 and 2 in non-small cell lung carcinoma. Br J Cancer. 2007 Mar 12;96(5):808-14. Epub 2007 Feb 13. PubMed PMID: 17299390.

(3) Jing H et al., Discoidin domain receptor 1: New star in cancer-targeted therapy and its complex role in breast carcinoma. Oncol Lett. 2018 Mar; 15(3):3403-3408. PMID: 29467865

DAXX amplification

DAXX (death-domain associated protein 6) is a transcriptional co-regulator that is a repressor of several transcription factors (including p53, SMAD4, AR). Its overexpression has also been described in association with several tumor types (1,2). It is a dual cancer driver with tumor suppressor function in several tumor types and oncogenic role in others (3).

References:

(1) Lin GJ et al., Daxx and TCF4 interaction links to oral squamous cell carcinoma growth by promoting cell cycle progression via induction of cyclin D1 expression. Clin Oral Investig. 2016 Apr;20(3):533-40. PMID: 26205068

(2) Tsourlakis MC et al., Overexpression of the chromatin remodeler death-domain-associated protein in prostate cancer is an independent predictor of early prostate-specific antigen recurrence. Hum Pathol. 2013 Sep;44(9):1789-96. PMID: 23642739

(3) Shi Y, et al. DAXX, as a Tumor Suppressor, Impacts DNA Damage Repair and Sensitizes BRCA-Proficient TNBC Cells to PARP Inhibitors. Neoplasia. 2019 Jun;21(6):533-544. doi: 10.1016/j.neo.2019.04.001. Epub 2019 Apr 24. PMID: 31029033.

CDKN1A amplification

CDKN1A (cyclin-dependent kinase inhibitor 1), also known as p21, which is activated by p53, is thought to play a role in the inhibition of p53-induced cell proliferation and apoptosis. Accordingly, CDKN1A loss of function has been described in the context of several tumor types, its amplification being the second most common type of CDKN1A alteration (in 0.12% of tumors) (1), however, the significance of this alteration in tumorigenesis is unclear.

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BIOMEDICAL INTERPRETATION

References:

(1) The AACR Project GENIE Consortium. AACR Project GENIE: powering precision medicine through an international consortium. Cancer Discovery. 2017 Aug;7(8):818-831. PMID: 28572459 Dataset Version 4.

Targeted therapies registered in ovarian cancer indication regardless of the molecular profile

BEVACIZUMAB is an approved VEGFR inhibitor for epithelial, fallopian tube or primary peritoneal ovarian cancer patients. In the same histology, the combination of BEVACIZUMAB and OLAPARIB is also approved as a first-line maintenance treatment for homologous repair deficient (HRD) patients who responded to platinum-based chemotherapy.

In recurrent platinum-sensitive ovarian cancer patients bevacizumab + carboplatin + gemcitabine increased the median progression-free survival (PFS) and the response rate compared to placebo + carboplatin + gemcitabine (12.4 vs. 8.4 months and 78.5% vs. 8.4%) (1). No significant improvement was observed in median overall survival (OS) (33.6 vs.32.9 months) (2). Bevacizumab + carboplatin + pemetrexed combination, bevacizumab maintenance and secondary cytoreductive surgery showed a benefit in OS as well (3). In platinum-resistant patients chemotherapy + bevacizumab treatment resulted in 6.7 months median PFS, 16.6 months median OS and 27.3% response rate, while in patients receiving chemotherapy alone median PFS was 3,4 months, median OS was 13.3 months and the response rate was 11.8% (4).

In a phase I study, platinum-resistant ovarian cancer patients received mirvetuximab soravtansine (folate receptor alpha (FR)-targeting antibody-drug conjugate) + bevacizumab treatment. The objective response rate (ORR) was 39% (complete response rate: 5/66, partial response rate: 21 /66), and the median PFS was 6.9 months (5).

OLAPARIB, NIRAPARIB and RUCAPARIB are PARP inhibitors approved as a maintenance treatment of patients with platinum sensitive ovarian cancer. For BRCA mutant of homologous repair deficient patients, these compounds are indicated in further treatment lines.

In a phase III study, niraparib improved PFS compared to placebo in advanced ovarian cancer who were in a complete or partial response to first-line platinum-based chemotherapy. Median PFS in the homologous recombination deficient population either receiving niraparib or placebo was 21.9 vs 10.4 months, and in the overall population 13.8 vs 8.2 months, respectively (6). In a phase III study of niraparib maintenance treatment, the median PFS was longer in the niraparib group than in the placebo group in BRCA mutant and BRCA wild-type groups as well. In the BRCA mutant subgroup the median PFS was 21.0 months for niraparib and 5.5 months for placebo. In the BRCA wild-type subgroups the median PFS was 9.3 months for niraparib and 3.9 months for placebo (7). In an open-label, single-arm phase II study (QUADRA), clinical activity of niraparib monotherapy was observed as the fourth or later line of therapy in patients with heavily pretreated ovarian cancer, especially in patients with HRD platinum-sensitive disease (8).

In a phase II study patients were treated with maintenance olaparib or placebo regardless of BRCA status. The estimated median PFS was 8.4 months and 4.8 months in the olaparib and placebo arms, respectively (9).

In a phase III clinical trial ovarian cancer patients received olaparib plus bevacizumab or placebo plus bevacizumab treatment. The median PFS was 22.1 months with olaparib plus bevacizumab and 16.6 months with placebo plus bevacizumab. In patients with HRD positive, BRCA mutant tumors the median PFS was longer in the olaparib group (37.2 vs. 17.7 months). The median PFS was also longer in patients with HRD-positive tumors that did not have BRCA mutations (28.1 vs. 16.6 months) (10).

In the phase III trial of rucaparib maintenance treatment, median PFS in patients with a BRCA-mutant carcinoma was 16.6 months in the rucaparib group versus 5.4 months in the placebo group. In patients with a homologous recombination deficient carcinoma, it was 13.6 months versus 5.4 months. In the intention-to-treat population, it was 10.8 months versus 5.4 months (11).

Based on a meta-analysis summarizing the results of 12 phase II/III studies, PARP inhibition significantly improved PFS in primary and recurrent ovarian cancer patients regardless of BRCA status, and HRD positive patients progressed significantly later after PARPi administration (12).

60% of the epithelial ovarian tumors overexpress EGFR. Erlotinib maintenance following first line therapy did not increase the PFS of ovarian cancer patients compared to observation (13). In previously treated ovarian cancer patients erlotinib monotherapy resulted in 6% response rate in a phase II trial (14).

The activation of KRAS, NRAS, HRAS, BRAF, MET or HER2 genes may cause resistance to EGFR inhibitor therapy (15, 16). Further studies have shown that mutations in other participants of the MAPK and PI3K signaling pathways such as PIK3CA and PTEN may also play a role in the development of resistance (17, 18). The most common mutations in ovarian tumors are KRAS - 11% (18), BRAF - 11% (19), PIK3CA - 12% (20), PTEN - 20% (19) and HER2 amplification - 18% (21).

In a phase II study aflibercept + docetaxel resulted in 54% response rate among recurrent epithelial ovarian cancer patients (22). Aflibercept monotherapy did not increase the OS time but mean time to repeat paracentesis was significantly longer with aflibercept than with placebo (23). Nintedanib + chemotherapy resulted in longer PFS than placebo + chemotherapy (18.3 vs. 16.6 hónap). Pazopanib therapy resulted in 15% response rate among epithelial ovarian cancer patients (24).

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Cediranib (VEGFR inhibitor) resulted in improved PFS in a phase III trial among recurrent platinum-sensitive ovarian cancer patients, but it increased toxicity as well (25). In a phase III trial, the combination of cediranib and olaparib failed to improve median PFS compared to chemotherapy in patients with platinum-sensitive recurrent ovarian cancer (26).
Trebananib + paclitaxel resulted in improved PFS compared to placebo + paclitaxel (27). Trebananib + pegylated liposomal doxorubicin resulted in increased response rate compared to placebo + pegylated liposomal doxorubicin, but median PFS was not improved (28).

In a preclinical study, the combination of PARP+ATR inhibition resulted in complete therapeutic response and tumor regression in BRCA mutant, PARPi- and platinum-resistant xenograft models (29).

Mirvetuximab soravtansine (MIRV), a folate receptor alpha (FR-alpha)-targeting antibody-drug conjugate (ADC), in combination with carboplatin and bevacizumab resulted in ORR of 81%, a median duration of response (DOR) of 10.7 months, and median PFS of 12.0 months, with a manageable adverse event profile in patients with recurrent platinum sensitive ovarian cancer (30).

In a phase Ib/II study, rebastinib and paclitaxel treatment resulted in an ORR of 29% and a CBR (clinical benefit rate) of 82% (5 partial responses (PR) and 9 case of stable disease (SD), n=17) at 8 weeks in paclitaxel/carboplatin pretreated (1 prior regimen) in advanced or metastatic platinum-resistant ovarian cancer patients (31).

Niraparib + dostarlimab treatment resulted in an ORR of 18%, with a disease control rate (DCR) of 65% in platinum-resistant ovarian cancer patients, including 3 (5%) with confirmed complete responses (CR), 8 (13%) with confirmed PRs, 28 (47%) with SD, and 20 (33%) with progressive disease (PD) (32).

In a phase III trial, gene therapy with VB-111 (ofranergene obadenovec), which has antiangiogenic effect and it can induce a tumor-directed viral immune response, in patients with heavily pretreated recurrent platinum-resistant epithelial ovarian cancer, showed cumulative response rate of 53% in the first 60 evaluable patients, the study is currently ongoing (33).

References:
(1) Aghajanian C et al., OCEANS: a randomized, double-blind, placebo-controlled phase III trial of chemotherapy with or without bevacizumab in patients with platinum-sensitive recurrent epithelial ovarian, primary peritoneal, or fallopian tube cancer. J Clin Oncol. 2012 Jun 10;30(17):2039-45. PubMed PMID: 22529265
(2) Aghajanian C et al., Final overall survival and safety analysis of OCEANS, a phase 3 trial of chemotherapy with or without bevacizumab in patients with platinum-sensitive recurrent ovarian cancer. Gynecol Oncol. 2015 Oct;139(1):10-6. PubMed PMID: 26271155
(3) Coleman RL et al., A phase III randomized controlled clinical trial of carboplatin and paclitaxel alone or in combination with bevacizumab followed by bevacizumab and secondary cytoreductive surgery in platinum-sensitive, recurrent ovarian, peritoneal primary and fallopian tube cancer (Gynecologic Oncology Group 0213). Gynecologic Oncology. 2015 Apr 1;137:3–4.
(4) Pujade-Lauraine E et al., Bevacizumab combined with chemotherapy for platinum-resistant recurrent ovarian cancer: The AURELIA open-label randomized phase III trial. J Clin Oncol. 2014 May 1;32(13):1302-8. PubMed PMID: 24637997
(5) O'Malley DM et al. Phase Ib study of mirvetuximab soravtansine, a folate receptor alpha (FR)-targeting antibody-drug conjugate (ADC), in combination with bevacizumab in patients with platinum-resistant ovarian cancer. Gynecol Oncol. 2020 May;157(2):379-385. doi: 10.1016/j.ygyno.2020.01.037. Epub 2020 Sep 18. PubMed PMID: 32081463.
(6) González-Martín A et al., Niraparib in Patients with Newly Diagnosed Advanced Ovarian Cancer. N Engl J Med. 2019 Dec 19;381(25):2391-2402. doi: 10.1056/NEJMoa1910962. Epub 2019 Sep 28. PMID: 31562799
(7) Mirza MR et al., Niraparib Maintenance Therapy in Platinum-Sensitive, Recurrent Ovarian Cancer. N Engl J Med. 2016 Dec 1;375(22):2154-2164. PubMed PMID: 27717299
(8) Moore KN et al. Niraparib monotherapy for late-line treatment of ovarian cancer (QUADRA): a multicentre, open-label, single-arm, phase 2 trial. Lancet Oncol. 2019 May;20(5):636-648. Epub 2019 Apr 1. PMID: 30948273
(9) Ledermann J et al., Olaparib maintenance therapy in platinum-sensitive relapsed ovarian cancer. N Engl J Med. 2012 Apr 12;366(15):1382-92. Epub 2012 Mar 27. PubMed PMID: 22452356
(10) Ray-Coquard I et al. Olaparib plus Bevacizumab as First-Line Maintenance in Ovarian Cancer. N Engl J Med. 2019 12 19;381(25):2416-2428. doi: 10.1056/NEJMoa1911361. PubMed PMID: 31851799.
(11) Coleman RL et al., Rucaparib maintenance treatment for recurrent ovarian carcinoma after response to platinum therapy (ARIEL3): a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet. 2017 Oct 28;390(10106):1949-1961. Epub 2017 Sep 12. Erratum in: Lancet. 2017 Oct 28;390(10106):1948. PubMed PMID: 28916367
(12) Ruscito I et al. Incorporating Parp-inhibitors in Primary and Recurrent Ovarian Cancer: A Meta-analysis of 12 phase II/III randomized controlled trials. Cancer Treat Rev. 2020 Jul;87:102040. PMID: 32485510

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BIOMEDICAL INTERPRETATION

(13) Vergote IB et al., Randomized phase III study of erlotinib versus observation in patients with no evidence of disease progression after first-line platin-based chemotherapy for ovarian carcinoma: a European Organisation for Research and Treatment of Cancer-Gynaecological Cancer Group, and Gynecologic Cancer Intergroup study. J Clin Oncol. 2014 Feb 1;32(4):320-6. PubMed PMID: 24366937

(14) Gordon AN et al., Efficacy and safety of erlotinib HCl, an epidermal growth factor receptor (HER1/EGFR) tyrosine kinase inhibitor, in patients with advanced ovarian carcinoma: results from a phase II multicenter study. Int J Gynecol Cancer. 2005 Sep-Oct;15(5):785-92. PubMed PMID: 16174225

(15) Leto SM et al., Primary and acquired resistance to EGFR-targeted therapies in colorectal cancer: impact on future treatment strategies. J Mol Med (Berl). 2014 Jul;92(7):709-22. PubMed PMID: 24811491

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

(17) Bardelli A et al., Molecular mechanisms of resistance to cetuximab and panitumumab in colorectal cancer. J Clin Oncol. 2010 Mar 1;28(7): 1254-61. PubMed PMID: 20100961

(18) Di Fiore F et al., Molecular determinants of anti-EGFR sensitivity and resistance in metastatic colorectal cancer. Br J Cancer. 2010 Dec 7;103 (12):1765-72. PubMed PMID: 21139621

(19) Kurman RJ et al., Molecular pathogenesis and extraovarian origin of epithelial ovarian cancer--shifting the paradigm. Hum Pathol. 2011 Jul;42 (7):918-31. PubMed PMID: 21683865

(20) Levine DA et al., Frequent mutation of the PIK3CA gene in ovarian and breast cancers. Clin Cancer Res. 2005 Apr 15;11 (8):2875-8. PubMed PMID: 15837735

(21) McAlpine JN et al., HER2 overexpression and amplification is present in a subset of ovarian mucinous carcinomas and can be targeted with trastuzumab therapy. BMC Cancer. 2009 Dec 10;9:433. PubMed PMID: 20003286

(22) Coleman RL et al., Phase 1-2 study of docetaxel plus aflibercept in patients with recurrent ovarian, primary peritoneal, or fallopian tube cancer. Lancet Oncol. 2011 Nov;12(12):1109-17. PubMed PMID: 21992853

(23) Gotlieb WH et al., Intravenous aflibercept for treatment of recurrent symptomatic malignant ascites in patients with advanced ovarian cancer: a phase 2, randomised, double-blind, placebo-controlled study. Lancet Oncol. 2012 Feb;13(2):154-62. PubMed PMID: 22192729

(24) Coward JI et al., New perspectives on targeted therapy in ovarian cancer. Int J Womens Health. 2015 Feb 4;7:189–203. PubMed PMID: 25678824

(25) Ledermann JA et al.; ICON6 collaborators. Cediranib in patients with relapsed platinum-sensitive ovarian cancer (ICON6): a randomised, double-blind, placebo-controlled phase 3 trial. Lancet. 2016 Mar 12;387(10023):1066-1074. PubMed PMID: 27025186

(26) Kenilworth NJ: AstraZeneca and MSD. Update on Phase III GY004 trial for cediranib added to Lynparza in platinum-sensitive relapsed ovarian cancer [press release]. March 12, 2020. bit.ly/2W8kpb0

(27) Monk BJ et al., Anti-angiopoietin therapy with trebananib for recurrent ovarian cancer (TRINOVA-1): a randomised, multicentre, double-blind, placebo-controlled phase 3 trial. Lancet Oncol. 2014 Jul;15(8):799-808. PubMed PMID: 24950985

(28) Marth C et al., ENGOT-ov-6/TRINOVA-2: Randomised, double-blind, phase 3 study of pegylated liposomal doxorubicin plus trebananib or placebo in women with recurrent partially platinum-sensitive or resistant ovarian cancer. Eur J Cancer. 2017 Jan;70:111-121. PubMed PMID: 27914241

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

(30) D.M. O'Malley et al., 833P Mirvetuximab soravtansine (MIRV), a folate receptor alpha (FR)-targeting antibody-drug conjugate (ADC), in combination with carboplatin (CARBO) and bevacizumab (BEV): Final results from a study in patients (pts) with recurrent platinum sensitive ovarian cancer. Annals of Oncology. 2020 Sept;31(4):S626-S627. doi.org/10.1016/j.annonc.2020.08.972.

(31) Hamilton, Erika P., et al. "839P A phase Ib/II study of rebastinib and paclitaxel in advanced or metastatic platinum-resistant ovarian cancer." Annals of Oncology 31 (2020): S629-S630. doi.org/10.1016/j.annonc.2020.08.978.

(32) Nalley, Catlin. Niraparib+ Dostarlimab for Platinum-Resistant Ovarian Cancer. 2020. doi:10.1097/01.COT.0000723544.69508.e8

(33) Arend RC, et al. Clinical trial in progress: pivotal study of VB-111 combined with paclitaxel versus paclitaxel for treatment of platinum-resistant ovarian cancer (OVAL, VB-111-701/GOG-3018). J Clin Oncol. 2020;38(suppl 15):TPS6097.doi:10.1200/JCO.2020.38.15_suppl.TPS6097

Immunotherapies in ovarian cancer

In a phase I/II study (TOPACIO/Keynote-162), patients with platinum-resistant ovarian cancer (PROC) were treated with the combination of NIRAPARIB+PEMBROLIZUMAB. Among the patients, the objective response rate (ORR) and disease control rate (DCR) were 25% and 68%, among the BRCA mutant patients, ORR and DCR were 45% and 73%, respectively (1).

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In a phase II study (MEDIOLA), platinum-sensitive, germline BRCA mutated, relapsed ovarian cancer patients were treated with DURVALUMAB + OLAPARIB. DCR at 28 weeks was 65.6% (21/32), the ORR was 71.9% with 7 complete responses (CR) seen, the median progression-free survival (PFS) was 11.1 months (2). In patients with non-germline BRCA mutant relapsed platinum-sensitive ovarian cancer, durvalumab + olaparib treatment resulted in an ORR of 31.3% (10/32) and a median PFS of 5.5 months, while the durvalumab + olaparib + bevacizumab triplet treatment resulted in an ORR of 77.4% (24/31) and a median PFS of 14.7 months according to preliminary analysis (3).

In a phase II study, epithelial ovarian, fallopian tube, or peritoneal cancer patients after NIVOLUMAB+BEVACIZUMAB treatment showed no complete responses and 10 partial responses, 6 patients had stable disease of at least 6 months. The median PFS was 9.4 months, the ORR was 21% (4).

In a phase II trial, the combination of PEMBROLIZUMAB with BEVACIZUMAB and cyclophosphamide demonstrated a disease control rate (DCR) of 95% in patients with recurrent ovarian cancer (n=40). In all patients, the ORR was 47.5%, and 52.6% (10/19) and 35.3% (6/17) in PD-L1 positive and negative patients, respectively (5).

According to a study, BRCA1 mutated high-grade serous ovarian carcinomas (HGSOC) presented a potent immunogenic phenotype, independent of TMB, therefore BRCA1 mutation may serve as a predictive biomarker in guiding ICI (immune checkpoint inhibitor) therapies for these patients (6). High TMB in case of ovarian cancer patients was associated with significantly longer DFS (disease-free survival) (16.4 vs 14.1 months) and OS (overall survival) (41.0 vs 32.1 months); median PFS for patients with and without DDR (DNA damage repair) alterations was 19.2 and 16.7 months, median OS was 54.6 and 41.5 months (7).

In a phase II study (KEYNOTE-100) with patients with advanced recurrent ovarian cancer, PEMBROLIZUMAB monotherapy resulted in ORR of 8.0% and PFS of 2.1 months in all patients, the median OS and ORR were increased in patients with higher PD-L1 expression (8).

In a phase II trial, with durvalumab in combination with paclitaxel and carboplatin, in advanced non-mucinous ovarian cancer patients, median OS was not reached; at 18 months, the OS rate was 69%, the median PFS was 14.5 months, and almost half the patients experienced disease progression (9).

In a phase I study of the VIGIL vaccine in combination with ATEZOLIZUMAB in patients with recurrent ovarian cancer, the median OS was not reached in the Vigil-first group versus 10.8 months in the atezolizumab-first group. A subset analysis of patients with wild-type BRCA1/2 demonstrated a more significant OS benefit for the Vigil-first patients (1 year OS rate of 100%), with median OS not reached, versus 5.2 months for the atezolizumab-first patients (1 year OS rate of 22.9%) (10).

References:

(1) Konstantinopoulos PA et al., TOPACIO/Keynote-162 (NCT02657889): A phase 1/2 study of niraparib + pembrolizumab in patients (pts) with advanced triple-negative breast cancer or recurrent ovarian cancer (ROC)—Results from ROC cohort. Journal of Clinical Oncology 2018 36: 15_suppl, 106-106.

(2) Drew Y et al., 1190PD Phase II study of olaparib+ durvalumab (MEDIOLA): Updated results in germline BRCA-mutated platinum-sensitive relapsed (PSR) ovarian cancer (OC). Annals of Oncology. 2019;30(suppl_5):v475-v532. doi: 10.1093/annonc/mdz253.

(3) Drew Y et al., Phase II study of olaparib (O) plus durvalumab (D) and bevacizumab (B) (MEDIOLA): Initial results in patients (pts) with non-germline BRCA-mutated (non-gBRCAm) platinum sensitive relapsed (PSR) ovarian cancer (OC). Annals of Oncology. 2020;31(suppl_4):S551-S589. doi: 10.1016/annonc/annonc276.

(4) Liu JF et al., A phase II trial of combination nivolumab and bevacizumab in recurrent ovarian cancer. Annals of Oncology, 2018. 29(suppl_8). doi:10.1093/annonc/mdy285.146

(5) Zsiros E et al. Efficacy and Safety of Pembrolizumab in Combination With Bevacizumab and Oral Metronomic Cyclophosphamide in the Treatment of Recurrent Ovarian Cancer: A Phase 2 Nonrandomized Clinical Trial. JAMA Oncol. 2020 Nov 19. Epub ahead of print. PMID: 33211063

(6) Dai Y et al., Potent immunogenicity in BRCA1-mutated patients with high-grade serous ovarian carcinoma. J Cell Mol Med. 2018 May 31;22(8): 3979-86. PMID: 29855141

(7) Tian W et al., Association of high tumor mutation (TMB) with DNA damage repair (DDR) alterations and better prognosis in ovarian cancer. Journal of Clinical Oncology. 2018;36:(15_suppl):5512-5512.

(8) Matulonis UA, et al. Antitumor activity and safety of pembrolizumab in patients with advanced recurrent ovarian cancer: results from the phase II KEYNOTE-100 study. Ann Oncol. 2019 Jul 1;30(7):1080-1087. doi: 10.1093/annonc/mdz135. PMID: 31046082.

(9) Westin SN, et al. Pharmacodynamic changes by durvalumab in combination with chemotherapy in women with untreated, advanced stage ovarian cancer. Presented at: 2020 American Association for Cancer Research Virtual Annual Meeting I; June 22-24, 2020. Abstract CT188. doi: 10.1158/1538-7445.AM2020-CT188

(10) Rocconi RP, et al. A phase I combination study of vigil and atezolizumab in recurrent/refractory advanced-stage ovarian cancer: Efficacy assessment in BRCA1/2-wt patients. J Clin Oncol. 2020;38(suppl 15):3002. doi:10.1200/JCO.2020.38.15_suppl.3002

Molecular alterations and mechanisms associated with resistance / reduced efficacy in case of immunotherapies

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BIOMEDICAL INTERPRETATION

Based on preclinical and clinical evidence, genetic alterations that may result in decreased efficacy or resistance to immunotherapies are loss of function mutations in the B2M (1), CBLB (2), JAK1/2 (3-6), NSD1 (7), PTEN (8, 9) and STK11 (10-12) genes as well as deletion of TET2 (13), and the activation of the WNT/beta-catenin signalling pathway (14). IDO expression (15) and IFNGR1 gene loss (6) may induce resistance to CTLA-4 targeting immunotherapies. Furthermore, immunotherapies were shown to be ineffective in case of non-small cell lung cancer (NSCLC) tumors harboring EGFR (16, 17), HER2 (18), or RB1 mutations (19), ROS1 translocations (18) and MET exon 14 skipping mutations (20). Immunotherapies were also ineffective in case of medullary thyroid carcinoma (MTC) and NSCLC tumors with RET fusions, and mutations (21, 22). Poor clinical outcome and hyperprogression have been reported in patients with MDM2, MDM4 or MYC amplifications after receiving immunotherapy (17, 23, 24).

References:

(1) Gettinger S et al., Impaired HLA Class I Antigen Processing and Presentation as a Mechanism of Acquired Resistance to Immune Checkpoint Inhibitors in Lung Cancer. Cancer Discov. 2017 Dec;7(12):1420-1435. Epub 2017 Oct 12. PubMed PMID: 29025772

(2) Peer S et al. Cblb-deficient T cells are less susceptible to PD-L1-mediated inhibition. Oncotarget. 2017 Jun 27;8(26):41841-41853. PubMed PMID: 28611299

(3) Shin DS et al., Primary Resistance to PD-1 Blockade Mediated by JAK1/2 Mutations. Cancer Discov. 2017 Feb;7(2):188-201. Epub 2016 Nov 30. PubMed PMID: 27903500

(4) Zaretsky JM et al., Mutations Associated with Acquired Resistance to PD-1 Blockade in Melanoma. N Engl J Med. 2016 Sep 1;375(9):819-29. Epub 2016 Jul 13. PubMed PMID: 27433843

(5) Nowicki TS et al., Mechanisms of Resistance to PD-1 and PD-L1 Blockade. Cancer J. 2018 Jan/Feb;24(1):47-53. Review. PubMed PMID: 29360728

(6) Gao J et al., Loss of IFN- Pathway Genes in Tumor Cells as a Mechanism of Resistance to Anti-CTLA-4 Therapy. Cell. 2016 Oct 6;167(2):397-404.e9. Epub 2016 Sep 22. PubMed PMID: 27667683

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

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

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

(10) Koyama S et al., STK11/LKB1 Deficiency Promotes Neutrophil Recruitment and Proinflammatory Cytokine Production to Suppress T-cell Activity in the Lung Tumor Microenvironment. Cancer Res. 2016 Mar 1;76(5):999-1008. Epub 2016 Feb 1. PubMed PMID: 26833127

(11) Skoulidis F et al., STK11/LKB1 Mutations and PD-1 Inhibitor Resistance in KRAS-Mutant Lung Adenocarcinoma. Cancer Discov. 2018 Jul;8(7): 822-835. PMID: 29773717

(12) Ricciuti B et al., Effect of STK11 mutations on efficacy of PD-1 inhibition in non-small cell lung cancer (NSCLC) and dependence on KRAS mutation status. Journal of Clinical Oncology. 2020;38(15_suppl):e15113-e15113. doi: 10.1200/JCO.2020.38.15_suppl.e15113.

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

(14) Spranger S et al. Melanoma-intrinsic -catenin signalling prevents anti-tumour immunity. Nature. 2015 Jul 09;523(7559):231-5. Epub 2015 Dec 11. PubMed PMID: 25970248

(15) Holmgaard RB et al., Indoleamine 2,3-dioxygenase is a critical resistance mechanism in antitumor T cell immunotherapy targeting CTLA-4. J Exp Med. 2013 Jul 01;210(7):1389-402. Epub 2013 Mar 10. PubMed PMID: 23752227

(16) Lisberg A et al., A Phase II Study of Pembrolizumab in EGFR-Mutant, PD-L1+, Tyrosine Kinase Inhibitor Naïve Patients With Advanced NSCLC. J Thorac Oncol. 2018 Aug;13(8):1138-1145. Epub 2018 Jun 1. PubMed PMID: 29874546

(17) Kato S et al. Hyperprogressors after Immunotherapy: Analysis of Genomic Alterations Associated with Accelerated Growth Rate. Clin Cancer Res. 2017 Aug 01;23(15):4242-4250. Epub 2017 Mar 28. PubMed PMID: 28351930

(18) Mazieres J et al. Immune checkpoint inhibitors for patients with advanced lung cancer and oncogenic driver alterations: results from the IMMUNOTARGET registry. Ann Oncol. 2019 Aug 1;30(8):1321-1328. PubMed PMID: 31125062.

(19) Bhateja P et al. Retinoblastoma mutation predicts poor outcomes in advanced non small cell lung cancer. Cancer Med. 2019 Apr;8(4):1459-1466. Epub 2019 Feb 17. PubMed PMID: 30773851

(20) Sabari JK et al., PD-L1 expression, tumor mutational burden, and response to immunotherapy in patients with MET exon 14 altered lung cancers. Ann Oncol. 2018 Oct 1;29(10):2085-2091. PMID: 30165371

(21) Offin M et al., Immunophenotype and Response to Immunotherapy of RET-Rearranged Lung Cancers. JCO Precis Oncol. 2019;3:PO. 18.00386. Epub 2019 May 16. PMID: 31192313

(22) Hegde A et al., Responsiveness to immune checkpoint inhibitors versus other systemic therapies in RET-aberrant malignancies. ESMO Open. 2020 Oct;5(5):e000799. PMID: 33097651

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BIOMEDICAL INTERPRETATION

(23) Weiqiang Ju et al. Association between MDM2/MDM4 amplification and PD-1/PD-L1 inhibitors-related hyperprogressive disease: A pan-cancer analysis. Journal of Clinical Oncology 2019 37:15_suppl, 2557-2557. doi: 10.1200/JCO.2019.37.15_suppl.2557
(24) Forschner A et al. MDM2, MDM4 and EGFR Amplifications and Hyperprogression in Metastatic Acral and Mucosal Melanoma. Cancers (Basel). 2020 Feb 26;12(3):. Epub 2020 Mar 26. PubMed PMID: 32110946

Molecular alterations and mechanisms associated with resistance / reduced efficacy in case of CDK inhibition

Resistance to CDK4/6 inhibitors (palbociclib, abemaciclib, ribociclib, lerociclib) may arise through diverse direct or indirect molecular mechanisms (1, 2).

Various cell cycle-specific mechanisms were reported to promote resistance to CDK4/6 inhibitors by the deregulation of the cyclin D-CDK4/6–INK4–RB pathway, the key regulator of G1-S transition. These alterations include loss of RB function due to mutations or regulatory suppression, amplification of CDKN2A (p16) alone or with the concurrent loss of RB, amplification or overexpression of CDK2/4/6/7, CCNE1 (cyclin E) and E2F. Other cell cycle related alterations that also might contribute to resistance are the overexpression of MDM2 and WEE1, and HDAC activation (1-3). Cell cycle-nonspecific mechanisms have also been identified to be involved in resistance to CDK4/6 inhibitors in breast cancer models, such as the activation of the FGFR or PI3K/AKT/mTOR pathways, or the loss of ER or PR expression (1).

According to preclinical evidences, resistance mechanisms can be categorized into irreversible (e.g. mutations of RB), and reversible (gain of cyclin E, overexpression of CDK2/4/6) types. Reversible resistance mechanisms were shown to be amenable to a drug holiday, leading to re-sensitisation to CDK4/6 inhibitors in vitro and in vivo (3, 4).

Combinations of CDK4/6 inhibitors with other targeted compounds were suggested to enhance the durability of response or may overcome resistance (5).

In urothelial and pancreatic cancer cell lines, combinations of CDK4/6 inhibitors with inhibitors targeting PI3K-AKT and RAS/MAPK exhibited synergism (6-8), and could reverse acquired resistance (7). In another study, MAPK induction was identified in preclinical models with acquired resistance to palbociclib, that sensitized cells to MEK inhibition (9). In KRAS-mutant colorectal and non-small cell lung cancer models, the combination of MEK and CDK4/6 inhibitors synergistically inhibited cancer cell growth in vitro and caused tumor regression in vivo (10, 11). The combination of CDK4/6 and MEK inhibitors are currently tested in several clinical trials.

References:

(1) Pandey K et al. Molecular mechanisms of resistance to CDK4/6 inhibitors in breast cancer: A review. Int J Cancer. 2019 Sep 1;145(5):1179-1188. doi: 10.1002/ijc.32020. Epub 2019 Jan 7. PMID: 30478914
(2) Niu Y et al. Cyclin-Dependent Kinases 4/6 Inhibitors in Breast Cancer: Current Status, Resistance, and Combination Strategies. J Cancer. 2019 Aug 29;10(22):5504-5517. doi: 10.7150/jca.32628. PMID: 31632494
(3) Martin LA et al., Abstract P3-03-09: Resistance to palbociclib depends on multiple targetable mechanisms highlighting the potential of drug holidays and drug switching to improve therapeutic outcome. Cancer Res. February 15 2017;77:(4 Supplement):P3-03-09. doi: 10.1158/1538-7445.SABCS16-P3-03-09
(4) Cornell L et al., MicroRNA-Mediated Suppression of the TGF- Pathway Confers Transmissible and Reversible CDK4/6 Inhibitor Resistance. Cell Rep. 2019 Mar 5;26(10):2667-2680.e7. doi: 10.1016/j.celrep.2019.02.023. PMID: 30840889
(5) Knudsen ES, Witkiewicz AK. The Strange Case of CDK4/6 Inhibitors: Mechanisms, Resistance, and Combination Strategies. Trends Cancer. 2017 Jan;3(1):39-55. doi: 10.1016/j.trecan.2016.11.006. PMID: 28303264
(6) Tong Z et al., Functional genomics identifies predictive markers and clinically actionable resistance mechanisms to CDK4/6 inhibition in bladder cancer. J Exp Clin Cancer Res. 2019 Jul 22;38(1):322. doi: 10.1186/s13046-019-1322-9. PMID: 31331377
(7) Goodwin CM et al., Abstract LB-287: Combination therapies with CDK4/6 inhibitors to treat KRAS-mutant pancreatic cancer. Cancer Res. July 1 2019;79:(13 Supplement):LB-287. doi: 10.1158/1538-7445.AM2019-LB-287.
(8) Franco J et al., CDK4/6 inhibitors have potent activity in combination with pathway selective therapeutic agents in models of pancreatic cancer. Oncotarget. 2014 Aug 15;5(15):6512-25. PMID: 25156567
(9) de Leeuw R et al. MAPK Reliance via Acquired CDK4/6 Inhibitor Resistance in Cancer. Clin Cancer Res. 2018 Sep 1;24(17):4201-4214. doi: 10.1158/1078-0432.CCR-18-0410. Epub 2018 May 8. PMID: 29739788
(10) Lee MS et al. Efficacy of the combination of MEK and CDK4/6 inhibitors in vitro and in vivo in KRAS mutant colorectal cancer models. Oncotarget. 2016 Jun 28;7(26):39595-39608. doi: 10.18632/oncotarget.9153. PMID: 27167191
(11) Haines E et al. Palbociclib resistance confers dependence on an FGFR-MAP kinase-mTOR-driven pathway in KRAS-mutant non-small cell lung cancer. Oncotarget. 2018 Aug 3;9(60):31572-31589. doi: 10.18632/oncotarget.25803. PMID: 30167080

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COMPOUND NAME	REFERENCES
SELUMETINIB	Balmanno K, Chell SD, Gillings AS, Hayat S, Cook SJ. Intrinsic resistance to the MEK1/2 inhibitor AZD6244 (ARRY-142886) is associated with weak ERK1/2 signalling and/or strong PI3K signalling in colorectal cancer cell lines. Int J Cancer. 2009 Nov 15;125(10):2332-41. doi: 10.1002/ijc.24604. PubMed PMID: 19637312. Kiessling MK, Curioni-Fontecedro A, Samaras P, Lang S, Scharl M, Aguzzi A, Oldrige DA, Maris JM, Rogler G. Targeting the mTOR Complex by Everolimus in NRAS Mutant Neuroblastoma. PLoS One. 2016 Jan 28;11(1): e0147682. doi: 10.1371/journal.pone.0147682. Erratum in: PLoS One. 2017 Jan 20;12 (1):e0170851. PubMed PMID: 26821351; PubMed Central PMCID: PMC4731059. Bennouna J, Lang I, Valladares-Ayerbes M, Boer K, Adenis A, Escudero P, Kim TY, Pover GM, Morris CD, Douillard JY. A Phase II, open-label, randomised study to assess the efficacy and safety of the MEK1/2 inhibitor AZD6244 (ARRY-142886) versus capecitabine monotherapy in patients with colorectal cancer who have failed one or two prior chemotherapeutic regimens. Invest New Drugs. 2011 Oct;29(5):1021-8. doi: 10.1007/s10637-010-9392-8. PubMed PMID: 20127139. Irving J, Matheson E, Minto L, Blair H, Case M, Halsey C, Swidenbank I, Ponthan F, Kirschner-Schwabe R, Groeneveld-Krentz S, Hof J, Allan J, Harrison C, Vormoor J, von Stackelberg A, Eckert C. Ras pathway mutations are highly prevalent in relapsed childhood acute lymphoblastic leukaemia, may act as relapse-drivers and confer sensitivity to MEK inhibition. Blood. 2014 Sep 24. pii: blood-2014-04-531871. [Epub ahead of print] PubMed PMID: 25253770. Alan L. Ho, M.D., Ph.D., Ravinder K. Grewal, M.D., Rebecca Leboeuf, M.D., Eric J. Sherman, M.D., David G. Pfister, M. D., Desiree Deandreis, M.D., Keith S. Pentlow, M.Sc., Pat B. Zanzonico, Ph.D., Sofia Haque, M.D., Somali Gavane, M. D., Ronald A. Ghossein, M.D., Julio C. Ricarte-Filho, Ph.D., José M. Domínguez, M.D., Ronglai Shen, Ph.D., R. Michael Tuttle, M.D., Steve M. Larson, M.D., and James A. Fagin, M.D., N Engl J Med. 2013 Feb 14; 368(7): 623–632., Selumetinib-Enhanced Radioiodine Uptake in Advanced Thyroid Cancer
JQ1	Mertz JA, Conery AR, Bryant BM, Sandy P, Balasubramanian S, Mele DA, Bergeron L, Sims RJ 3rd. Targeting MYC dependence in cancer by inhibiting BET bromodomains. Proc Natl Acad Sci U S A. 2011 Oct 4;108(40):16669-74. doi: 10.1073/pnas.1108190108. Epub 2011 Sep 26. PubMed PMID: 21949397; PubMed Central PMCID: PMC3189078. Delmore JE, Issa GC, Lemieux ME, Rahl PB, Shi J, Jacobs HM, Kastritis E, Gilpatrick T, Paranal RM, Qi J, Chesi M, Schinzel AC, McKeown MR, Heffernan TP, Vakoc CR, Bergsagel PL, Ghobrial IM, Richardson PG, Young RA, Hahn WC, Anderson KC, Kung AL, Bradner JE, Mitsiades CS. BET bromodomain inhibition as a therapeutic strategy to target c-Myc. Cell. 2011 Sep 16;146(6):904-17. doi: 10.1016/j.cell.2011.08.017. Epub 2011 Sep 1. PubMed PMID: 21889194; PubMed Central PMCID: PMC3187920.
RIVICICLIB	Mariaule G, Belmont P. Cyclin-dependent kinase inhibitors as marketed anticancer drugs: where are we now? A short survey. Molecules. 2014 Sep 11;19(9):14366-82. doi: 10.3390/molecules190914366. Review. PubMed PMID: 25215591.
RGB-286638	Mariaule G, Belmont P. Cyclin-dependent kinase inhibitors as marketed anticancer drugs: where are we now? A short survey. Molecules. 2014 Sep 11;19(9):14366-82. doi: 10.3390/molecules190914366. Review. PubMed PMID: 25215591.
RONICICLIB	Ayaz P, Andres D, Kwiatkowski DA, Kolbe CC, Lienau P, Siemeister G, Lücking U, Stegmann CM. Conformational Adaption May Explain the Slow Dissociation Kinetics of Roniciclib (BAY 1000394), a Type I CDK Inhibitor with Kinetic Selectivity for CDK2 and CDK9. ACS Chem Biol. 2016 Jun 17;11(6):1710-9. doi: 10.1021/acschembio.6b00074. Epub 2016 Apr 19. PubMed PMID: 27090615. Siemeister G, Lücking U, Wengner AM, Lienau P, Steinke W, Schatz C, Mumberg D, Ziegelbauer K. BAY 1000394, a novel cyclin-dependent kinase inhibitor, with potent antitumor activity in mono- and in combination treatment upon oral application. Mol Cancer Ther. 2012 Oct;11(10):2265-73. doi: 10.1158/1535-7163.MCT-12-0286. Epub 2012 Jul 19. PubMed PMID: 22821149.
TRAMETINIB	D.M. Gershenson1, A. Miller2, W. Brady2, J. Paul3, K. Carty3, W. Rodgers4, D. Millan5, R.L. Coleman6, K.N. Moore7, S. Banerjee8, K. Connolly9, A.A. Secord10, D.M. O'Malley11, O. Dorigo12, S. Gaillard13, H. Gabra14, P. Hanjani15, H. Huang2, L. Wenzel16, C. Gourley17. A Randomized Phase II/III Study to Assess the Efficacy of Trametinib in Patients with Recurrent or Progressive Low-Grade Serous Ovarian or Peritoneal Cancer. Annals of Oncology (2019) 30 (suppl_5): v851-v934. doi: 10.1093/annonc/mdz394. Jing J, Greshock J, Holbrook JD, Gilmartin A, Zhang X, McNeil E, Conway T, Moy C, Laquerre S, Bachman K, Wooster R, Degenhardt Y. Comprehensive predictive biomarker analysis for MEK inhibitor GSK1120212. Mol Cancer Ther. 2012 Mar;11(3):720-9. doi: 10.1158/1535-7163.MCT-11-0505. Epub 2011 Dec 14. PubMed PMID: 22169769. Ikeda M, Ioka T, Fukutomi A, Morizane C, Kasuga A, Takahashi H, Todaka A, Okusaka T, Creasy CL, Gorman S, Felitsky DJ, Kobayashi M, Zhang F, Furuse J. Efficacy and safety of trametinib in Japanese patients with advanced biliary tract cancers refractory to gemcitabine. Cancer Sci. 2018 Jan;109(1):215-224. doi: 10.1111/cas.13438. Epub 2017 Dec 9. PubMed PMID: 29121415; PubMed Central PMCID: PMC5765304. KIM, Richard D., et al. SWOG S1310: Randomized phase II trial of single agent MEK inhibitor trametinib vs. 5-fluorouracil or capecitabine in refractory advanced biliary cancer. 2017. Heuck CJ, Jethava Y, Khan R, van Rhee F, Zangari M, Chavan S, Robbins K, Miller SE, Matin A, Mohan M, Ali SM, Stephens PJ, Ross JS, Miller VA, Davies F, Barlogie B, Morgan G. Inhibiting MEK in MAPK pathway-activated myeloma. Leukemia. 2016 Apr;30(4):976-80. doi: 10.1038/leu.2015.208. Epub 2015 Jul 31. PubMed PMID: 26228812; PubMed Central PMCID: PMC4832073.

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COMPOUND NAME	REFERENCES
MIRDAMETINIB	Sogabe S, Togashi Y, Kato H, Kogita A, Mizukami T, Sakamoto Y, Banno E, Terashima M, Hayashi H, De Velasco MA, Sakai K, Fujita Y, Tomida S, Yasuda T, Takeyama Y, Okuno K, Nishio K. MEK inhibitor for gastric cancer with MEK1 gene mutations. Mol Cancer Ther. 2014 Sep 24. pii: molcanther.0429.2014. [Epub ahead of print] PubMed PMID: 25253779. Kiessling MK, Curioni-Fontecedro A, Samaras P, Lang S, Scharl M, Aguzzi A, Oldrige DA, Maris JM, Rogler G. Targeting the mTOR Complex by Everolimus in NRAS Mutant Neuroblastoma. PLoS One. 2016 Jan 28;11(1): e0147682. doi: 10.1371/journal.pone.0147682. Erratum in: PLoS One. 2017 Jan 20;12 (1):e0170851. PubMed PMID: 26821351; PubMed Central PMCID: PMC4731059. Ryan MB, Der CJ, Wang-Gillam A, Cox AD. Targeting RAS-mutant cancers: is ERK the key? Trends Cancer. 2015 Nov 1;1(3):183-198. PubMed PMID: 26858988; PubMed Central PMCID: PMC4743050. Shannon S, Jia D, Entersz I, Beelen P, Yu M, Carcione C, Carcione J, Mahtabfar A, Vaca C, Weaver M, Shreiber D, Zahn JD, Liu L, Lin H, Foty RA. Inhibition of glioblastoma dispersal by the MEK inhibitor PD0325901. BMC Cancer. 2017 02 10;17(1):121. doi: 10.1186/s12885-017-3107-x. Epub 2017 Apr 10. PubMed PMID: 28187762; PubMed Central PMCID: PMC5303286. Glassmann A, Winter J, Kraus D, Veit N, Probstmeier R. Pharmacological suppression of the Ras/MAPK pathway in thyroid carcinoma cells can provoke opposite effects on cell migration and proliferation: The appearance of yin-yang effects and the need of combinatorial treatments. Int J Oncol. 2014 Sep 23. doi: 10.3892/ijo.2014.2668. [Epub ahead of print] PubMed PMID: 25269412.
MILCICLIB	Weiss GJ, Hidalgo M, Borad MJ, Laheru D, Tibes R, Ramanathan RK, Blaydorn L, Jameson G, Jimeno A, Isaacs JD, Scaburri A, Pacciarini MA, Fiorentini F, Ciomei M, Von Hoff DD. Phase I study of the safety, tolerability and pharmacokinetics of PHA-848125AC, a dual tropomyosin receptor kinase A and cyclin-dependent kinase inhibitor, in patients with advanced solid malignancies. Invest New Drugs. 2012 Dec;30(6):2334-43. doi: 10.1007/s10637-011-9774-6. Epub 2011 Dec 9. PubMed PMID: 22160853; PubMed Central PMCID: PMC3561458.
ZOTIRACICLIB	Goh KC, Novotny-Diermayr V, Hart S, Ong LC, Loh YK, Cheong A, Tan YC, Hu C, Jayaraman R, William AD, Sun ET, Dymock BW, Ong KH, Ethirajulu K, Burrows F, Wood JM. TG02, a novel oral multi-kinase inhibitor of CDKs, JAK2 and FLT3 with potent anti-leukemic properties. Leukemia. 2012 Feb;26(2):236-43. doi: 10.1038/leu.2011.218. Epub 2011 Aug 23. PubMed PMID: 21860433.
ALVOCIDIB	Senderowicz AM. Flavopiridol: the first cyclin-dependent kinase inhibitor in human clinical trials. Invest New Drugs. 1999;17(3):313-20. Review. PubMed PMID: 10665481.
DINACICLIB	Parry D, Guzi T, Shanahan F, Davis N, Prabhavalkar D, Wiswell D, Seghezzi W, Paruch K, Dwyer MP, Doll R, Nomeir A, Windsor W, Fischmann T, Wang Y, Oft M, Chen T, Kirschmeier P, Lees EM. Dinaciclib (SCH 727965), a novel and potent cyclin-dependent kinase inhibitor. Mol Cancer Ther. 2010 Aug;9(8):2344-53. doi: 10.1158/1535-7163.MCT-10-0324. Epub 2010 Jul 27. PubMed PMID: 20663931. Chen Z, Wang Z, Pang JC, Yu Y, Bieerkehazhi S, Lu J, Hu T, Zhao Y, Xu X, Zhang H, Yi JS, Liu S, Yang J. Multiple CDK inhibitor dinaciclib suppresses neuroblastoma growth via inhibiting CDK2 and CDK9 activity. Sci Rep. 2016 Jul 5;6:29090. doi: 10.1038/srep29090. PubMed PMID: 27378523; PubMed Central PMCID: PMC4932496.
AT 7519	Mariaule G, Belmont P. Cyclin-dependent kinase inhibitors as marketed anticancer drugs: where are we now? A short survey. Molecules. 2014 Sep 11;19(9):14366-82. doi: 10.3390/molecules190914366. Review. PubMed PMID: 25215591.
AZD5438	Byth KF, Thomas A, Hughes G, Forder C, McGregor A, Geh C, Oakes S, Green C, Walker M, Newcombe N, Green S, Growcott J, Barker A, Wilkinson RW. AZD5438, a potent oral inhibitor of cyclin-dependent kinases 1, 2, and 9, leads to pharmacodynamic changes and potent antitumor effects in human tumor xenografts. Mol Cancer Ther. 2009 Jul; 8(7):1856-66. doi: 10.1158/1535-7163.MCT-08-0836. Epub 2009 Jun 9. PubMed PMID: 19509270.
AZD1208	Brasó-Maristany F, Filosto S, Catchpole S, Marlow R, Quist J, Francesch-Domenech E, Plumb DA, Zakka L, Gazinska P, Liccardi G, Meier P, Gris-Oliver A, Cheang MC, Perdrix-Rosell A, Shafat M, Noël E, Patel N, McEachern K, Scaltriti M, Castel P, Noor F, Buus R, Mathew S, Watkins J, Serra V, Marra P, Grigoriadis A, Tutt AN. PIM1 kinase regulates cell death, tumor growth and chemotherapy response in triple-negative breast cancer. Nat Med. 2016 11;22(11):1303-1313. doi: 10.1038/nm.4198. Epub 2016 October 24. PubMed PMID: 27775704; PubMed Central PMCID: PMC5552044.
SIROLIMUS	Benson C, Vitfell-Rasmussen J, Maruzzo M, Fisher C, Tunariu N, Mitchell S, Al-Muderis O, Thway K, Larkin J, Judson I. A retrospective study of patients with malignant PEComa receiving treatment with sirolimus or temsirolimus: the Royal Marsden Hospital experience. Anticancer Res. 2014 Jul;34(7):3663-8. PMID: 24982384. Takeuchi H, Kondo Y, Fujiwara K, Kanzawa T, Aoki H, Mills GB, Kondo S. Synergistic augmentation of rapamycin-induced autophagy in malignant glioma cells by phosphatidylinositol 3-kinase/protein kinase B inhibitors. Cancer Res. 2005 Apr 15;65(8):3336-46. PubMed PMID: 15833867. Rouanne M, Loriot Y, Lebret T, Soria JC. Novel therapeutic targets in advanced urothelial carcinoma. Crit Rev Oncol Hematol. 2016 Feb;98:106-15. doi: 10.1016/j.critrevonc.2015.10.021. Epub 2015 Nov 9. Review. PubMed PMID: 26589398. Rizell M, Andersson M, Cahlin C, Hafström L, Olausson M, Lindnér P. Effects of the mTOR inhibitor sirolimus in patients with hepatocellular and cholangiocellular cancer. Int J Clin Oncol. 2008 Feb;13(1):66-70. doi: 10.1007 /s10147-007-0733-3. Epub 2008 Feb 29. PubMed PMID: 18307022. Bergamo F, Maruzzo M, Basso U, Montesco MC, Zagonel V, Gringeri E, Cillo U. Neoadjuvant sirolimus for a large hepatic perivascular epithelioid cell tumor (PEComa). World J Surg Oncol. 2014 Feb 27;12:46. doi: 10.1186/1477-7819-12-46. PubMed PMID: 24575738; PubMed Central PMCID: PMC3943801.

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COMPOUND NAME	REFERENCES
MK-8776	Dai Y, Chen S, Kmieciak M, Zhou L, Lin H, Pei XY, Grant S. The novel Chk1 inhibitor MK-8776 sensitizes human leukemia cells to HDAC inhibitors by targeting the intra-S checkpoint and DNA replication and repair. Mol Cancer Ther. 2013 Jun;12(6):878-89. doi: 10.1158/1535-7163.MCT-12-0902. PubMed PMID: 23536721; PubMed Central PMCID: PMC3681875.
PREXASERTIB	Heidler CL, Roth EK, Thiemann M, Blattmann C, Perez RL, Huber PE, Kovac M, Amthor B, Neu-Yilik G, Kulozik AE. Prexasertib (LY2606368) reduces clonogenic survival by inducing apoptosis in primary patient-derived osteosarcoma cells and synergizes with cisplatin and talazoparib. Int J Cancer. 2019 Nov 28;:. doi: 10.1002/ijc.32814. Epub 2019 Jun 28. PubMed PMID: 31782150. Ritu Chaudhary, Robbert Slebos, Feifei Song, Keegan McCleary-Sharpe, Jude Masannat, Aik Choon Tan, Xuefeng Wang, Nelusha Amaladas, Wenjuan Wu, Gerald Hall, Christine H. Chung. Effects of prexasertib, a CHK1 inhibitor, in the immune microenvironment of head and neck squamous cell carcinoma (HNSCC). J Clin Oncol. 2020;38:(suppl; abstr e18541). doi: 10.1200/JCO.2020.38.15_suppl.e18541. Gatti-Mays ME, Karzai FH, Soltani SN, Zimmer A, Green JE, Lee MJ, Trepel JB, Yuno A, Lipkowitz S, Nair J, McCoy A, Lee JM. A Phase II Single Arm Pilot Study of the CHK1 Inhibitor Prexasertib (LY2606368) in BRCA Wild-Type, Advanced Triple-Negative Breast Cancer. Oncologist. 2020 Jun 08;:. doi: 10.1634/theoncologist.2020-0491. Epub 2020 Jul 08. PubMed PMID: 32510664. Parmar K, Kochupurakkal BS, Lazaro JB, Wang ZC, Palakurthi S, Kirschmeier PT, Yang C, Sambel LA, Färkkilä A, Reznichenko E, Reavis HD, Dunn CE, Zou L, Do KT, Konstantinopoulos PA, Matulonis UA, Liu JF, D'Andrea AD, Shapiro GI. The CHK1 Inhibitor Prexasertib Exhibits Monotherapy Activity in High-Grade Serous Ovarian Cancer Models and Sensitizes to PARP Inhibition. Clin Cancer Res. 2019 10 15;25(20):6127-6140. doi: 10.1158/1078-0432.CCR-19-0448. Epub 2019 Jul 13. PubMed PMID: 31409614; PubMed Central PMCID: PMC6801076. Lee JM, Nair J, Zimmer A, Lipkowitz S, Annunziata CM, Merino MJ, Swisher EM, Harrell MI, Trepel JB, Lee MJ, Bagheri MH, Botesteanu DA, Steinberg SM, Minasian L, Ekwede I, Kohn EC. Prexasertib, a cell cycle checkpoint kinase 1 and 2 inhibitor, in BRCA wild-type recurrent high-grade serous ovarian cancer: a first-in-class proof-of-concept phase 2 study. Lancet Oncol. 2018 02;19(2):207-215. doi: 10.1016/S1470-2045(18)30009-3. Epub 2018 Jul 18. PubMed PMID: 29361470.
SCH 900776	Guertin AD, Martin MM, Roberts B, Hurd M, Qu X, Miselis NR, Liu Y, Li J, Feldman I, Benita Y, Bloecher A, Toniatti C, Shumway SD. Unique functions of CHK1 and WEE1 underlie synergistic anti-tumor activity upon pharmacologic inhibition. Cancer Cell Int. 2012 Nov 13;12(1):45. doi: 10.1186/1475-2867-12-45. PubMed PMID: 23148684; PubMed Central PMCID: PMC3517755.
PF-477736	Bryant C, Rawlinson R, Massey AJ. Chk1 inhibition as a novel therapeutic strategy for treating triple-negative breast and ovarian cancers. BMC Cancer. 2014 Aug 7;14:570. doi: 10.1186/1471-2407-14-570. PubMed PMID: 25104095; PubMed Central PMCID: PMC4137066.
RABUSERTIB	Wang FZ, Fei HR, Cui YJ, Sun YK, Li ZM, Wang XY, Yang XY, Zhang JG, Sun BL. The checkpoint 1 kinase inhibitor LY2603618 induces cell cycle arrest, DNA damage response and autophagy in cancer cells. Apoptosis. 2014 Sep;19(9):1389-98. doi: 10.1007/s10495-014-1010-3. PubMed PMID: 24928205.
DASATINIB	Nam S, Kim D, Cheng JQ, Zhang S, Lee JH, Buettner R, Mirosevich J, Lee FY, Jove R. Action of the Src family kinase inhibitor, dasatinib (BMS-354825), on human prostate cancer cells. Cancer Res. 2005 Oct 15;65(20):9185-9. PubMed PMID: 16230377. Kluger HM, Dudek AZ, McCann C, Ritacco J, Southard N, Jilaveanu LB, Molinaro A, Sznol M. A phase 2 trial of dasatinib in advanced melanoma. Cancer. 2011 May 15;117(10):2202-8. doi: 10.1002/cncr.25766. Epub 2010 Nov 29. PubMed PMID: 21523734; PubMed Central PMCID: PMC3116034. Verstovsek S, Tefferi A, Cortes J, O'Brien S, Garcia-Manero G, Pardanani A, Akin C, Faderl S, Manshouri T, Thomas D, Kantarjian H. Phase II study of dasatinib in Philadelphia chromosome-negative acute and chronic myeloid diseases, including systemic mastocytosis. Clin Cancer Res. 2008 Jun 15;14(12):3906-15. doi: 10.1158/1078-0432.CCR-08-0366. PubMed PMID: 18559612. Weisberg E, Manley P, Mestan J, Cowan-Jacob S, Ray A, Griffin JD. AMN107 (nilotinib): a novel and selective inhibitor of BCR-ABL. Br J Cancer. 2006 Jun 19;94(12):1765-9. Epub 2006 May 23. Review. PubMed PMID: 16721371; PubMed Central PMCID: PMC2361347. Redaelli S, Piazza R, Rostagno R, Magistroni V, Perini P, Marega M, Gambacorti-Passerini C, Boschelli F. Activity of bosutinib, dasatinib, and nilotinib against 18 imatinib-resistant BCR/ABL mutants. J Clin Oncol. 2009 Jan 20;27(3):469-71. doi: 10.1200/JCO.2008.19.8853. Epub 2008 Dec 15. PubMed PMID: 19075254.
BI-847325	Phadke MS, Sini P, Smalley KS. The Novel ATP-Competitive MEK/Aurora Kinase Inhibitor BI-847325 Overcomes Acquired BRAF Inhibitor Resistance through Suppression of Mcl-1 and MEK Expression. Mol Cancer Ther. 2015 Jun;14(6):1354-64. doi: 10.1158/1535-7163.MCT-14-0832. Epub 2015 Apr 14. PubMed PMID: 25873592; PubMed Central PMCID: PMC4458462.

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COMPOUND NAME	REFERENCES
BINIMETINIB	Thumar J, Shahbazian D, Aziz SA, Jilaveanu LB, Kluger HM. MEK targeting in N-RAS mutated metastatic melanoma. Mol Cancer. 2014 Mar 4;13:45. doi: 10.1186/1476-4598-13-45. PubMed PMID: 24588908; PubMed Central PMCID: PMC3945937. Hamidi H, Lu M, Chau K, Anderson L, Fejzo M, Ginther C, Linnartz R, Zubel A, Slamon DJ, Finn RS. KRAS mutational subtype and copy number predict in vitro response of human pancreatic cancer cell lines to MEK inhibition. Br J Cancer. 2014 Aug 28. doi: 10.1038/bjc.2014.475. [Epub ahead of print] PubMed PMID: 25167228. Ryan MB, Der CJ, Wang-Gillam A, Cox AD. Targeting RAS-mutant cancers: is ERK the key? Trends Cancer. 2015 Nov 1;1(3):183-198. PubMed PMID: 26858988; PubMed Central PMCID: PMC4743050. Kiessling MK, Curioni-Fontecedro A, Samaras P, Lang S, Scharl M, Aguzzi A, Oldrige DA, Maris JM, Rogler G. Targeting the mTOR Complex by Everolimus in NRAS Mutant Neuroblastoma. PLoS One. 2016 Jan 28;11(1): e0147682. doi: 10.1371/journal.pone.0147682. Erratum in: PLoS One. 2017 Jan 20;12 (1):e0170851. PubMed PMID: 26821351; PubMed Central PMCID: PMC4731059. Sarah E. Woodfield, Linna Zhang, Kathleen A. Scorsone, Yin Liu, and Peter E. Zage, Published online 2016 Mar 1. doi: 10.1186/s12885-016-2199-z, PMCID: PMC4772351, Binimetinib inhibits MEK and is effective against neuroblastoma tumor cells with low NF1 expression
COBIMETINIB	Ryan MB, Der CJ, Wang-Gillam A, Cox AD. Targeting RAS-mutant cancers: is ERK the key? Trends Cancer. 2015 Nov 1;1(3):183-198. PubMed PMID: 26858988; PubMed Central PMCID: PMC4743050. Singh A, Ruan Y, Tippett T, Narendran A. Targeted inhibition of MEK1 by cobimetinib leads to differentiation and apoptosis in neuroblastoma cells. J Exp Clin Cancer Res. 2015 Sep 18;34:104. doi: 10.1186/s13046-015-0222-x. PubMed PMID: 26384788; PubMed Central PMCID: PMC4575431.
PD98059	Reiners JJ Jr, Lee JY, Clift RE, Dudley DT, Myrand SP. PD98059 is an equipotent antagonist of the aryl hydrocarbon receptor and inhibitor of mitogen-activated protein kinase kinase. Mol Pharmacol. 1998 Mar;53(3):438-45. PubMed PMID: 9495809.
ARRY-300	Ryan MB, Der CJ, Wang-Gillam A, Cox AD. Targeting RAS-mutant cancers: is ERK the key? Trends Cancer. 2015 Nov 1;1(3):183-198. PubMed PMID: 26858988; PubMed Central PMCID: PMC4743050.
AS703988	Ryan MB, Der CJ, Wang-Gillam A, Cox AD. Targeting RAS-mutant cancers: is ERK the key? Trends Cancer. 2015 Nov 1;1(3):183-198. PubMed PMID: 26858988; PubMed Central PMCID: PMC4743050.
CH5126766	Ryan MB, Der CJ, Wang-Gillam A, Cox AD. Targeting RAS-mutant cancers: is ERK the key? Trends Cancer. 2015 Nov 1;1(3):183-198. PubMed PMID: 26858988; PubMed Central PMCID: PMC4743050. Ishii N, Harada N, Joseph EW, Ohara K, Miura T, Sakamoto H, Matsuda Y, Tomii Y, Tachibana-Kondo Y, Iikura H, Aoki T, Shimma N, Arisawa M, Sowa Y, Poulikakos PI, Rosen N, Aoki Y, Sakai T. Enhanced inhibition of ERK signaling by a novel allosteric MEK inhibitor, CH5126766, that suppresses feedback reactivation of RAF activity. Cancer Res. 2013 Jul 1;73(13):4050-60. doi: 10.1158/0008-5472.CAN-12-3937. Epub 2013 May 10. PubMed PMID: 23667175; PubMed Central PMCID: PMC4115369.
U0126	Solenkova NV, Solodushko V, Cohen MV, Downey JM. Endogenous adenosine protects preconditioned heart during early minutes of reperfusion by activating Akt. Am J Physiol Heart Circ Physiol. 2006 Jan;290(1):H441-9. Epub 2005 Sep 9. PubMed PMID: 16155103.
WX-554	Akinleye A, Furqan M, Mukhi N, Ravella P, Liu D. MEK and the inhibitors: from bench to bedside. J Hematol Oncol. 2013 Apr 12;6:27. doi: 10.1186/1756-8722-6-27. Review. PubMed PMID: 23587417; PubMed Central PMCID: PMC3626705. Ryan MB, Der CJ, Wang-Gillam A, Cox AD. Targeting RAS-mutant cancers: is ERK the key? Trends Cancer. 2015 Nov 1;1(3):183-198. PubMed PMID: 26858988; PubMed Central PMCID: PMC4743050.
TAK-733	von Euw E, Atefi M, Attar N, Chu C, Zachariah S, Burgess BL, Mok S, Ng C, Wong DJ, Chmielowski B, Lichter DI, Koya RC, McCannel TA, Izmailova E, Ribas A. Antitumor effects of the investigational selective MEK inhibitor TAK733 against cutaneous and uveal melanoma cell lines. Mol Cancer. 2012 Apr 19;11:22. PubMed PMID: 22515704; PubMed Central PMCID: PMC3444881. Ryan MB, Der CJ, Wang-Gillam A, Cox AD. Targeting RAS-mutant cancers: is ERK the key? Trends Cancer. 2015 Nov 1;1(3):183-198. PubMed PMID: 26858988; PubMed Central PMCID: PMC4743050.
RO4987655	Zimmer L, Barlesi F, Martinez-Garcia M, Dieras V, Schellens JH, Spano JP, Middleton MR, Calvo E, Paz-Ares L, Larkin J, Pacey S, Venturi M, Kraeber-Bodéré F, Tessier JJ, Eberhardt WE, Paques M, Guarin E, Meresse V, Soria JC. Phase I expansion and pharmacodynamic study of the oral MEK inhibitor RO4987655 (CH4987655) in selected patients with advanced cancer with RAS-RAF mutations. Clin Cancer Res. 2014 Aug 15;20(16):4251-61. doi: 10.1158/1078-0432.CCR-14-0341. Epub 2014 Jun 19. PubMed PMID: 24947927. Akinleye A, Furqan M, Mukhi N, Ravella P, Liu D. MEK and the inhibitors: from bench to bedside. J Hematol Oncol. 2013 Apr 12;6:27. doi: 10.1186/1756-8722-6-27. Review. PubMed PMID: 23587417; PubMed Central PMCID: PMC3626705. Ryan MB, Der CJ, Wang-Gillam A, Cox AD. Targeting RAS-mutant cancers: is ERK the key? Trends Cancer. 2015 Nov 1;1(3):183-198. PubMed PMID: 26858988; PubMed Central PMCID: PMC4743050.
GDC-0623	Ryan MB, Der CJ, Wang-Gillam A, Cox AD. Targeting RAS-mutant cancers: is ERK the key? Trends Cancer. 2015 Nov 1;1(3):183-198. PubMed PMID: 26858988; PubMed Central PMCID: PMC4743050.

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COMPOUND NAME	REFERENCES
E6201	Ryan MB, Der CJ, Wang-Gillam A, Cox AD. Targeting RAS-mutant cancers: is ERK the key? Trends Cancer. 2015 Nov 1;1(3):183-198. PubMed PMID: 26858988; PubMed Central PMCID: PMC4743050. Kumar V, Schuck EL, Pelletier RD, Farah N, Condon KB, Ye M, Rowbottom C, King BM, Zhang ZY, Saxton PL, Wong YN. Pharmacokinetic characterization of a natural product-inspired novel MEK1 inhibitor E6201 in preclinical species. Cancer Chemother Pharmacol. 2012 Jan;69(1):229-37. doi: 10.1007/s00280-011-1687-8. Epub 2011 Jun 23. PubMed PMID: 21698359.
REFAMETINIB	Akinleye A, Furqan M, Mukhi N, Ravella P, Liu D. MEK and the inhibitors: from bench to bedside. J Hematol Oncol. 2013 Apr 12;6:27. doi: 10.1186/1756-8722-6-27. Review. PubMed PMID: 23587417; PubMed Central PMCID: PMC3626705. Ryan MB, Der CJ, Wang-Gillam A, Cox AD. Targeting RAS-mutant cancers: is ERK the key? Trends Cancer. 2015 Nov 1;1(3):183-198. PubMed PMID: 26858988; PubMed Central PMCID: PMC4743050.
AZD8330	Ryan MB, Der CJ, Wang-Gillam A, Cox AD. Targeting RAS-mutant cancers: is ERK the key? Trends Cancer. 2015 Nov 1;1(3):183-198. PubMed PMID: 26858988; PubMed Central PMCID: PMC4743050. Cohen RB, Aamdal S, Nyakas M, Cavallin M, Green D, Learoyd M, Smith I, Kurzrock R. A phase I dose-finding, safety and tolerability study of AZD8330 in patients with advanced malignancies. Eur J Cancer. 2013 May;49(7):1521-9. doi: 10.1016/j.ejca.2013.01.013. Epub 2013 Feb 21. PubMed PMID: 23433846.
PIMASERTIB	Ryan MB, Der CJ, Wang-Gillam A, Cox AD. Targeting RAS-mutant cancers: is ERK the key? Trends Cancer. 2015 Nov 1;1(3):183-198. PubMed PMID: 26858988; PubMed Central PMCID: PMC4743050. Akinleye A, Furqan M, Mukhi N, Ravella P, Liu D. MEK and the inhibitors: from bench to bedside. J Hematol Oncol. 2013 Apr 12;6:27. doi: 10.1186/1756-8722-6-27. Review. PubMed PMID: 23587417; PubMed Central PMCID: PMC3626705. Martinelli E, Troiani T, D'Aiuto E, Morgillo F, Vitagliano D, Capasso A, Costantino S, Ciuffreda LP, Merolla F, Vecchione L, De Vriendt V, Tejpar S, Nappi A, Sforza V, Martini G, Berrino L, De Palma R, Ciardiello F. Antitumor activity of pimasertib, a selective MEK 1/2 inhibitor, in combination with PI3K/mTOR inhibitors or with multi-targeted kinase inhibitors in pimasertib-resistant human lung and colorectal cancer cells. Int J Cancer. 2013 Nov;133(9):2089-101. doi: 10.1002/ijc.28236. Epub 2013 May 29. PubMed PMID: 23629727.
BIRABRESIB	Coudé MM, Braun T, Berrou J, Dupont M, Bertrand S, Masse A, Raffoux E, Itzykson R, Delord M, Riveiro ME, Herait P, Baruchel A, Dombret H, Gardin C. BET inhibitor OTX015 targets BRD2 and BRD4 and decreases c-MYC in acute leukemia cells. Oncotarget. 2015 Jul 10;6(19):17698-712. doi: 10.18632/oncotarget.4131. PubMed PMID: 25989842; PubMed Central PMCID: PMC4627339.
RO6870810	SHAPIRO, Geoffrey I., et al. Abstract A49: Clinically efficacy of the BET bromodomain inhibitor TEN-010 in an open-label substudy with patients with documented NUT-midline carcinoma (NMC). 2015.
NEO2734	Spriano F, Gaudio E, Cascione L, Tarantelli C, Melle F, Motta G, Priebe V, Rinaldi A, Golino G, Mensah AA, Aresu L, Zucca E, Pileri S, Witcher M, Brown B, Wahlestedt C, Giles F, Stathis A, Bertoni F. Antitumor activity of the dual BET and CBP/EP300 inhibitor NEO2734. Blood Adv. 2020 Sep 08;4(17):4124-4135. doi: 10.1182/bloodadvances.2020001879. PubMed PMID: 32882003; PubMed Central PMCID: PMC7479962. Ryan KR, Giles F, Morgan GJ. Targeting both BET and CBP/EP300 proteins with the novel dual inhibitors NEO2734 and NEO1132 leads to anti-tumor activity in Multiple Myeloma. Eur J Haematol. 2020 Sep 30;:. doi: 10.1111/ejh.13525. Epub 2020 Oct 30. PubMed PMID: 32997383.
CC-90010	Moreno V, Sepulveda JM, Vieito M, Hernández-Guerrero T, Doger B, Saavedra O, Ferrero O, Sarmiento R, Arias M, De Alvaro J, Di Martino J, Zuraek M, Sanchez-Pérez T, Aronchik I, Filvaroff EH, Lamba M, Hanna B, Nikolova Z, Braña I. Phase I study of CC-90010, a reversible, oral BET inhibitor in patients with advanced solid tumors and relapsed/refractory non-Hodgkin's lymphoma. Ann Oncol. 2020 Mar 30;:. doi: 10.1016/j.annonc.2020.03.294. Epub 2020 Jun 30. PubMed PMID: 32240793.
PELABRESIB	Albrecht BK, Gehling VS, Hewitt MC, Vaswani RG, Côté A, Leblanc Y, Nasveschuk CG, Bellon S, Bergeron L, Campbell R, Cantone N, Cooper MR, Cummings RT, Jayaram H, Joshi S, Mertz JA, Neiss A, Normant E, O'Meara M, Pardo E, Poy F, Sandy P, Supko J, Sims RJ 3rd, Harmange JC, Taylor AM, Audia JE. Identification of a Benzoisoxazoloazepine Inhibitor (CPI-0610) of the Bromodomain and Extra-Terminal (BET) Family as a Candidate for Human Clinical Trials. J Med Chem. 2016 Feb 25;59(4):1330-9. doi: 10.1021/acs.jmedchem.5b01882. Epub 2016 Feb 4. PubMed PMID: 26815195.
AZD5153	Rhyasen GW, Hattersley MM, Yao Y, Dulak A, Wang W, Petteruti P, Dale IL, Boiko S, Cheung T, Zhang J, Wen S, Castriotta L, Lawson D, Collins M, Bao L, Ahdesmaki MJ, Walker G, O'Connor G, Yeh TC, Rabow AA, Dry JR, Reimer C, Lyne P, Mills GB, Fawell SE, Waring MJ, Zinda M, Clark E, Chen H. AZD5153: A Novel Bivalent BET Bromodomain Inhibitor Highly Active against Hematologic Malignancies. Mol Cancer Ther. 2016 Nov;15(11):2563-2574. Epub 2016 Aug 29. PubMed PMID: 27573426.
MOLIBRESIB	DAWSON, Mark, et al. A phase I study of GSK525762, a selective bromodomain (BRD) and extra terminal protein (BET) inhibitor: results from part 1 of phase I/II open label single agent study in patients with acute myeloid leukemia (AML). 2017.
BMS-986158	Ocaña A, Nieto-Jiménez C, Pandiella A. BET inhibitors as novel therapeutic agents in breast cancer. Oncotarget. 2017 Aug 1;8(41):71285-71291. doi: 10.18632/oncotarget.19744. eCollection 2017 Sep 19. Review. PubMed PMID: 29050361; PubMed Central PMCID: PMC5642636.

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COMPOUND NAME	REFERENCES
ADAVOSERTIB	Caldwell JT, Edwards H, Buck SA, Ge Y, Taub JW. Targeting the wee1 kinase for treatment of pediatric Down syndrome acute myeloid leukemia. Pediatr Blood Cancer. 2014 Oct;61(10):1767-73. doi: 10.1002/pbc.25081. Epub 2014 Jun 24. PubMed PMID: 24962331. Ma H, Takahashi A, Sejimo Y, Adachi A, Kubo N, Isono M, Yoshida Y, Kanai T, Ohno T, Nakano T. Targeting of Carbon Ion-Induced G2 Checkpoint Activation in Lung Cancer Cells Using Wee-1 Inhibitor MK-1775. Radiat Res. 2015 Dec;184(6):660-9. doi: 10.1667/RR14171.1. Epub 2015 Feb 08. PubMed PMID: 26645158. Hirai H, Iwasawa Y, Okada M, Arai T, Nishibata T, Kobayashi M, Kimura T, Kaneko N, Ohtani J, Yamanaka K, Itadani H, Takahashi-Suzuki I, Fukasawa K, Oki H, Nambu T, Jiang J, Sakai T, Arakawa H, Sakamoto T, Sagara T, Yoshizumi T, Mizuarai S, Kotani H. Small-molecule inhibition of Wee1 kinase by MK-1775 selectively sensitizes p53-deficient tumor cells to DNA-damaging agents. Mol Cancer Ther. 2009 Nov;8(11):2992-3000. doi: 10.1158/1535-7163.MCT-09-0463. PubMed PMID: 19887545. Lheureux S, Cristea MC, Bruce JP, Garg S, Cabanero M, Mantia-Smaldone G, Olawaiye AB, Ellard SL, Weberpals JI, Wahner Hendrickson AE, Fleming GF, Welch S, Dhani NC, Stockley T, Rath P, Karakasis K, Jones GN, Jenkins S, Rodriguez-Canales J, Tracy M, Tan Q, Bowering V, Udagani S, Wang L, Kunos CA, Chen E, Pugh TJ, Oza AM. Adavosertib plus gemcitabine for platinum-resistant or platinum-refractory recurrent ovarian cancer: a double-blind, randomised, placebo-controlled, phase 2 trial. Lancet. 2021 Jan 23;397(10271):281-292. doi: 10.1016/S0140-6736(20)32554-X. PubMed PMID: 33485453. Leijen S, van Geel RM, Pavlick AC, Tibes R, Rosen L, Razak AR, Lam R, Demuth T, Rose S, Lee MA, Freshwater T, Shumway S, Liang LW, Oza AM, Schellens JH, Shapiro GI. Phase I Study Evaluating WEE1 Inhibitor AZD1775 As Monotherapy and in Combination With Gemcitabine, Cisplatin, or Carboplatin in Patients With Advanced Solid Tumors. J Clin Oncol. 2016 Dec 20;34(36):4371-4380. doi: 10.1200/JCO.2016.67.5991. Epub 2016 Oct 31. PubMed PMID: 27601554.
Barasertib	Goto H, Yoshino Y, Ito M, Nagai J, Kumamoto T, Inukai T, Sakurai Y, Miyagawa N, Keino D, Yokosuka T, Iwasaki F, Hamanoue S, Shiomi M, Goto S. Aurora B kinase as a therapeutic target in acute lymphoblastic leukemia. Cancer Chemother Pharmacol. 2020 Apr;85(4):773-783. doi: 10.1007/s00280-020-04045-9. Epub 2020 Jun 06. PubMed PMID: 32144432. Kantarjian HM, Martinelli G, Jabbour EJ, Quintás-Cardama A, Ando K, Bay JO, Wei A, Gröpper S, Papayannidis C, Owen K, Pike L, Schmitt N, Stockman PK, Giagounidis A, . Stage I of a phase 2 study assessing the efficacy, safety, and tolerability of barasertib (AZD1152) versus low-dose cytosine arabinoside in elderly patients with acute myeloid leukemia. Cancer. 2013 Jul 15;119(14):2611-9. doi: 10.1002/cncr.28113. Epub 2013 Jun 19. PubMed PMID: 23605952; PubMed Central PMCID: PMC4132839. Diaz RJ, Golbourn B, Shekarforoush M, Smith CA, Rutka JT. Aurora kinase B/C inhibition impairs malignant glioma growth in vivo. J Neurooncol. 2012 Jul;108(3):349-60. doi: 10.1007/s11060-012-0835-2. Epub 2012 Jun 01. PubMed PMID: 22382783.
FADRACICLIB	Kawakami M, Mustachio LM, Rodriguez-Canales J, Mino B, Roszik J, Tong P, Wang J, Lee JJ, Myung JH, Heymach JV, Johnson FM, Hong S, Zheng L, Hu S, Villalobos PA, Behrens C, Wistuba I, Freemantle S, Liu X, Dmitrovsky E. Next-Generation CDK2/9 Inhibitors and Anaphase Catastrophe in Lung Cancer. J Natl Cancer Inst. 2017 Jun 1;109(6). doi: 10.1093/jnci/djw297. PubMed PMID: 28376145. Chantkran W, Hsieh YC, Zheleva D, Frame S, Wheadon H, Copland M. Interrogation of novel CDK2/9 inhibitor fadraciclib (CYC065) as a potential therapeutic approach for AML. Cell Death Discov. 2021 Jun 10;7(1):137. doi: 10.1038/s41420-021-00496-y. Epub 2021 June 10. PubMed PMID: 34112754.
SELICICLIB	Kawakami M, Mustachio LM, Rodriguez-Canales J, Mino B, Roszik J, Tong P, Wang J, Lee JJ, Myung JH, Heymach JV, Johnson FM, Hong S, Zheng L, Hu S, Villalobos PA, Behrens C, Wistuba I, Freemantle S, Liu X, Dmitrovsky E. Next-Generation CDK2/9 Inhibitors and Anaphase Catastrophe in Lung Cancer. J Natl Cancer Inst. 2017 Jun 1;109(6). doi: 10.1093/jnci/djw297. PubMed PMID: 28376145.
SNS-032	Mariaule G, Belmont P. Cyclin-dependent kinase inhibitors as marketed anticancer drugs: where are we now? A short survey. Molecules. 2014 Sep 11;19(9):14366-82. doi: 10.3390/molecules190914366. Review. PubMed PMID: 25215591.
CD437	Larsson CA, Moyer SM, Liu B, Michel KA, Pant V, Yang P, Wong J, El-Naggar AK, Krahe R, Lozano G. Synergistic and additive effect of retinoic acid in circumventing resistance to p53 restoration. Proc Natl Acad Sci U S A. 2018 02 27;115(9):2198-2203. doi: 10.1073/pnas.1719001115. Epub 2018 Oct 13. PubMed PMID: 29440484; PubMed Central PMCID: PMC5834709.
M3814	Sun Q, Guo Y, Liu X, Czauderna F, Carr MI, Zenke FT, Blaukat A, Vassilev LT. Therapeutic Implications of p53 Status on Cancer Cell Fate Following Exposure to Ionizing Radiation and the DNA-PK Inhibitor M3814. Mol Cancer Res. 2019 12;17(12):2457-2468. doi: 10.1158/1541-7786.MCR-19-0362. Epub 2019 Jul 24. PubMed PMID: 31551253.
FIMEPINOSTAT	Qian C, Lai CJ, Bao R, Wang DG, Wang J, Xu GX, Atoyan R, Qu H, Yin L, Samson M, Zifcak B, Ma AW, DellaRocca S, Borek M, Zhai HX, Cai X, Voi M. Cancer network disruption by a single molecule inhibitor targeting both histone deacetylase activity and phosphatidylinositol 3-kinase signaling. Clin Cancer Res. 2012 Aug 01;18(15):4104-13. doi: 10.1158/1078-0432.CCR-12-0055. Epub 2012 Sep 12. PubMed PMID: 22693356. Daniel J. Landsburg, Radhakrishnan Ramchandren, Petronella J Lugtenburg, Kevin R. Kelly, Anas Younes, Robert Gharavi, David P. Tuck, Stefan Klaus Barta; A Pooled Analysis of Relapsed/Refractory Diffuse Large B-Cell Lymphoma Patients Treated with the Dual PI3K and HDAC Inhibitor Fimepinostat (CUDC-907), Including Patients with MYC-Altered Disease. Blood 2018; 132 (Supplement 1): 4184. doi: https://doi.org/10.1182/blood-2018-99-112527

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COMPOUND NAME	REFERENCES
PAZOPANIB	Gupta S, Spiess PE. The prospects of pazopanib in advanced renal cell carcinoma. Ther Adv Urol. 2013 Oct;5(5): 223-32. doi: 10.1177/1756287213495099. PubMed PMID: 24082917; PubMed Central PMCID: PMC3763778. Ganjoo KN, Villalobos VM, Kamaya A, Fisher GA, Butrynski JE, Morgan JA, Wagner AJ, D'Adamo D, McMillan A, Demetri GD, George S. A multicenter phase II study of pazopanib in patients with advanced gastrointestinal stromal tumors (GIST) following failure of at least imatinib and sunitinib. Ann Oncol. 2014 Jan;25(1):236-40. doi: 10.1093 /annonc/mdt484. PubMed PMID: 24356634. Hashimoto A, Takada K, Takimoto R, Horiguchi H, Sato T, Iyama S, Murase K, Ono K, Tatekoshi A, Hayashi T, Miyanishi K, Sato Y, Kobune M, Hirayama Y, Kitamura H, Nakanishi K, Masumori N, Hasegawa T, Kato J. [Effective treatment of metastatic rhabdomyosarcoma with pazopanib]. Gan To Kagaku Ryoho. 2014 Aug;41(8):1041-4. Japanese. PubMed PMID: 25132042. Sonpavde G, Hutson TE. Pazopanib: a novel multitargeted tyrosine kinase inhibitor. Curr Oncol Rep. 2007 Mar;9(2): 115-9. Review. PubMed PMID: 17288876. Nguyen DT, Shayahi S. Pazopanib: approval for soft-tissue sarcoma. J Adv Pract Oncol. 2013 Jan;4(1):53-7. Review. PubMed PMID: 25031981; PubMed Central PMCID: PMC4093375.
ENTOSPLETINIB	Burd A, Levine RL, Ruppert AS, Mims AS, Borate U, Stein EM, Patel P, Baer MR, Stock W, Deininger M, Blum W, Schiller G, Olin R, Litzow M, Foran J, Lin TL, Ball B, Boyiadzis M, Traer E, Odenike O, Arellano M, Walker A, Duong VH, Kovacsovics T, Collins R, Shoben AB, Heerema NA, Foster MC, Vergilio JA, Brennan T, Vietz C, Severson E, Miller M, Rosenberg L, Marcus S, Yocum A, Chen T, Stefanos M, Druker B, Byrd JC. Precision medicine treatment in acute myeloid leukemia using prospective genomic profiling: feasibility and preliminary efficacy of the Beat AML Master Trial. Nat Med. 2020 Oct 26;:. doi: 10.1038/s41591-020-1089-8. Epub 2020 Nov 26. PubMed PMID: 33106665.
PEVONEDISTAT	Burd A, Levine RL, Ruppert AS, Mims AS, Borate U, Stein EM, Patel P, Baer MR, Stock W, Deininger M, Blum W, Schiller G, Olin R, Litzow M, Foran J, Lin TL, Ball B, Boyiadzis M, Traer E, Odenike O, Arellano M, Walker A, Duong VH, Kovacsovics T, Collins R, Shoben AB, Heerema NA, Foster MC, Vergilio JA, Brennan T, Vietz C, Severson E, Miller M, Rosenberg L, Marcus S, Yocum A, Chen T, Stefanos M, Druker B, Byrd JC. Precision medicine treatment in acute myeloid leukemia using prospective genomic profiling: feasibility and preliminary efficacy of the Beat AML Master Trial. Nat Med. 2020 Oct 26;:. doi: 10.1038/s41591-020-1089-8. Epub 2020 Nov 26. PubMed PMID: 33106665.
BEVACIZUMAB	Srivastava H, Dewan A, Sharma SK, Negi P, Dewan AK, Pasricha S, Mehrotra K. Adjuvant Radiation Therapy and Temozolomide in Gliosarcoma: Is It Enough? Case Series of Seven Patients. Asian J Neurosurg. 2018 Apr-Jun;13(2): 297-301. doi: 10.4103/ajns.AJNS_151_16. PubMed PMID: 29682024; PubMed Central PMCID: PMC5898095. Coleman RL, Brady MF, Herzog TJ, Sabbatini P, Armstrong DK, Walker JL, et al. A phase III randomized controlled clinical trial of carboplatin and paclitaxel alone or in combination with bevacizumab followed by bevacizumab and secondary cytoreductive surgery in platinum-sensitive, recurrent ovarian, peritoneal primary and fallopian tube cancer (Gynecologic Oncology Group 0213). Gynecologic Oncology. 2015 Apr 1;137:3–4. Echarri MJ, Lopez-Martin A, Hitt R. Targeted Therapy in Locally Advanced and Recurrent/Metastatic Head and Neck Squamous Cell Carcinoma (LA-R/M HNSCC). Cancers (Basel). 2016 Feb 26;8(3). pii: E27. doi: 10.3390 /cancers8030027. Review. PubMed PMID: 26927178; PubMed Central PMCID: PMC4810111. L. Moreno, V. Moroz, C. Owens, D. Valteau-Couanet, M. Gambart, V. Castel, N. van Eijkelenburg, A. Castellano, K. Nysom, N. Gerber, G. Laureys, R. Ladenstein, E. Thebaud, D. Murphy, B. Morland, S. Vaidya, M. Elliott, A.D. Pearson, K. Wheatley. LBA64 - Bevacizumab for children with relapsed & refractory high-risk neuroblastoma (RR-HRNB): Results of the BEACON-neuroblastoma randomized phase II trial - A European ITCC-SIOPEN trial. Annals of Oncology. 2019;30:(Supplement 5):v901. doi: 10.1093/annonc/mdz394.061. Lou E, Sumrall AL, Turner S, Peters KB, Desjardins A, Vredenburgh JJ, McLendon RE, Herndon JE 2nd, McSherry F, Norfleet J, Friedman HS, Reardon DA. Bevacizumab therapy for adults with recurrent/progressive meningioma: a retrospective series. J Neurooncol. 2012 Aug;109(1):63-70. doi: 10.1007/s11060-012-0861-0. Epub 2012 Apr 26. PubMed PMID: 22535433; PubMed Central PMCID: PMC3404217.
SGI-1776	Leung MS, Chan KK, Dai WJ, Wong CY, Au KY, Wong PY, Wong CC, Lee TK, Ng IO, Kao WJ, Lo RC. Anti-tumour effects of PIM kinase inhibition on progression and chemoresistance of hepatocellular carcinoma. J Pathol. 2020 Sep;252(1):65-76. doi: 10.1002/path.5492. Epub 2020 Jan 31. PubMed PMID: 32558942.
AMG 900	Carducci M, Shaheen M, Markman B, Hurvitz S, Mahadevan D, Kotasek D, Goodman OB, Rasmussen E, Chow V, Juan G, Friberg GR, Gamelin E, Vogl FD, Desai J. A phase 1, first-in-human study of AMG 900, an orally administered pan-Aurora kinase inhibitor, in adult patients with advanced solid tumors. Invest New Drugs. 2018 12; 36(6):1060-1071. doi: 10.1007/s10637-018-0625-6. Epub 2018 Jun 07. PubMed PMID: 29980894; PubMed Central PMCID: PMC6639057.

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COMPOUND NAME	REFERENCES
BERZOSERTIB	Yap TA, O'Carrigan B, Penney MS, Lim JS, Brown JS, de Miguel Luken MJ, Tunariu N, Perez-Lopez R, Rodrigues DN, Riisnaes R, Figueiredo I, Carreira S, Hare B, McDermott K, Khalique S, Williamson CT, Natrajan R, Pettitt SJ, Lord CJ, Banerji U, Pollard J, Lopez J, de Bono JS. Phase I Trial of First-in-Class ATR Inhibitor M6620 (VX-970) as Monotherapy or in Combination With Carboplatin in Patients With Advanced Solid Tumors. J Clin Oncol. 2020 Jun 22;:JCO1902404. doi: 10.1200/JCO.19.02404. Epub 2020 Jul 22. PubMed PMID: 32568634. Hall AB, Newsome D, Wang Y, Boucher DM, Eustace B, Gu Y, Hare B, Johnson MA, Milton S, Murphy CE, Takemoto D, Tolman C, Wood M, Charlton P, Charrier JD, Furey B, Golec J, Reaper PM, Pollard JR. Potentiation of tumor responses to DNA damaging therapy by the selective ATR inhibitor VX-970. Oncotarget. 2014 Jul 30;5(14):5674-85. doi: 10.18632/oncotarget.2158. PubMed PMID: 25010037; PubMed Central PMCID: PMC4170644. Konstantinopoulos PA, Cheng SC, Wahner Hendrickson AE, Penson RT, Schumer ST, Doyle LA, Lee EK, Kohn EC, Duska LR, Crispens MA, Olawaiye AB, Winer IS, Barroilhet LM, Fu S, McHale MT, Schilder RJ, Färkkilä A, Chowdhury D, Curtis J, Quinn RS, Bowes B, D'Andrea AD, Shapiro GI, Matulonis UA. Berzosertib plus gemcitabine versus gemcitabine alone in platinum-resistant high-grade serous ovarian cancer: a multicentre, open-label, randomised, phase 2 trial. Lancet Oncol. 2020 07;21(7):957-968. doi: 10.1016/S1470-2045(20)30180-7. Epub 2020 Jul 15. PubMed PMID: 32553118.
ABEMACICLIB	Raub TJ, Wishart GN, Kulanthaivel P, Staton BA, Ajamie RT, Sawada GA, Gelbert LM, Shannon HE, Sanchez-Martinez C, De Dios A. Brain Exposure of Two Selective Dual CDK4 and CDK6 Inhibitors and the Antitumor Activity of CDK4 and CDK6 Inhibition in Combination with Temozolomide in an Intracranial Glioblastoma Xenograft. Drug Metab Dispos. 2015 Sep;43(9):1360-71. doi: 10.1124/dmd.114.062745. Epub 2015 Jan 06. PubMed PMID: 26149830. MORSCHHAUSER, Franck, et al. Clinical activity of abemaciclib (LY2835219), a cell cycle inhibitor selective for CDK4 and CDK6, in patients with relapsed or refractory mantle cell lymphoma. 2014. http://ascopubs.org/doi/abs/10.1200/JCO.2017.35.15_suppl.TPS4150 Dickler MN, Tolaney SM, Rugo HS, Cortés J, Diéras V, Patt D, Wildiers H, Hudis CA, O'Shaughnessy J, Zamora E, Yardley DA, Frenzel M, Koustenis A, Baselga J. MONARCH 1, A Phase II Study of Abemaciclib, a CDK4 and CDK6 Inhibitor, as a Single Agent, in Patients with Refractory HR(+)/HER2(-) Metastatic Breast Cancer. Clin Cancer Res. 2017 Sep 1;23(17):5218-5224. doi: 10.1158/1078-0432.CCR-17-0754. Epub 2017 May 22. PubMed PMID: 28533223; PubMed Central PMCID: PMC5581697.
PALBOCICLIB	Fry DW, Harvey PJ, Keller PR, Elliott WL, Meade M, Trachet E, Albassam M, Zheng X, Leopold WR, Pryer NK, Toogood PL. Specific inhibition of cyclin-dependent kinase 4/6 by PD 0332991 and associated antitumor activity in human tumor xenografts. Mol Cancer Ther. 2004 Nov;3(11):1427-38. PubMed PMID: 15542782. Konecny GE, Wahner Hendrickson AE, Jatoi A, Burton JK, Paroly J, Glaspy JA, et al. A multicenter open-label phase II study of the efficacy and safety of palbociclib a cyclin-dependent kinases 4 and 6 inhibitor in patients with recurrent ovarian cancer. JCO. 2016 May 20;34(15_suppl):5557–5557. LEONARD, John P., et al. Selective CDK4/6 inhibition with tumor responses by PD0332991 in patients with mantle cell lymphoma. Blood, 2012, 119.20: 4597-4607. Kollmann K, Briand C, Bellutti F, Schicher N, Blunder S, Zojer M, Hoeller C. The interplay of CDK4 and CDK6 in melanoma. Oncotarget. 2019 Feb 15;10(14):1346-1359. doi: 10.18632/oncotarget.26515. eCollection 2019 Feb 15. PubMed PMID: 30858922; PubMed Central PMCID: PMC6402717. Dosil MA, Mirantes C, Eritja N, Felip I, Navaridas R, Gatius S, Santacana M, Colàs E, Moiola C, Schoenenberger JA, Encinas M, Garí E, Matias-Guiu X, Dolcet X. Palbociclib has antitumour effects on Pten-deficient endometrial neoplasias. J Pathol. 2017 Jun;242(2):152-164. doi: 10.1002/path.4896. Epub 2017 Apr 28. PubMed PMID: 28349562.
EPRENETAPOPT	Fransson Å, Glaessgen D, Alfredsson J, Wiman KG, Bajalica-Lagercrantz S, Mohell N. Strong synergy with APR-246 and DNA-damaging drugs in primary cancer cells from patients with TP53 mutant High-Grade Serous ovarian cancer. J Ovarian Res. 2016 May 14;9(1):27. doi: 10.1186/s13048-016-0239-6. PubMed PMID: 27179933; PubMed Central PMCID: PMC4868029.
RIBOCICLIB	Condorelli R, Spring L, O'Shaughnessy J, Lacroix L, Bailleux C, Scott V, Dubois J, Nagy RJ, Lanman RB, Iafrate AJ, Andre F, Bardia A. Polyclonal RB1 mutations and acquired resistance to CDK 4/6 inhibitors in patients with metastatic breast cancer. Ann Oncol. 2018 Mar 1;29(3):640-645. doi: 10.1093/annonc/mdx784. PubMed PMID: 29236940.
TAK-960	Hikichi Y, Honda K, Hikami K, Miyashita H, Kaieda I, Murai S, Uchiyama N, Hasegawa M, Kawamoto T, Sato T, Ichikawa T, Cao S, Nie Z, Zhang L, Yang J, Kuida K, Kupperman E. TAK-960, a novel, orally available, selective inhibitor of polo-like kinase 1, shows broad-spectrum preclinical antitumor activity in multiple dosing regimens. Mol Cancer Ther. 2012 Mar;11(3):700-9. doi: 10.1158/1535-7163.MCT-11-0762. Epub 2011 Dec 21. PubMed PMID: 22188812.
NMS-P937	Sero V, Tavanti E, Vella S, Hattinger CM, Fanelli M, Michelacci F, Versteeg R, Valsasina B, Gudeman B, Picci P, Serra M. Targeting polo-like kinase 1 by NMS-P937 in osteosarcoma cell lines inhibits tumor cell growth and partially overcomes drug resistance. Invest New Drugs. 2014 Sep 7. [Epub ahead of print] PubMed PMID: 25193492.
GSK-461364	Olmos D, Barker D, Sharma R, Brunetto AT, Yap TA, Taegtmeyer AB, Barriuso J, Medani H, Degenhardt YY, Allred AJ, Smith DA, Murray SC, Lampkin TA, Dar MM, Wilson R, de Bono JS, Blagden SP. Phase I study of GSK461364, a specific and competitive Polo-like kinase 1 inhibitor, in patients with advanced solid malignancies. Clin Cancer Res. 2011 May 15;17(10):3420-30. doi: 10.1158/1078-0432.CCR-10-2946. Epub 2011 Apr 1. PubMed PMID: 21459796.
BI 2536	Oliveira JC, Pezuk JA, Brassesco MS, Morales AG, Queiroz RG, Scrideli CA, Tone LG. PLK1 expression and BI 2536 effects in childhood acute lymphoblastic leukemia. Pediatr Blood Cancer. 2014 Jul;61(7):1227-31. doi: 10.1002/pbc.24978. Epub 2014 Feb 12. PubMed PMID: 24519995.

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COMPOUND NAME	REFERENCES
VOLASERTIB	Gjertsen BT, Schöffski P. Discovery and development of the Polo-like kinase inhibitor volasertib in cancer therapy. Leukemia. 2014 Jul 16. doi: 10.1038/leu.2014.222. [Epub ahead of print] PubMed PMID: 25027517.
PK7088	Liu X, Wilcken R, Joerger AC, Chuckowree IS, Amin J, Spencer J, Fersht AR. Small molecule induced reactivation of mutant p53 in cancer cells. Nucleic Acids Res. 2013 Jul;41(12):6034-44. doi: 10.1093/nar/gkt305. Epub 2013 Nov 29. PubMed PMID: 23630318; PubMed Central PMCID: PMC3695503.
WITHANONE	Sundar D, Yu Y, Katiyar SP, Putri JF, Dhanjal JK, Wang J, Sari AN, Kolettas E, Kaul SC, Wadhwa R. Wild type p53 function in p53Y220C mutant harboring cells by treatment with Ashwagandha derived anticancer withanolides: bioinformatics and experimental evidence. J Exp Clin Cancer Res. 2019 Feb 26;38(1):103. doi: 10.1186/s13046-019-1099-x. Epub 2019 Nov 26. PubMed PMID: 30808373; PubMed Central PMCID: PMC6390572.
WITHAFERIN A	Sundar D, Yu Y, Katiyar SP, Putri JF, Dhanjal JK, Wang J, Sari AN, Kolettas E, Kaul SC, Wadhwa R. Wild type p53 function in p53Y220C mutant harboring cells by treatment with Ashwagandha derived anticancer withanolides: bioinformatics and experimental evidence. J Exp Clin Cancer Res. 2019 Feb 26;38(1):103. doi: 10.1186/s13046-019-1099-x. Epub 2019 Nov 26. PubMed PMID: 30808373; PubMed Central PMCID: PMC6390572.
NINTEDANIB	Hilberg F, Roth GJ, Krssak M, Kautschitsch S, Sommergruber W, Tontsch-Grunt U, Garin-Chesa P, Bader G, Zoephel A, Quant J, Heckel A, Rettig WJ. BIBF 1120: triple angiokinase inhibitor with sustained receptor blockade and good antitumor efficacy. Cancer Res. 2008 Jun 15;68(12):4774-82. doi: 10.1158/0008-5472.CAN-07-6307. PubMed PMID: 18559524. Capdevila J, Carrato A, Tabernero J, Grande E. What could Nintedanib (BIBF 1120), a triple inhibitor of VEGFR, PDGFR, and FGFR, add to the current treatment options for patients with metastatic colorectal cancer? Crit Rev Oncol Hematol. 2014 May 14. pii: S1040-8428(14)00083-3. doi: 10.1016/j.critrevonc.2014.05.004. [Epub ahead of print] Review. PubMed PMID: 24924525. Mulligan LM. RET revisited: expanding the oncogenic portfolio. Nat Rev Cancer. 2014 Mar;14(3):173-86. doi: 10.1038/nrc3680. Review. PubMed PMID: 24561444. Kim Y, Lee SJ, Lee JY, Lee SH, Sun JM, Park K, An HJ, Cho JY, Kang EJ, Lee HY, Kim J, Keam B, Kim HR, Lee KE, Choi MY, Lee KH, Ahn MJ. Clinical trial of nintedanib in patients with recurrent or metastatic salivary gland cancer of the head and neck: A multicenter phase 2 study (Korean Cancer Study Group HN14-01). Cancer. 2017 Jun 1;123(11):1958-1964. doi: 10.1002/cncr.30537. Epub 2017 Jan 19. PubMed PMID: 28102887. du Bois A, Kristensen G, Ray-Coquard I, Reuss A, Pignata S, Colombo N, Denison U, Vergote I, Del Campo JM, Ottevanger P, Heubner M, Minarik T, Sevin E, de Gregorio N, Bidziński M, Pfisterer J, Malander S, Hilpert F, Mirza MR, Scambia G, Meier W, Nicoletto MO, Bjørge L, Lortholary A, Sailer MO, Merger M, Harter P; AGO Study Group led Gynecologic Cancer Intergroup/European Network of Gynaecologic Oncology Trials Groups Intergroup Consortium. Standard first-line chemotherapy with or without nintedanib for advanced ovarian cancer (AGO-OVAR 12): a randomised, double-blind, placebo-controlled phase 3 trial. Lancet Oncol. 2016 Jan;17(1):78-89. doi: 10.1016/S1470-2045(15)00366-6. Epub 2015 Nov 16. PubMed PMID: 26590673.
PONATINIB	Ren M, Hong M, Liu G, Wang H, Patel V, Biddinger P, Silva J, Cowell J, Hao Z. Novel FGFR inhibitor ponatinib suppresses the growth of non-small cell lung cancer cells overexpressing FGFR1. Oncol Rep. 2013 Jun;29(6):2181-90. doi: 10.3892/or.2013.2386. Epub 2013 Apr 4. PubMed PMID: 23563700. O'Hare T, Shakespeare WC, Zhu X, Eide CA, Rivera VM, Wang F, Adrian LT, Zhou T, Huang WS, Xu Q, Metcalf CA 3rd, Tyner JW, Loriaux MM, Corbin AS, Wardwell S, Ning Y, Keats JA, Wang Y, Sundaramoorthi R, Thomas M, Zhou D, Snodgrass J, Commodore L, Sawyer TK, Dalgarno DC, Deininger MW, Druker BJ, Clackson T. AP24534, a pan-BCR-ABL inhibitor for chronic myeloid leukemia, potently inhibits the T315I mutant and overcomes mutation-based resistance. Cancer Cell. 2009 Nov 6;16(5):401-12. doi: 10.1016/j.ccr.2009.09.028. PubMed PMID: 19878872; PubMed Central PMCID: PMC2804470. Katoh M. FGFR inhibitors: Effects on cancer cells, tumor microenvironment and whole-body homeostasis (Review). Int J Mol Med. 2016 Jul;38(1):3-15. doi: 10.3892/ijmm.2016.2620. Epub 2016 May 31. Review. PubMed PMID: 27245147; PubMed Central PMCID: PMC4899036. Sadovnik I, Lierman E, Peter B, Herrmann H, Suppan V, Stefanzl G, Haas O, Lion T, Pickl W, Cools J, Vandenberghe P, Valent P. Identification of Ponatinib as a potent inhibitor of growth, migration, and activation of neoplastic eosinophils carrying FIP1L1-PDGFRA. Exp Hematol. 2014 Apr;42(4):282-293.e4. doi: 10.1016/j.exphem.2013.12.007. Epub 2014 Jan 6. PubMed PMID: 24407160. Gibbons DL, Pricl S, Posocco P, Laurini E, Fermeglia M, Sun H, Talpaz M, Donato N, Quintás-Cardama A. Molecular dynamics reveal BCR-ABL1 polymutants as a unique mechanism of resistance to PAN-BCR-ABL1 kinase inhibitor therapy. Proc Natl Acad Sci U S A. 2014 Mar 4;111(9):3550-5. doi: 10.1073/pnas.1321173111. Epub 2014 Feb 18. PubMed PMID: 24550512; PubMed Central PMCID: PMC3948238.

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COMPOUND NAME	REFERENCES
CELECOXIB	Yang J, Yue JB, Liu J, Sun XD, Hu XD, Sun JJ, Li YH, Yu JM. Effect of celecoxib on inhibiting tumor repopulation during radiotherapy in human FaDu squamous cell carcinoma. Contemp Oncol (Pozn). 2014;18(4):260-7. doi: 10.5114/wo.2014.43932. Epub 2014 Aug 3. PubMed PMID: 25258584; PubMed Central PMCID: PMC4171473. Bieniek J, Childress C, Swatski MD, Yang W. COX-2 inhibitors arrest prostate cancer cell cycle progression by down-regulation of kinetochore/centromere proteins. Prostate. 2014 Jul;74(10):999-1011. doi: 10.1002/pros.22815. Epub 2014 May 07. PubMed PMID: 24802614. Hsu AL, Ching TT, Wang DS, Song X, Rangnekar VM, Chen CS. The cyclooxygenase-2 inhibitor celecoxib induces apoptosis by blocking Akt activation in human prostate cancer cells independently of Bcl-2. J Biol Chem. 2000 Apr 14;275(15):11397-403. doi: 10.1074/jbc.275.15.11397. PubMed PMID: 10753955. Bertagnolli MM, Eagle CJ, Zauber AG, Redston M, Solomon SD, Kim K, Tang J, Rosenstein RB, Wittes J, Corle D, Hess TM, Woloj GM, Boisserie F, Anderson WF, Viner JL, Bagheri D, Burn J, Chung DC, Dewar T, Foley TR, Hoffman N, Macrae F, Pruitt RE, Saltzman JR, Salzberg B, Sylwestrowicz T, Gordon GB, Hawk ET; APC Study Investigators.. Celecoxib for the prevention of sporadic colorectal adenomas. N Engl J Med. 2006 Aug 31;355(9):873-84. PubMed PMID: 16943400. Solomon SD, McMurray JJ, Pfeffer MA, Wittes J, Fowler R, Finn P, Anderson WF, Zauber A, Hawk E, Bertagnolli M; Adenoma Prevention with Celecoxib (APC) Study Investigators.. Cardiovascular risk associated with celecoxib in a clinical trial for colorectal adenoma prevention. N Engl J Med. 2005 Mar 17;352(11):1071-80. PubMed PMID: 15713944.
SUNITINIB	O'Farrell AM, Foran JM, Fiedler W, Serve H, Paquette RL, Cooper MA, Yuen HA, Louie SG, Kim H, Nicholas S, Heinrich MC, Berdel WE, Bello C, Jacobs M, Scigalla P, Manning WC, Kelsey S, Cherrington JM. An innovative phase I clinical study demonstrates inhibition of FLT3 phosphorylation by SU11248 in acute myeloid leukemia patients. Clin Cancer Res. 2003 Nov 15;9(15):5465-76. PubMed PMID: 14654525. Zimmermann K, Schmittel A, Steiner U, Asemissen AM, Knoedler M, Thiel E, Miller K, Keilholz U. Sunitinib treatment for patients with advanced clear-cell renal-cell carcinoma after progression on sorafenib. Oncology. 2009;76(5):350-4. doi: 10.1159/000209961. Epub 2009 Mar 24. PubMed PMID: 19321976. Roskoski R Jr. Sunitinib: a VEGF and PDGF receptor protein kinase and angiogenesis inhibitor. Biochem Biophys Res Commun. 2007 May 4;356(2):323-8. Epub 2007 Mar 7. PubMed PMID: 17367763. Schueneman AJ, Himmelfarb E, Geng L, Tan J, Donnelly E, Mendel D, McMahon G, Hallahan DE. SU11248 maintenance therapy prevents tumor regrowth after fractionated irradiation of murine tumor models. Cancer Res. 2003 Jul 15;63(14):4009-16. PubMed PMID: 12873999. Stalker L, Pemberton J, Moorehead RA. Inhibition of proliferation and migration of luminal and claudin-low breast cancer cells by PDGFR inhibitors. Cancer Cell Int. 2014 Sep 5;14(1):89. doi: 10.1186/s12935-014-0089-5. eCollection 2014. PubMed PMID: 25253994; PubMed Central PMCID: PMC4172847.
AZD1480	Gudernova I, Balek L, Varecha M, Kucerova JF, Kunova Bosakova M, Fafilek B, Palusova V, Uldrijan S, Trantirek L, Krejci P. Inhibitor repurposing reveals ALK, LTK, FGFR, RET and TRK kinases as the targets of AZD1480. Oncotarget. 2017 12 12;8(65):109319-109331. doi: 10.18632/oncotarget.22674. Epub 2017 Dec 27. PubMed PMID: 29312610; PubMed Central PMCID: PMC5752523. Yan S, Li Z, Thiele CJ. Inhibition of STAT3 with orally active JAK inhibitor, AZD1480, decreases tumor growth in Neuroblastoma and Pediatric Sarcomas In vitro and In vivo. Oncotarget. 2013 Mar;4(3):433-45. doi: 10.18632/oncotarget.930. PubMed PMID: 23531921; PubMed Central PMCID: PMC3717306. Wang SW, Hu J, Guo QH, Zhao Y, Cheng JJ, Zhang DS, Fei Q, Li J, Sun YM. AZD1480, a JAK inhibitor, inhibits cell growth and survival of colorectal cancer via modulating the JAK2/STAT3 signaling pathway. Oncol Rep. 2014 Sep 10. doi: 10.3892/or.2014.3477. [Epub ahead of print] PubMed PMID: 25216185.
IMATINIB	Redaelli S, Piazza R, Rostagno R, Magistroni V, Perini P, Marega M, Gambacorti-Passerini C, Boschelli F. Activity of bosutinib, dasatinib, and nilotinib against 18 imatinib-resistant BCR/ABL mutants. J Clin Oncol. 2009 Jan 20;27(3):469-71. doi: 10.1200/JCO.2008.19.8853. Epub 2008 Dec 15. PubMed PMID: 19075254. Olshen A, Tang M, Cortes J, Gonen M, Hughes T, Branford S, Quintás-Cardama A, Michor F. Dynamics of chronic myeloid leukemia response to dasatinib, nilotinib, and high-dose imatinib. Haematologica. 2014 Sep 12. pii: haematol.2013.085977. [Epub ahead of print] PubMed PMID: 25216683. Saini M, Jha AN, Abrari A, Ali S. Expression of proto-oncogene KIT is up-regulated in subset of human meningiomas. BMC Cancer. 2012 Jun 6;12:212. doi: 10.1186/1471-2407-12-212. PubMed PMID: 22672386; PubMed Central PMCID: PMC3443037. Malavaki CJ, Roussidis AE, Gialeli C, Kletsas D, Tsegenidis T, Theocharis AD, Tzanakakis GN, Karamanos NK. Imatinib as a key inhibitor of the platelet-derived growth factor receptor mediated expression of cell surface heparan sulfate proteoglycans and functional properties of breast cancer cells. FEBS J. 2013 May;280(10):2477-89. doi: 10.1111/febs.12163. Epub 2013 Feb 27. PubMed PMID: 23374223. Lankat-Buttgereit B, Hörsch D, Barth P, Arnold R, Blöcker S, Göke R. Effects of the tyrosine kinase inhibitor imatinib on neuroendocrine tumor cell growth. Digestion. 2005;71(3):131-40. doi: 10.1159/000084647. Epub 2005 Aug 22. PubMed PMID: 15785039.

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COMPOUND NAME	REFERENCES
TALETRECTINIB	Katayama R, Gong B, Togashi N, Miyamoto M, Kiga M, Iwasaki S, Kamai Y, Tominaga Y, Takeda Y, Kagoshima Y, Shimizu Y, Seto Y, Oh-Hara T, Koike S, Nakao N, Hanzawa H, Watanabe K, Yoda S, Yanagitani N, Hata AN, Shaw AT, Nishio M, Fujita N, Isoyama T. The new-generation selective ROS1/NTRK inhibitor DS-6051b overcomes crizotinib resistant ROS1-G2032R mutation in preclinical models. Nat Commun. 2019 08 09;10(1):3604. doi: 10.1038/s41467-019-11496-z. Epub 2019 Jan 09. PubMed PMID: 31399568; PubMed Central PMCID: PMC6688997.
LENVATINIB	Glen H, Mason S, Patel H, Macleod K, Brunton VG. E7080, a multi-targeted tyrosine kinase inhibitor suppresses tumor cell migration and invasion. BMC Cancer. 2011 Jul 22;11:309. doi: 10.1186/1471-2407-11-309. PubMed PMID: 21781317; PubMed Central PMCID: PMC3154179. Mulligan LM. RET revisited: expanding the oncogenic portfolio. Nat Rev Cancer. 2014 Mar;14(3):173-86. doi: 10.1038/nrc3680. Review. PubMed PMID: 24561444. Matsui J, Yamamoto Y, Funahashi Y, Tsuruoka A, Watanabe T, Wakabayashi T, Uenaka T, Asada M. E7080, a novel inhibitor that targets multiple kinases, has potent antitumor activities against stem cell factor producing human small cell lung cancer H146, based on angiogenesis inhibition. Int J Cancer. 2008 Feb 1;122(3):664-71. PubMed PMID: 17943726. Tohyama O, Matsui J, Kodama K, Hata-Sugi N, Kimura T, Okamoto K, Minoshima Y, Iwata M, Funahashi Y. Antitumor activity of lenvatinib (e7080): an angiogenesis inhibitor that targets multiple receptor tyrosine kinases in preclinical human thyroid cancer models. J Thyroid Res. 2014;2014:638747. doi: 10.1155/2014/638747. Epub 2014 Feb 10. PubMed PMID: 25295214; PubMed Central PMCID: PMC4177084. Schlumberger M, Tahara M, Wirth LJ, Robinson B, Brose MS, Elisei R, Habra MA, Newbold K, Shah MH, Hoff AO, Gianoukakis AG, Kiyota N, Taylor MH, Kim SB, Krzyzanowska MK, Dutcus CE, de las Heras B, Zhu J, Sherman SI. Lenvatinib versus placebo in radioiodine-refractory thyroid cancer. N Engl J Med. 2015 Feb 12;372(7):621-30. doi: 10.1056/NEJMoa1406470. PubMed PMID: 25671254.
SORAFENIB	Berk V, Kaplan MA, Tonyali O, Buyukberber S, Balakan O, Ozkan M, Demirci U, Ozturk T, Bilici A, Tastekin D, Ozdemir N, Unal OU, Oflazoglu U, Turkmen E, Erdogan B, Uyeturk U, Oksuzoglu B, Cinkir HY, Yasar N, Gumus M. Efficiency and side effects of sorafenib therapy for advanced hepatocellular carcinoma: a retrospective study by the anatolian society of medical oncology. Asian Pac J Cancer Prev. 2013;14(12):7367-9. PubMed PMID: 24460304. Mulligan LM. RET revisited: expanding the oncogenic portfolio. Nat Rev Cancer. 2014 Mar;14(3):173-86. doi: 10.1038/nrc3680. Review. PubMed PMID: 24561444. Mao WF, Shao MH, Gao PT, Ma J, Li HJ, Li GL, Han BH, Yuan CG. The important roles of RET, VEGFR2 and the RAF/MEK/ERK pathway in cancer treatment with sorafenib. Acta Pharmacol Sin. 2012 Oct;33(10):1311-8. doi: 10.1038/aps.2012.76. Epub 2012 Sep 3. PubMed PMID: 22941289; PubMed Central PMCID: PMC4002706. Jain L, Woo S, Gardner ER, Dahut WL, Kohn EC, Kummar S, Mould DR, Giaccone G, Yarchoan R, Venitz J, Figg WD. Population pharmacokinetic analysis of sorafenib in patients with solid tumours. Br J Clin Pharmacol. 2011 Aug;72(2):294-305. doi: 10.1111/j.1365-2125.2011.03963.x. PubMed PMID: 21392074; PubMed Central PMCID: PMC3162659. Kim S, Yazici YD, Calzada G, Wang ZY, Younes MN, Jasser SA, El-Naggar AK, Myers JN. Sorafenib inhibits the angiogenesis and growth of orthotopic anaplastic thyroid carcinoma xenografts in nude mice. Mol Cancer Ther. 2007 Jun;6(6):1785-92. PubMed PMID: 17575107.
METFORMIN	Zi FM, He JS, Li Y, Wu C, Yang L, Yang Y, Wang LJ, He DH, Zhao Y, Wu WJ, Zheng GF, Han XY, Huang H, Yi Q, Cai Z. Metformin displays anti-myeloma activity and synergistic effect with dexamethasone in vitro and in xenograft models. Cancer Lett. 2014 Oct 8. pii: S0304-3835(14)00591-6. doi: 10.1016/j.canlet.2014.09.050. [Epub ahead of print] PubMed PMID: 25305450. El-Benhawy SA, El-Sheredy HG. Metformin and survival in diabetic patients with breast cancer. J Egypt Public Health Assoc. 2014 Dec;89(3):148-53. doi: 10.1097/01.EPX.0000456620.00173.c0. PubMed PMID: 25534180. Tan XL, Bhattacharyya KK, Dutta SK, Bamlet WR, Rabe KG, Wang E, Smyrk TC, Oberg AL, Petersen GM, Mukhopadhyay D. Metformin suppresses pancreatic tumor growth with inhibition of NFB/STAT3 inflammatory signaling. Pancreas. 2015 May;44(4):636-47. doi: 10.1097/MPA.0000000000000308. PubMed PMID: 25875801; PubMed Central PMCID: PMC4399019. Kato K, Gong J, Iwama H, Kitanaka A, Tani J, Miyoshi H, Nomura K, Mimura S, Kobayashi M, Aritomo Y, Kobara H, Mori H, Himoto T, Okano K, Suzuki Y, Murao K, Masaki T. The antidiabetic drug metformin inhibits gastric cancer cell proliferation in vitro and in vivo. Mol Cancer Ther. 2012 Mar;11(3):549-60. doi: 10.1158/1535-7163.MCT-11-0594. Epub 2012 Jan 5. PubMed PMID: 22222629. Cao X, Wen ZS, Wang XD, Li Y, Liu KY, Wang X. The Clinical Effect of Metformin on the Survival of Lung Cancer Patients with Diabetes: A Comprehensive Systematic Review and Meta-analysis of Retrospective Studies. J Cancer. 2017 Aug 2;8(13):2532-2541. doi: 10.7150/jca.19750. eCollection 2017. PubMed PMID: 28900491; PubMed Central PMCID: PMC5595083.

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COMPOUND NAME	REFERENCES
RUXOLITINIB	Verstovsek S, Passamonti F, Rambaldi A, Barosi G, Rosen PJ, Rumi E, Gattoni E, Pieri L, Guglielmelli P, Elena C, He S, Contel N, Mookerjee B, Sandor V, Cazzola M, Kantarjian HM, Barbui T, Vannucchi AM. A phase 2 study of ruxolitinib, an oral JAK1 and JAK2 Inhibitor, in patients with advanced polycythemia vera who are refractory or intolerant to hydroxyurea. Cancer. 2014 Feb 15;120(4):513-20. PubMed PMID: 24258498; PubMed Central PMCID: PMC4231215. An HJ, Choi EK, Kim JS, Hong SW, Moon JH, Shin JS, Ha SH, Kim KP, Hong YS, Lee JL, Choi EK, Lee JS, Jin DH, Kim TW. INCB018424 induces apoptotic cell death through the suppression of pJAK1 in human colon cancer cells. Neoplasma. 2013 Sep 20. doi: 10.4149/neo_2014_009. [Epub ahead of print] PubMed PMID: 24050550. Furumoto Y, Gadina M. The arrival of JAK inhibitors: advancing the treatment of immune and hematologic disorders. BioDrugs. 2013 Oct;27(5):431-8. doi: 10.1007/s40259-013-0040-7. Review. PubMed PMID: 23743669; PubMed Central PMCID: PMC3778139. Rumi E, Milosevic JD, Casetti I, Dambruoso I, Pietra D, Boveri E, Boni M, Bernasconi P, Passamonti F, Kralovics R, Cazzola M. Efficacy of ruxolitinib in chronic eosinophilic leukemia associated with a PCM1-JAK2 fusion gene. J Clin Oncol. 2013 Jun 10;31(17):e269-71. doi: 10.1200/JCO.2012.46.4370. Epub 2013 Apr 29. PubMed PMID: 23630205. Loh ML, Tasian SK, Rabin KR, Brown P, Magoon D, Reid JM, Chen X, Ahern CH, Weigel BJ, Blaney SM. A phase 1 dosing study of ruxolitinib in children with relapsed or refractory solid tumors, leukemias, or myeloproliferative neoplasms: A Children's Oncology Group phase 1 consortium study (ADVL1011). Pediatr Blood Cancer. 2015 Oct;62 (10):1717-24. doi: 10.1002/pbc.25575. Epub 2015 May 13. PubMed PMID: 25976292; PubMed Central PMCID: PMC4546537.
TEMSIROLIMUS	Liu W, Huang S, Chen Z, Wang H, Wu H, Zhang D. Temsirolimus, the mTOR inhibitor, induces autophagy in adenoid cystic carcinoma: In vitro and in vivo. Pathol Res Pract. 2014 Mar 30. pii: S0344-0338(14)00095-8. doi: 10.1016/j.prp. 2014.03.008. [Epub ahead of print] PubMed PMID: 24767255. Mounier N, Vignot S, Spano JP. [Update on clinical activity of CCI779 (temsirolimus), mTOR inhibitor]. Bull Cancer. 2006 Nov;93(11):1139-43. Review. French. PubMed PMID: 17145584. Takano M, Kikuchi Y, Kudoh K, Goto T, Furuya K, Kikuchi R, Kita T, Fujiwara K, Shiozawa T, Aoki D. Weekly administration of temsirolimus for heavily pretreated patients with clear cell carcinoma of the ovary: a report of six cases. Int J Clin Oncol. 2011 Oct;16(5):605-9. doi: 10.1007/s10147-010-0177-z. Epub 2011 Jan 18. PubMed PMID: 21243393. Pachow D, Andrae N, Kliese N, Angenstein F, Stork O, Wilisch-Neumann A, Kirches E, Mawrin C. mTORC1 inhibitors suppress meningioma growth in mouse models. Clin Cancer Res. 2013 Mar 1;19(5):1180-9. doi: 10.1158/1078-0432. CCR-12-1904. Epub 2013 Feb 13. PubMed PMID: 23406776. Zeng Z, Sarbassov dos D, Samudio IJ, Yee KW, Munsell MF, Ellen Jackson C, Giles FJ, Sabatini DM, Andreeff M, Konopleva M. Rapamycin derivatives reduce mTORC2 signaling and inhibit AKT activation in AML. Blood. 2007 Apr 15;109(8):3509-12. Epub 2006 Dec 19. PubMed PMID: 17179228; PubMed Central PMCID: PMC1852241.
RIDAFOROLIMUS	Gozgit JM, Squillace RM, Wongchenko MJ, Miller D, Wardwell S, Mohemmad Q, Narasimhan NI, Wang F, Clackson T, Rivera VM. Combined targeting of FGFR2 and mTOR by ponatinib and ridaforolimus results in synergistic antitumor activity in FGFR2 mutant endometrial cancer models. Cancer Chemother Pharmacol. 2013 May;71(5):1315-23. doi: 10.1007/s00280-013-2131-z. Epub 2013 Mar 7. PubMed PMID: 23468082. Tsoref D, Welch S, Lau S, Biagi J, Tonkin K, Martin LA, Ellard S, Ghatage P, Elit L, Mackay HJ, Allo G, Tsao MS, Kamel-Reid S, Eisenhauer EA, Oza AM. Phase II study of oral ridaforolimus in women with recurrent or metastatic endometrial cancer. Gynecol Oncol. 2014 Aug 28. pii: S0090-8258(14)01074-9. doi: 10.1016/j.ygyno.2014.06.033. [Epub ahead of print] PubMed PMID: 25173583. http://www.ncbi.nlm.nih.gov/pubmed/26077241
REGORAFENIB	Strumberg D, Schultheis B. Regorafenib for cancer. Expert Opin Investig Drugs. 2012 Jun;21(6):879-89. doi: 10.1517 /13543784.2012.684752. Review. PubMed PMID: 22577890. Mross K, Frost A, Steinbild S, Hedbom S, Büchert M, Fasol U, Unger C, Krätzschmar J, Heinig R, Boix O, Christensen O. A phase I dose-escalation study of regorafenib (BAY 73-4506), an inhibitor of oncogenic, angiogenic, and stromal kinases, in patients with advanced solid tumors. Clin Cancer Res. 2012 May 1;18(9):2658-67. doi: 10.1158 /1078-0432.CCR-11-1900. Epub 2012 Mar 15. PubMed PMID: 22421192. Yan Y, Grothey A. Molecular profiling in the treatment of colorectal cancer: focus on regorafenib. Onco Targets Ther. 2015 Oct 15;8:2949-57. doi: 10.2147/OTT.S79145. Review. PubMed PMID: 26508880; PubMed Central PMCID: PMC4610887. George S, Feng Y, Von Mehren M, Choy E, Corless CL, Hornick JL, Butrynski JE, Wagner AJ, Solomon S, Morgan JA, Heinrich MC. Prolonged survival and disease control in the academic phase II trial of regorafenib in GIST: Response based on genotype. S. Bozzarelli L. Rimassa L. Giordano S. Sala M.C. Tronconi M. Baretti N. Personeni T. Pressiani A. Santoro. Regorafenib in patients with refractory metastatic pancreatic cancer. An open-label phase II study (RESOUND). Annals of Oncology, Volume 27, Issue suppl_6, 1 October 2016, 692P, https://doi.org/10.1093/annonc/mdw371.84

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COMPOUND NAME	REFERENCES
AZD8055	Jin ZZ, Wang W, Fang DL, Jin YJ. mTOR inhibition sensitizes ONC201-induced anti-colorectal cancer cell activity. Biochem Biophys Res Commun. 2016 Sep 30;478(4):1515-20. doi: 10.1016/j.bbrc.2016.08.126. Epub 2016 Aug 24. PubMed PMID: 27565731. Xu DQ, Toyoda H, Yuan XJ, Qi L, Chelakkot VS, Morimoto M, Hanaki R, Kihira K, Hori H, Komada Y, Hirayama M. Anti-tumor effect of AZD8055 against neuroblastoma cells in vitro and in vivo. Exp Cell Res. 2018 04 15;365(2):177-184. doi: 10.1016/j.yexcr.2018.02.032. Epub 2018 Jun 28. PubMed PMID: 29499203.
RES 529	Weinberg MA. RES-529: a PI3K/AKT/mTOR pathway inhibitor that dissociates the mTORC1 and mTORC2 complexes. Anticancer Drugs. 2016 Jul;27(6):475-87. doi: 10.1097/CAD.0000000000000354. PubMed PMID: 26918392; PubMed Central PMCID: PMC4881730.
GDC 0349	Pei Z, Blackwood E, Liu L, Malek S, Belvin M, Koehler MF, Ortwine DF, Chen H, Cohen F, Kenny JR, Bergeron P, Lau K, Ly C, Zhao X, Estrada AA, Truong T, Epler JA, Nonomiya J, Trinh L, Sideris S, Lesnick J, Bao L, Vijapurkar U, Mukadam S, Tay S, Deshmukh G, Chen YH, Ding X, Friedman LS, Lyssikatos JP. Discovery and Biological Profiling of Potent and Selective mTOR Inhibitor GDC-0349. ACS Med Chem Lett. 2012 Nov 29;4(1):103-7. doi: 10.1021/ml3003132. eCollection 2013 Jan 10. PubMed PMID: 24900569; PubMed Central PMCID: PMC4027466.
CC-115	Mortensen DS, Perrin-Ninkovic SM, Shevlin G, Elsner J, Zhao J, Whitefield B, Tehrani L, Sapienza J, Riggs JR, Parnes JS, Papa P, Packard G, Lee BG, Harris R, Correa M, Bahmanyar S, Richardson SJ, Peng SX, Leisten J, Khambatta G, Hickman M, Gamez JC, Bisonette RR, Apuy J, Cathers BE, Canan SS, Moghaddam MF, Raymon HK, Worland P, Narla RK, Fultz KE, Sankar S. Optimization of a Series of Triazole Containing Mammalian Target of Rapamycin (mTOR) Kinase Inhibitors and the Discovery of CC-115. J Med Chem. 2015 Jul 23;58(14):5599-608. doi: 10.1021/acs.jmedchem.5b00627. Epub 2015 Jul 8. PubMed PMID: 26102506.
MLN0128	Rubens JA, Wang SZ, Price A, Weingart MF, Allen SJ, Orr BA, Eberhart CG, Raabe EH. The TORC1/2 inhibitor TAK228 sensitizes atypical teratoid rhabdoid tumors to cisplatin-induced cytotoxicity. Neuro Oncol. 2017 Jun 3. doi: 10.1093/neuonc/nox067. [Epub ahead of print] PubMed PMID: 28582547.
OSI-027	Bhagwat SV, Gokhale PC, Crew AP, Cooke A, Yao Y, Mantis C, Kahler J, Workman J, Bittner M, Dudkin L, Epstein DM, Gibson NW, Wild R, Arnold LD, Houghton PJ, Pachter JA. Preclinical characterization of OSI-027, a potent and selective inhibitor of mTORC1 and mTORC2: distinct from rapamycin. Mol Cancer Ther. 2011 Aug;10(8):1394-406. doi: 10.1158/1535-7163.MCT-10-1099. Epub 2011 Jun 14. PubMed PMID: 21673091.
ONATASERTIB	Rama Krishna Narla, Sophie Peng, Jim Gamez, Jason Katz, Julius Apuy, Mehran Moghaddam, Kimberly E. Fultz, Sabita Sankar, Deborah S. Mortensen, Heather K. Raymon. Antitumor activity of mTOR kinase inhibitor CC-223 in a mouse model of prostate cancer. [abstract]. In: Proceedings of the AACR-NCI-EORTC International Conference: Molecular Targets and Cancer Therapeutics; 2013 Oct 19-23; Boston, MA. Philadelphia (PA): AACR; Mol Cancer Ther 2013;12(11 Suppl):Abstract nr A165.
VISTUSERTIB	Zheng B, Mao JH, Qian L, Zhu H, Gu DH, Pan XD, Yi F, Ji DM. Pre-clinical evaluation of AZD-2014, a novel mTORC1/2 dual inhibitor, against renal cell carcinoma. Cancer Lett. 2015 Feb 28;357(2):468-75. doi: 10.1016/j.canlet.2014.11.012. Epub 2014 Nov 12. PubMed PMID: 25444920. Ezell SA, Mayo M, Bihani T, Tepsuporn S, Wang S, Passino M, Grosskurth SE, Collins M, Parmentier J, Reimer C, Byth KF. Synergistic induction of apoptosis by combination of BTK and dual mTORC1/2 inhibitors in diffuse large B cell lymphoma. Oncotarget. 2014 Jul 15;5(13):4990-5001. PubMed PMID: 24970801; PubMed Central PMCID: PMC4148116.
VENETOCLAX	Davids MS, Roberts AW, Seymour JF, Pagel JM, Kahl BS, Wierda WG, Puvvada S, Kipps TJ, Anderson MA, Salem AH, Dunbar M, Zhu M, Peale F, Ross JA, Gressick L, Desai M, Kim SY, Verdugo M, Humerickhouse RA, Gordon GB, Gerecitano JF. Phase I First-in-Human Study of Venetoclax in Patients With Relapsed or Refractory Non-Hodgkin Lymphoma. J Clin Oncol. 2017 Mar 10;35(8):826-833. doi: 10.1200/JCO.2016.70.4320. Epub 2017 Jan 17. PubMed PMID: 28095146; PubMed Central PMCID: PMC5455685. Kater AP, Wu JQ, Kipps T, Eichhorst B, Hillmen P, D'Rozario J, Assouline S, Owen C, Robak T, de la Serna J, Jaeger U, Cartron G, Montillo M, Dubois J, Eldering E, Mellink C, Van Der Kevie-Kersemaekers AM, Kim SY, Chyla B, Punnoose E, Bolen CR, Assaf ZJ, Jiang Y, Wang J, Lefebure M, Boyer M, Humphrey K, Seymour JF. Venetoclax Plus Rituximab in Relapsed Chronic Lymphocytic Leukemia: 4-Year Results and Evaluation of Impact of Genomic Complexity and Gene Mutations From the MURANO Phase III Study. J Clin Oncol. 2020 Sep 28;:JCO2000948. doi: 10.1200/JCO.20.00948. Epub 2020 Oct 28. PubMed PMID: 32986498. Al-Sawaf O, Zhang C, Tandon M, Sinha A, Fink AM, Robrecht S, Samoylova O, Liberati AM, Pinilla-Ibarz J, Opat S, Sivcheva L, Le Dû K, Fogliatto LM, Niemann CU, Weinkove R, Robinson S, Kipps TJ, Tausch E, Schary W, Ritgen M, Wendtner CM, Kreuzer KA, Eichhorst B, Stilgenbauer S, Hallek M, Fischer K. Venetoclax plus obinutuzumab versus chlorambucil plus obinutuzumab for previously untreated chronic lymphocytic leukaemia (CLL14): follow-up results from a multicentre, open-label, randomised, phase 3 trial. Lancet Oncol. 2020 Sep;21(9):1188-1200. doi: 10.1016/S1470-2045(20)30443-5. PubMed PMID: 32888452. DiNardo CD, Jonas BA, Pullarkat V, Thirman MJ, Garcia JS, Wei AH, Konopleva M, Döhner H, Letai A, Fenaux P, Koller E, Havelange V, Leber B, Esteve J, Wang J, Pejsa V, Hájek R, Porkka K, Illés Á, Lavie D, Lemoli RM, Yamamoto K, Yoon SS, Jang JH, Yeh SP, Turgut M, Hong WJ, Zhou Y, Potluri J, Pratz KW. Azacitidine and Venetoclax in Previously Untreated Acute Myeloid Leukemia. N Engl J Med. 2020 08 13;383(7):617-629. doi: 10.1056/NEJMoa2012971. PubMed PMID: 32786187.
DUVELISIB	Thorpe LM, Yuzugullu H, Zhao JJ. PI3K in cancer: divergent roles of isoforms, modes of activation and therapeutic targeting. Nat Rev Cancer. 2015 Jan;15(1):7-24. doi: 10.1038/nrc3860. Review. PubMed PMID: 25533673; PubMed Central PMCID: PMC4384662. Flinn IW, Hillmen P, Montillo M, Nagy Z, Illés Á, Etienne G, Delgado J, Kuss BJ, Tam CS, Gasztonyi Z, Offner F, Lunin S, Bosch F, Davids MS, Lamanna N, Jaeger U, Ghia P, Cymbalista F, Portell CA, Skarbnik AP, Cashen AF, Weaver DT, Kelly VM, Turnbull B, Stilgenbauer S. The phase 3 DUO trial: duvelisib vs ofatumumab in relapsed and refractory CLL/SLL. Blood. 2018 12 06;132(23):2446-2455. doi: 10.1182/blood-2018-05-850461. Epub 2018 Aug 04. PubMed PMID: 30287523; PubMed Central PMCID: PMC6284216.

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COMPOUND NAME	REFERENCES
ASPIRIN	Ng K, Meyerhardt JA, Chan AT, Sato K, Chan JA, Niedzwiecki D, Saltz LB, Mayer RJ, Benson AB 3rd, Schaefer PL, Whittom R, Hantel A, Goldberg RM, Venook AP, Ogino S, Giovannucci EL, Fuchs CS. Aspirin and COX-2 inhibitor use in patients with stage III colon cancer. J Natl Cancer Inst. 2014 Nov 27;107(1):345. doi: 10.1093/jnci/dju345. Print 2015 Jan. PubMed PMID: 25432409; PubMed Central PMCID: PMC4271076.
ACALISIB	Thorpe LM, Yuzugullu H, Zhao JJ. PI3K in cancer: divergent roles of isoforms, modes of activation and therapeutic targeting. Nat Rev Cancer. 2015 Jan;15(1):7-24. doi: 10.1038/nrc3860. Review. PubMed PMID: 25533673; PubMed Central PMCID: PMC4384662.
ENZALUTAMIDE	Sternberg CN, de Bono JS, Chi KN, Fizazi K, Mulders P, Cerbone L, Hirmand M, Forer D, Scher HI. Improved outcomes in elderly patients with metastatic castration-resistant prostate cancer treated with the androgen receptor inhibitor enzalutamide: results from the phase III AFFIRM trial. Ann Oncol. 2014 Feb;25(2):429-34. doi: 10.1093 /annonc/mdt571. PubMed PMID: 24478320. Scher HI, Fizazi K, Saad F, Taplin ME, Sternberg CN, Miller K, de Wit R, Mulders P, Chi KN, Shore ND, Armstrong AJ, Flaig TW, Fléchon A, Mainwaring P, Fleming M, Hainsworth JD, Hirmand M, Selby B, Seely L, de Bono JS, . Increased survival with enzalutamide in prostate cancer after chemotherapy. N Engl J Med. 2012 Sep 27;367(13): 1187-97. doi: 10.1056/NEJMoa1207506. Epub 2012 Sep 15. PubMed PMID: 22894553. Hussain M, Fizazi K, Saad F, Rathenborg P, Shore N, Ferreira U, Ivashchenko P, Demirhan E, Modelska K, Phung , Krivoshik A, Sternberg CN. Enzalutamide in Men with Nonmetastatic, Castration-Resistant Prostate Cancer. N Engl J Med. 2018 Jun 28;378(26):2465-2474. doi: 10.1056/NEJMoa1800536. PubMed PMID: 29949494. Beer TM, Armstrong AJ, Rathkopf DE, Loriot Y, Sternberg CN, Higano CS, Iversen P, Bhattacharya S, Carles J, Chowdhury S, Davis ID, de Bono JS, Evans CP, Fizazi K, Joshua AM, Kim CS, Kimura G, Mainwaring P, Mansbach H, Miller K, Noonberg SB, Perabo F, Phung D, Saad F, Scher HI, Taplin ME, Venner PM, Tombal B; PREVAIL Investigators.. Enzalutamide in metastatic prostate cancer before chemotherapy. N Engl J Med. 2014 Jul 31;371(5): 424-33. doi: 10.1056/NEJMoa1405095. PubMed PMID: 24881730; PubMed Central PMCID: PMC4418931. Davis ID, Martin AJ, Stockler MR, Begbie S, Chi KN, Chowdhury S, Coskinas X, Frydenberg M, Hague WE, Horvath LG, Joshua AM, Lawrence NJ, Marx G, McCaffrey J, McDermott R, McJannett M, North SA, Parnis F, Parulekar W, Pook DW, Reaume MN, Sandhu SK, Tan A, Tan TH, Thomson A, Tu E, Vera-Badillo F, Williams SG, Yip S, Zhang AY, Zielinski RR, Sweeney CJ, . Enzalutamide with Standard First-Line Therapy in Metastatic Prostate Cancer. N Engl J Med. 2019 07 11;381(2):121-131. doi: 10.1056/NEJMoa1903835. Epub 2019 Oct 02. PubMed PMID: 31157964.
NS-398	Joki T, Heese O, Nikas DC, Bello L, Zhang J, Kraeft SK, Seyfried NT, Abe T, Chen LB, Carroll RS, Black PM. Expression of cyclooxygenase 2 (COX-2) in human glioma and in vitro inhibition by a specific COX-2 inhibitor, NS-398. Cancer Res. 2000 Sep 1;60(17):4926-31. PubMed PMID: 10987308.
TILMACOXIB	Yashiro M, Nakazawa K, Tendo M, Kosaka K, Shinto O, Hirakawa K. Selective cyclooxygenase-2 inhibitor downregulates the paracrine epithelial-mesenchymal interactions of growth in scirrhous gastric carcinoma. Int J Cancer. 2007 Feb 1;120(3):686-93. PubMed PMID: 17096355.
AXITINIB	Gross-Goupil M, François L, Quivy A, Ravaud A. Axitinib: a review of its safety and efficacy in the treatment of adults with advanced renal cell carcinoma. Clin Med Insights Oncol. 2013 Oct 29;7:269-77. doi: 10.4137/CMO.S10594. Epub 2013 October 29. PubMed PMID: 24250243; PubMed Central PMCID: PMC3825605. B. Rini, O. Rixe, R. Bukowski, M. D. Michaelson, G. Wilding, G. Hudes, O. Bolte, H. Steinfeldt, S. D. Reich and R. Motzer. AG-013736, a multi-target tyrosine kinase receptor inhibitor, demonstrates anti-tumor activity in a Phase 2 study of cytokine-refractory, metastatic renal cell cancer (RCC). J Clin Oncol (Meeting Abstracts) June 2005 vol. 23 no. 16_suppl 4509. Cohen EE, Tortorici M, Kim S, Ingrosso A, Pithavala YK, Bycott P. A Phase II trial of axitinib in patients with various histologic subtypes of advanced thyroid cancer: long-term outcomes and pharmacokinetic/pharmacodynamic analyses. Cancer Chemother Pharmacol. 2014 Dec;74(6):1261-70. doi: 10.1007/s00280-014-2604-8. Epub 2014 Oct 15. PubMed PMID: 25315258; PubMed Central PMCID: PMC4236619. Donson, A., Werner, E., Amani, V., Griesinger, A., Witt, D., Nellan, A, Foreman, N. EPND-12: Tyrosine kinase inhibitors axitinib, imatinib, and pazopanib are selectively potent in ependymoma. 2017. Neuro-Oncology, 19(Suppl 4), iv17. http://doi.org/10.
BOSUTINIB	Stansfield L, Hughes TE, Walsh-Chocolaad TL. Bosutinib: a second-generation tyrosine kinase inhibitor for chronic myelogenous leukemia. Ann Pharmacother. 2013 Dec;47(12):1703-11. doi: 10.1177/1060028013503124. Review. PubMed PMID: 24396109. Creedon H, Brunton VG. Src kinase inhibitors: promising cancer therapeutics? Crit Rev Oncog. 2012;17(2):145-59. Review. PubMed PMID: 22471705. Redaelli S, Piazza R, Rostagno R, Magistroni V, Perini P, Marega M, Gambacorti-Passerini C, Boschelli F. Activity of bosutinib, dasatinib, and nilotinib against 18 imatinib-resistant BCR/ABL mutants. J Clin Oncol. 2009 Jan 20;27(3): 469-71. doi: 10.1200/JCO.2008.19.8853. Epub 2008 Dec 15. PubMed PMID: 19075254. Rabbani SA, Valentino ML, Arakelian A, Ali S, Boschelli F. SKI-606 (Bosutinib) blocks prostate cancer invasion, growth, and metastasis in vitro and in vivo through regulation of genes involved in cancer growth and skeletal metastasis. Mol Cancer Ther. 2010 May;9(5):1147-57. doi: 10.1158/1535-7163.MCT-09-0962. Epub 2010 Apr 27. PubMed PMID: 20423991. Keller G, Schafhausen P, Brummendorf TH. Bosutinib: a dual SRC/ABL kinase inhibitor for the treatment of chronic myeloid leukemia. Expert Rev Hematol. 2009 Oct;2(5):489-97. doi: 10.1586/ehm.09.42. Review. PubMed PMID: 21083014.

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COMPOUND NAME	REFERENCES
OLVEREMBATINIB	Wang Y, Zhang L, Tang X, Luo J, Tu Z, Jiang K, Ren X, Xu F, Chan S, Li Y, Zhang Z, Ding K. GZD824 as a FLT3, FGFR1 and PDGFR Inhibitor Against Leukemia In Vitro and In Vivo. Transl Oncol. 2020 Apr;13(4):100766. doi: 10.1016/j.tranon.2020.100766. Epub 2020 April 01. PubMed PMID: 32247263; PubMed Central PMCID: PMC7125355.
DERAZANTINIB	Hall TG, Yu Y, Eathiraj S, Wang Y, Savage RE, Lapierre JM, Schwartz B, Abbadessa G. Preclinical Activity of ARQ 087, a Novel Inhibitor Targeting FGFR Dysregulation. PLoS One. 2016;11(9):e0162594. doi: 10.1371/journal.pone.0162594. Epub 2016 September 14. PubMed PMID: 27627808; PubMed Central PMCID: PMC5023172.
Flumatinib	Zhao J, Quan H, Xu Y, Kong X, Jin L, Lou L. Flumatinib, a selective inhibitor of BCR-ABL/PDGFR/KIT, effectively overcomes drug resistance of certain KIT mutants. Cancer Sci. 2014 Jan;105(1):117-25. doi: 10.1111/cas.12320. Epub 2014 Jan 4. PubMed PMID: 24205792; PubMed Central PMCID: PMC4317885.
FAMITINIB	Zhou A, Zhang W, Chang C, Chen X, Zhong D, Qin Q, Lou D, Jiang H, Wang J. Phase I study of the safety, pharmacokinetics and antitumor activity of famitinib. Cancer Chemother Pharmacol. 2013 Nov;72(5):1043-53. doi: 10.1007/s00280-013-2282-y. Epub 2013 Sep 17. PubMed PMID: 24043137.
BARICITINIB	Fridman JS, Scherle PA, Collins R, Burn TC, Li Y, Li J, Covington MB, Thomas B, Collier P, Favata MF, Wen X, Shi J, McGee R, Haley PJ, Shepard S, Rodgers JD, Yeleswaram S, Hollis G, Newton RC, Metcalf B, Friedman SM, Vaddi K. Selective inhibition of JAK1 and JAK2 is efficacious in rodent models of arthritis: preclinical characterization of INCB028050. J Immunol. 2010 May 1;184(9):5298-307. doi: 10.4049/jimmunol.0902819. Epub 2010 Apr 2. PubMed PMID: 20363976. Shi JG, Chen X, Lee F, Emm T, Scherle PA, Lo Y, Punwani N, Williams WV, Yeleswaram S. The Pharmacokinetics, Pharmacodynamics and Safety of Baricitinib, an Oral JAK 1/2 Inhibitor, in Healthy Volunteers. J Clin Pharmacol. 2014 Jun 26. doi: 10.1002/jcph.354. [Epub ahead of print] PubMed PMID: 24965573.
AZD0424	Fischer PM. Approved and Experimental Small-Molecule Oncology Kinase Inhibitor Drugs: A Mid-2016 Overview. Med Res Rev. 2017 Mar;37(2):314-367. doi: 10.1002/med.21409. Epub 2016 Oct 24. Review. PubMed PMID: 27775829. Nowak D, Boehrer S, Hochmuth S, Trepohl B, Hofmann W, Hoelzer D, Hofmann WK, Mitrou PS, Ruthardt M, Chow KU. Src kinase inhibitors induce apoptosis and mediate cell cycle arrest in lymphoma cells. Anticancer Drugs. 2007 Oct;18(9):981-95. PubMed PMID: 17704648. Nowak D, Boehrer S, Hochmuth S, Trepohl B, Hofmann W, Hoelzer D, Hofmann WK, Mitrou PS, Ruthardt M, Chow KU. Src kinase inhibitors induce apoptosis and mediate cell cycle arrest in lymphoma cells. Anticancer Drugs. 2007 Oct;18(9):981-95. PubMed PMID: 17704648.
AT9283	Kimura S. AT-9283, a small-molecule multi-targeted kinase inhibitor for the potential treatment of cancer. Curr Opin Investig Drugs. 2010 Dec;11(12):1442-9. Review. PubMed PMID: 21154126. Dawson MA, Curry JE, Barber K, Beer PA, Graham B, Lyons JF, Richardson CJ, Scott MA, Smyth T, Squires MS, Thompson NT, Green AR, Wallis NG. AT9283, a potent inhibitor of the Aurora kinases and Jak2, has therapeutic potential in myeloproliferative disorders. Br J Haematol. 2010 Jul;150(1):46-57. doi: 10.1111/j.1365-2141.2010.08175.x. Epub 2010 May 7. PubMed PMID: 20507304. Harry BL, Eckhardt SG, Jimeno A. JAK2 inhibition for the treatment of hematologic and solid malignancies. Expert Opin Investig Drugs. 2012 May;21(5):637-55. doi: 10.1517/13543784.2012.677432. Review. PubMed PMID: 22493978.
SULINDAC	Itano O, Yang K, Fan K, Kurihara N, Shinozaki H, Abe S, Jin B, Gravaghi C, Edelmann W, Augenlicht L, Kopelovich L, Kucherlapati R, Lamprecht S, Lipkin M. Sulindac effects on inflammation and tumorigenesis in the intestine of mice with Apc and Mlh1 mutations. Carcinogenesis. 2009 Nov;30(11):1923-6. doi: 10.1093/carcin/bgp200. Epub 2009 Feb 15. PubMed PMID: 19755659; PubMed Central PMCID: PMC2783002.

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COMPOUND NAME	REFERENCES
ALISERTIB	Venkataraman S, Alimova I, Tello T, Harris PS, Knipstein JA, Donson AM, Foreman NK, Liu AK, Vibhakar R. Targeting Aurora Kinase A enhances radiation sensitivity of atypical teratoid rhabdoid tumor cells. J Neurooncol. 2012 May;107(3):517-26. doi: 10.1007/s11060-011-0795-y. Epub 2012 Jan 15. PubMed PMID: 22246202; PubMed Central PMCID: PMC4681522. Owonikoko TK, Niu H, Nackaerts K, Csoszi T, Ostoros G, Mark Z, Baik C, Joy AA, Chouaid C, Jaime JC, Kolek V, Majem M, Roubec J, Santos ES, Chiang AC, Speranza G, Belani CP, Chiappori A, Patel MR, Czebe K, Byers L, Bahamon B, Li C, Sheldon-Waniga E, Kong EF, Williams M, Badola S, Shin H, Bedford L, Ecsedy JA, Bryant M, Jones S, Simmons J, Leonard EJ, Ullmann CD, Spigel DR, . Randomized Phase II Study of Paclitaxel plus Alisertib versus Paclitaxel plus Placebo as Second-Line Therapy for SCLC: Primary and Correlative Biomarker Analyses. J Thorac Oncol. 2020 02;15(2):274-287. doi: 10.1016/j.jtho.2019.10.013. Epub 2019 Apr 23. PubMed PMID: 31655296. Görgün G, Calabrese E, Hideshima T, Ecsedy J, Perrone G, Mani M, Ikeda H, Bianchi G, Hu Y, Cirstea D, Santo L, Tai YT, Nahar S, Zheng M, Bandi M, Carrasco RD, Raje N, Munshi N, Richardson P, Anderson KC. A novel Aurora-A kinase inhibitor MLN8237 induces cytotoxicity and cell-cycle arrest in multiple myeloma. Blood. 2010 Jun 24;115(25): 5202-13. doi: 10.1182/blood-2009-12-259523. Epub 2010 April 09. PubMed PMID: 20382844; PubMed Central PMCID: PMC2892955. Barr PM, Li H, Spier C, Mahadevan D, LeBlanc M, Ul Haq M, Huber BD, Flowers CR, Wagner-Johnston ND, Horwitz SM, Fisher RI, Cheson BD, Smith SM, Kahl BS, Bartlett NL, Friedberg JW. Phase II Intergroup Trial of Alisertib in Relapsed and Refractory Peripheral T-Cell Lymphoma and Transformed Mycosis Fungoides: SWOG 1108. J Clin Oncol. 2015 Jul 20;33(21):2399-404. doi: 10.1200/JCO.2014.60.6327. Epub 2015 June 15. PubMed PMID: 26077240; PubMed Central PMCID: PMC4500834. Melichar B, Adenis A, Lockhart AC, Bennouna J, Dees EC, Kayaleh O, Obermannova R, DeMichele A, Zatloukal P, Zhang B, Ullmann CD, Schusterbauer C. Safety and activity of alisertib, an investigational aurora kinase A inhibitor, in patients with breast cancer, small-cell lung cancer, non-small-cell lung cancer, head and neck squamous-cell carcinoma, and gastro-oesophageal adenocarcinoma: a five-arm phase 2 study. Lancet Oncol. 2015 Apr;16(4):395-405. doi: 10.1016/S1470-2045(15)70051-3. Epub 2015 February 27. PubMed PMID: 25728526.
NIRAPARIB	X. Wu, J. Zhu, R. Yin, J. Yang, J. Liu, J. Wang, L. Wu, Z. Liu, Y. Gao, D. Wang, G. Lou, H. Yang, Q. Zhou, B. Kong, Y. Huang, L. Chen, G. Li, R. An, K. Wang, Y. Zhang. Individualized starting dose of niraparib in Chinese patients with platinum-sensitive recurrent ovarian cancer (PSROC): A randomized, double-blind, placebo-controlled, phase III trial (NORA). DOI:https://doi.org/10.1016/j.annonc.2020.08.2259 Wu XH, Zhu JQ, Yin RT, Yang JX, Liu JH, Wang J, Wu LY, Liu ZL, Gao YN, Wang DB, Lou G, Yang HY, Zhou Q, Kong BH, Huang Y, Chen LP, Li GL, An RF, Wang K, Zhang Y, Yan XJ, Lu X, Lu WG, Hao M, Wang L, Cui H, Chen QH, Abulizi G, Huang XH, Tian XF, Wen H, Zhang C, Hou JM, Mirza MR. Niraparib maintenance therapy in patients with platinum-sensitive recurrent ovarian cancer using an individualized starting dose (NORA): a randomized, double-blind, placebo-controlled phase III trial. Ann Oncol. 2021 Jan 14;:. doi: 10.1016/j.annonc.2020.12.018. Epub 2021 Feb 14. PubMed PMID: 33453391. Antonio A, Bhavana B, Ignace I, René R, Whitney W, Mansoor R MR, Colleen C, Domenica D, Paul P, Gilles G, Klaus K, Kris K, Andrés A, Richard G RG, Christof C, Roisin E RE, Bente B, Floor F, Pilar P, Ashley F AF, Maria J MJ, Mark S MS, Giorgia G, William H WH, Ilan I, Kaiming K, Izabela A IA, Yong Y, Divya D, Bradley J BJ, . Niraparib in Patients with Newly Diagnosed Advanced Ovarian Cancer. N Engl J Med. 2019 12 19;381(25):2391-2402. doi: 10.1056 /NEJMoa1910962. Epub 2019 Jun 28. PubMed PMID: 31562799 Mirza MR, Monk BJ, Herrstedt J, Oza AM, Mahner S, Redondo A, Fabbro M, Ledermann JA, Lorusso D, Vergote I, Ben-Baruch NE, Marth C, Mądry R, Christensen RD, Berek JS, Dørum A, Tinker AV, du Bois A, González-Martín A, Follana P, Benigno B, Rosenberg P, Gilbert L, Rimel BJ, Buscema J, Balser JP, Agarwal S, Matulonis UA; ENGOT-OV16/NOVA Investigators. Niraparib Maintenance Therapy in Platinum-Sensitive, Recurrent Ovarian Cancer. N Engl J Med. 2016 Dec 1;375(22):2154-2164. Epub 2016 Oct 7. PubMed PMID: 27717299.
IDELALISIB	Thorpe LM, Yuzugullu H, Zhao JJ. PI3K in cancer: divergent roles of isoforms, modes of activation and therapeutic targeting. Nat Rev Cancer. 2015 Jan;15(1):7-24. doi: 10.1038/nrc3860. Review. PubMed PMID: 25533673; PubMed Central PMCID: PMC4384662. Jones JA, Robak T, Brown JR, Awan FT, Badoux X, Coutre S, Loscertales J, Taylor K, Vandenberghe E, Wach M, Wagner-Johnston N, Ysebaert L, Dreiling L, Dubowy R, Xing G, Flinn IW, Owen C. Efficacy and safety of idelalisib in combination with ofatumumab for previously treated chronic lymphocytic leukaemia: an open-label, randomised phase 3 trial. Lancet Haematol. 2017 Mar;4(3):e114-e126. doi: 10.1016/S2352-3026(17)30019-4. PubMed PMID: 28257752. Miller BW, Przepiorka D, de Claro RA, Lee K, Nie L, Simpson N, Gudi R, Saber H, Shord S, Bullock J, Marathe D, Mehrotra N, Hsieh LS, Ghosh D, Brown J, Kane RC, Justice R, Kaminskas E, Farrell AT, Pazdur R. FDA approval: idelalisib monotherapy for the treatment of patients with follicular lymphoma and small lymphocytic lymphoma. Clin Cancer Res. 2015 Apr 1;21(7):1525-9. doi: 10.1158/1078-0432.CCR-14-2522. Epub 2015 Feb 2. PubMed PMID: 25645861.

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COMPOUND NAME	REFERENCES
SACITUZUMAB GOVITECAN	Kalinsky K, Diamond JR, Vahdat LT, Tolaney SM, Juric D, O'Shaughnessy J, Moroose RL, Mayer IA, Abramson VG, Goldenberg DM, Sharkey RM, Maliakal P, Hong Q, Goswami T, Wegener WA, Bardia A. Sacituzumab Govitecan in Previously Treated Hormone Receptor-Positive/HER2-Negative Metastatic Breast Cancer: Final Results from a Phase 1/2, Single-Arm, Basket Trial. Ann Oncol. 2020 Sep 15;:. doi: 10.1016/j.annonc.2020.09.004. Epub 2020 Sep 15. PubMed PMID: 32946924. Tagawa ST, Balar AV, Petrylak DP, Kalebasty AR, Loriot Y, Fléchon A, Jain RK, Agarwal N, Bupathi M, Barthelemy P, Beuzeboc P, Palmbos P, Kyriakopoulos CE, Pouessel D, Sternberg CN, Hong Q, Goswami T, Itri LM, Grivas P. TROPHY-U-01: A Phase II Open-Label Study of Sacituzumab Govitecan in Patients With Metastatic Urothelial Carcinoma Progressing After Platinum-Based Chemotherapy and Checkpoint Inhibitors. J Clin Oncol. 2021 Apr 30;: JCO2003489. doi: 10.1200/JCO.20.03489. Epub 2021 April 30. PubMed PMID: 33929895. Bardia A, Hurvitz SA, Tolaney SM, Loirat D, Punie K, Oliveira M, Brufsky A, Sardesai SD, Kalinsky K, Zelnak AB, Weaver R, Traina T, Dalenc F, Aftimos P, Lynce F, Diab S, Cortés J, O'Shaughnessy J, Diéras V, Ferrario C, Schmid P, Carey LA, Gianni L, Piccart MJ, Loibl S, Goldenberg DM, Hong Q, Olivo MS, Itri LM, Rugo HS, . Sacituzumab Govitecan in Metastatic Triple-Negative Breast Cancer. N Engl J Med. 2021 04 22;384(16):1529-1541. doi: 10.1056/NEJMoa2028485. PubMed PMID: 33882206. Bardia A, Mayer IA, Vahdat LT, Tolaney SM, Isakoff SJ, Diamond JR, O'Shaughnessy J, Moroose RL, Santin AD, Abramson VG, Shah NC, Rugo HS, Goldenberg DM, Sweidan AM, Iannone R, Washkowitz S, Sharkey RM, Wegener WA, Kalinsky K. Sacituzumab Govitecan-hziy in Refractory Metastatic Triple-Negative Breast Cancer. N Engl J Med. 2019 02 21;380(8):741-751. doi: 10.1056/NEJMoa1814213. PubMed PMID: 30786188.
OLAPARIB	Hiroyuki Yasojima, Harukaze Yamamoto, Norikazu Masuda, Kenjiro Aogi, Masato Takahashi, Kan Yonemori, Masahiro Takeuchi, Akinobu Hamada, Kenji Tamura, Tamie Sukigara, Ritsuko Nagasaka, Rie Nakano, Yukie Tsujimoto, Yuka Morioka, Kiyomi Higuchi, Yasuhiro Fujiwara. A phase I/II trial of olaparib in combination with eribulin in patients with advanced or metastatic triple negative breast cancer (TNBC) previously treated with anthracyclines and taxanes: First results from phase I. DOI: 10.1200/jco.2015.33.15_suppl.1038 Journal of Clinical Oncology 33, no. 15_suppl (May 20 2015) 1038-1038. Choy E, Butrynski JE, Harmon DC, Morgan JA, George S, Wagner AJ, D'Adamo D, Cote GM, Flamand Y, Benes CH, Haber DA, Baselga JM, Demetri GD. Phase II study of olaparib in patients with refractory Ewing sarcoma following failure of standard chemotherapy. BMC Cancer. 2014 Nov 5;14:813. doi: 10.1186/1471-2407-14-813. PubMed PMID: 25374341; PubMed Central PMCID: PMC4230717. Leichman L, Groshen S, O'Neil BH, Messersmith W, Berlin J, Chan E, Leichman CG, Cohen SJ, Cohen D, Lenz HJ, Gold P, Boman B, Fielding A, Locker G, Cason RC, Hamilton SR, Hochster HS. Phase II Study of Olaparib (AZD-2281) After Standard Systemic Therapies for Disseminated Colorectal Cancer. Oncologist. 2016 Feb;21(2):172-7. doi: 10.1634/theoncologist.2015-0319. Epub 2016 Jan 19. PubMed PMID: 26786262; PubMed Central PMCID: PMC4746089. Bang YJ, Im SA, Lee KW, Cho JY, Song EK, Lee KH, Kim YH, Park JO, Chun HG, Zang DY, Fielding A, Rowbottom J, Hodgson D, O'Connor MJ, Yin X, Kim WH. Randomized, Double-Blind Phase II Trial With Prospective Classification by ATM Protein Level to Evaluate the Efficacy and Tolerability of Olaparib Plus Paclitaxel in Patients With Recurrent or Metastatic Gastric Cancer. J Clin Oncol. 2015 Nov 20;33(33):3858-65. doi: 10.1200/JCO.2014.60.0320. Epub 2015 Aug 17. PubMed PMID: 26282658. Bang YJ, Xu RH, Chin K, Lee KW, Park SH, Rha SY, Shen L, Qin S, Xu N, Im SA, Locker G, Rowe P, Shi X, Hodgson D, Liu YZ, Boku N. Olaparib in combination with paclitaxel in patients with advanced gastric cancer who have progressed following first-line therapy (GOLD): a double-blind, randomised, placebo-controlled, phase 3 trial. Lancet Oncol. 2017 Dec;18(12):1637-1651. doi: 10.1016/S1470-2045(17)30682-4. Epub 2017 Nov 2. PubMed PMID: 29103871.
NILOTINIB	Reinwald M, Schleyer E, Kiewe P, Blau IW, Burmeister T, Pursche S, Neumann M, Notter M, Thiel E, Hofmann WK, Kolb HJ, Burdach S, Bender HU. Efficacy and pharmacologic data of second-generation tyrosine kinase inhibitor nilotinib in BCR-ABL-positive leukemia patients with central nervous system relapse after allogeneic stem cell transplantation. Biomed Res Int. 2014;2014:637059. doi: 10.1155/2014/637059. Epub 2014 Jun 15. PubMed PMID: 25025064; PubMed Central PMCID: PMC4082894. Redaelli S, Piazza R, Rostagno R, Magistroni V, Perini P, Marega M, Gambacorti-Passerini C, Boschelli F. Activity of bosutinib, dasatinib, and nilotinib against 18 imatinib-resistant BCR/ABL mutants. J Clin Oncol. 2009 Jan 20;27(3): 469-71. doi: 10.1200/JCO.2008.19.8853. Epub 2008 Dec 15. PubMed PMID: 19075254. Wei J, Freytag M, Schober Y, Nockher WA, Mautner VF, Friedrich RE, Manley PW, Kluwe L, Kurtz A. Nilotinib is more potent than imatinib for treating plexiform neurofibroma in vitro and in vivo. PLoS One. 2014 Oct 23;9(10):e107760. doi: 10.1371/journal.pone.0107760. eCollection 2014. PubMed PMID: 25340526; PubMed Central PMCID: PMC4207688. An X, Tiwari AK, Sun Y, Ding PR, Ashby CR Jr, Chen ZS. BCR-ABL tyrosine kinase inhibitors in the treatment of Philadelphia chromosome positive chronic myeloid leukemia: a review. Leuk Res. 2010 Oct;34(10):1255-68. doi: 10.1016/j.leukres.2010.04.016. Review. PubMed PMID: 20537386. Swords R, Mahalingam D, Padmanabhan S, Carew J, Giles F. Nilotinib: optimal therapy for patients with chronic myeloid leukemia and resistance or intolerance to imatinib. Drug Des Devel Ther. 2009 Sep 21;3:89-101. PubMed PMID: 19920925; PubMed Central PMCID: PMC2769239.
ZANDELISIB	Andrew David Zelenetz, Deepa Jagadeesh, Nishitha M. Reddy, Anastasios Stathis, Huda S. Salman, Adam Steven Asch, Vaishalee Padgaonkar Kenkre, Haresh S. Jhangiani, Alexia Iasonos, Jacob D. Soumerai, Judith Llorin, John M. Pagel. Results of the PI3K inhibitor ME-401 alone or with rituximab in relapsed/refractory (R/R) follicular lymphoma (FL). Journal of Clinical Oncology 37, no. 15_suppl (May 20, 2019) 7512-7512. doi: 10.1200/JCO.2019.37.15_suppl.7512

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COMPOUND NAME	REFERENCES
SHC 014748M	Fan L, Wang C, Zhao L, Wang Z, Zhang X, Liu X, Cao L, Xu W, Li J. SHC014748M, a novel selective inhi-bitor of PI3K, demonstrates promising preclinical antitumor activity in B cell lymphomas and chronic lymphocytic leukemia. Neoplasia. 2020 12;22(12):714-724. doi: 10.1016/j.neo.2020.10.004. Epub 2020 Jan 23. PubMed PMID: 33142237; PubMed Central PMCID: PMC7586065.
ENMD-2076	Tentler JJ, Bradshaw-Pierce EL, Serkova NJ, Hasebroock KM, Pitts TM, Diamond JR, Fletcher GC, Bray MR, Eckhardt SG. Assessment of the in vivo antitumor effects of ENMD-2076, a novel multitargeted kinase inhibitor, against primary and cell line-derived human colorectal cancer xenograft models. Clin Cancer Res. 2010 Jun 01;16 (11):2989-2998. doi: 10.1158/1078-0432.CCR-10-0325. Epub 2010 April 20. PubMed PMID: 20406842; PubMed Central PMCID: PMC3928713. Wang X, Sinn AL, Pollok K, Sandusky G, Zhang S, Chen L, Liang J, Crean CD, Suvannasankha A, Abonour R, Sidor C, Bray MR, Farag SS. Preclinical activity of a novel multiple tyrosine kinase and aurora kinase inhibitor, ENMD-2076, against multiple myeloma. Br J Haematol. 2010 Aug;150(3):313-25. doi: 10.1111/j.1365-2141.2010.08248.x. Epub 2010 June 15. PubMed PMID: 20560971. Fletcher GC, Brokx RD, Denny TA, Hembrough TA, Plum SM, Fogler WE, Sidor CF, Bray MR. ENMD-2076 is an orally active kinase inhibitor with antiangiogenic and antiproliferative mechanisms of action. Mol Cancer Ther. 2011 Jan;10 (1):126-37. doi: 10.1158/1535-7163.MCT-10-0574. Epub 2010 Dec 21. PubMed PMID: 21177375. Diamond JR, Eckhardt SG, Tan AC, Newton TP, Selby HM, Brunkow KL, Kachaeva MI, Varella-Garcia M, Pitts TM, Bray MR, Fletcher GC, Tentler JJ. Predictive biomarkers of sensitivity to the aurora and angiogenic kinase inhibitor ENMD-2076 in preclinical breast cancer models. Clin Cancer Res. 2013 Jan 01;19(1):291-303. doi: 10.1158/1078-0432. CCR-12-1611. Epub 2012 November 07. PubMed PMID: 23136197; PubMed Central PMCID: PMC3537923.
MK-5108	Shimomura T, Hasako S, Nakatsuru Y, Mita T, Ichikawa K, Kodera T, Sakai T, Nambu T, Miyamoto M, Takahashi I, Miki S, Kawanishi N, Ohkubo M, Kotani H, Iwasawa Y. MK-5108, a highly selective Aurora-A kinase inhibitor, shows antitumor activity alone and in combination with docetaxel. Mol Cancer Ther. 2010 Jan;9(1):157-66. doi: 10.1158 /1535-7163.MCT-09-0609. Epub 2010 January 06. PubMed PMID: 20053775. Shan W, Akinfenwa PY, Savannah KB, Kolomeyevskaya N, Laucirica R, Thomas DG, Odunsi K, Creighton CJ, Lev DC, Anderson ML. A small-molecule inhibitor targeting the mitotic spindle checkpoint impairs the growth of uterine leiomyosarcoma. Clin Cancer Res. 2012 Jun 15;18(12):3352-65. doi: 10.1158/1078-0432.CCR-11-3058. Epub 2012 April 25. PubMed PMID: 22535157; PubMed Central PMCID: PMC5042205.
UMBRALISIB	Maharaj K, Powers JJ, Achille A, Mediavilla-Varela M, Gamal W, Burger KL, Fonseca R, Jiang K, Miskin HP, Maryanski D, Monastyrskyi A, Duckett DR, Roush WR, Cleveland JL, Sahakian E, Pinilla-Ibarz J. The dual PI3K/CK1 inhibitor umbralisib exhibits unique immunomodulatory effects on CLL T cells. Blood Adv. 2020 Jul 14;4(13):3072-3084. doi: 10.1182/bloodadvances.2020001800. PubMed PMID: 32634240; PubMed Central PMCID: PMC7362385.
MLN8054	Manfredi MG, Ecsedy JA, Meetze KA, Balani SK, Burenkova O, Chen W, Galvin KM, Hoar KM, Huck JJ, LeRoy PJ, Ray ET, Sells TB, Stringer B, Stroud SG, Vos TJ, Weatherhead GS, Wysong DR, Zhang M, Bolen JB, Claiborne CF. Antitumor activity of MLN8054, an orally active small-molecule inhibitor of Aurora A kinase. Proc Natl Acad Sci U S A. 2007 Mar 06;104(10):4106-11. doi: 10.1073/pnas.0608798104. Epub 2007 February 23. PubMed PMID: 17360485; PubMed Central PMCID: PMC1820716. Moretti L, Niermann K, Schleicher S, Giacalone NJ, Varki V, Kim KW, Kopsombut P, Jung DK, Lu B. MLN8054, a small molecule inhibitor of aurora kinase a, sensitizes androgen-resistant prostate cancer to radiation. Int J Radiat Oncol Biol Phys. 2011 Jul 15;80(4):1189-97. doi: 10.1016/j.ijrobp.2011.01.060. Epub 2011 April 20. PubMed PMID: 21514073.
LY3295668	Du J, Yan L, Torres R, Gong X, Bian H, Marugán C, Boehnke K, Baquero C, Hui YH, Chapman SC, Yang Y, Zeng Y, Bogner SM, Foreman RT, Capen A, Donoho GP, Van Horn RD, Barnard DS, Dempsey JA, Beckmann RP, Marshall MS, Chio LC, Qian Y, Webster YW, Aggarwal A, Chu S, Bhattachar S, Stancato LF, Dowless MS, Iversen PW, Manro JR, Walgren JL, Halstead BW, Dieter MZ, Martinez R, Bhagwat SV, Kreklau EL, Lallena MJ, Ye XS, Patel BKR, Reinhard C, Plowman GD, Barda DA, Henry JR, Buchanan SG, Campbell RM. Aurora A-Selective Inhibitor LY3295668 Leads to Dominant Mitotic Arrest, Apoptosis in Cancer Cells, and Shows Potent Preclinical Antitumor Efficacy. Mol Cancer Ther. 2019 12;18(12):2207-2219. doi: 10.1158/1535-7163.MCT-18-0529. Epub 2019 Jun 17. PubMed PMID: 31530649.
SAR260301	Thorpe LM, Yuzugullu H, Zhao JJ. PI3K in cancer: divergent roles of isoforms, modes of activation and therapeutic targeting. Nat Rev Cancer. 2015 Jan;15(1):7-24. doi: 10.1038/nrc3860. Review. PubMed PMID: 25533673; PubMed Central PMCID: PMC4384662.
AZD8186	Thorpe LM, Yuzugullu H, Zhao JJ. PI3K in cancer: divergent roles of isoforms, modes of activation and therapeutic targeting. Nat Rev Cancer. 2015 Jan;15(1):7-24. doi: 10.1038/nrc3860. Review. PubMed PMID: 25533673; PubMed Central PMCID: PMC4384662.
IPI-549	De Henau O, Rausch M, Winkler D, Campesato LF, Liu C, Cymerman DH, Budhu S, Ghosh A, Pink M, Tchaicha J, Douglas M, Tibbitts T, Sharma S, Proctor J, Kosmider N, White K, Stern H, Soglia J, Adams J, Palombella VJ, McGovern K, Kutok JL, Wolchok JD, Merghoub T. Overcoming resistance to checkpoint blockade therapy by targeting PI3K in myeloid cells. Nature. 2016 11 17;539(7629):443-447. doi: 10.1038/nature20554. Epub 2016 Nov 09. PubMed PMID: 27828943; PubMed Central PMCID: PMC5634331.
AZD6482	Kumar DT, Doss CG. Investigating the Inhibitory Effect of Wortmannin in the Hotspot Mutation at Codon 1047 of PIK3CA Kinase Domain: A Molecular Docking and Molecular Dynamics Approach. Adv Protein Chem Struct Biol. 2016;102:267-97. doi: 10.1016/bs.apcsb.2015.09.008. Epub 2015 Oct 29. Review. PubMed PMID: 26827608.
PUQUITINIB	Xie C, He Y, Zhen M, Wang Y, Xu Y, Lou L. Puquitinib, a novel orally available PI3K inhibitor, exhibits potent antitumor efficacy against acute myeloid leukemia. Cancer Sci. 2017 Jul;108(7):1476-1484. doi: 10.1111/cas.13263. Epub 2017 May 23. PubMed PMID: 28418085; PubMed Central PMCID: PMC5497803.
CEP-37440	Iragavarapu C, Mustafa M, Akinleye A, Furqan M, Mittal V, Cang S, Liu D. Novel ALK inhibitors in clinical use and development. J Hematol Oncol. 2015 Feb 27;8:17. doi: 10.1186/s13045-015-0122-8. Review. PubMed PMID: 25888090; PubMed Central PMCID: PMC4349797.

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COMPOUND NAME	REFERENCES
TOZASERTIB LACTATE	Harrington EA, Bebbington D, Moore J, Rasmussen RK, Ajose-Adeogun AO, Nakayama T, Graham JA, Demur C, Hercend T, Diu-Hercend A, Su M, Golec JM, Miller KM. VX-680, a potent and selective small-molecule inhibitor of the Aurora kinases, suppresses tumor growth in vivo. Nat Med. 2004 Mar;10(3):262-7. doi: 10.1038/nm1003. Epub 2004 February 22. PubMed PMID: 14981513.
ENSARTINIB	Lovly CM, Heuckmann JM, de Stanchina E, Chen H, Thomas RK, Liang C, Pao W. Insights into ALK-driven cancers revealed through development of novel ALK tyrosine kinase inhibitors. Cancer Res. 2011 Jul 15;71(14):4920-31. doi: 10.1158/0008-5472.CAN-10-3879. Epub 2011 May 25. PubMed PMID: 21613408; PubMed Central PMCID: PMC3138877.
GSK2636771	Thorpe LM, Yuzugullu H, Zhao JJ. PI3K in cancer: divergent roles of isoforms, modes of activation and therapeutic targeting. Nat Rev Cancer. 2015 Jan;15(1):7-24. doi: 10.1038/nrc3860. Review. PubMed PMID: 25533673; PubMed Central PMCID: PMC4384662.
ASP3026	S. Kuromitsu, M. Mori, I. Shimada, Y. Kondoh, N. Shindoh, T. Soga, T. Furutani, S. Konagai, H. Sakagami, M. Nakata, Y. Ueno, H. Fushiki, R. Saito, M. Sasamata, H. Mano, M. Kudou. Abstract A227: Antitumor activities of ASP3026 against EML4-ALK-dependent tumor models. Mol. Cancer Ther., 10 (2011) Abstract 227
AMG 319	Thorpe LM, Yuzugullu H, Zhao JJ. PI3K in cancer: divergent roles of isoforms, modes of activation and therapeutic targeting. Nat Rev Cancer. 2015 Jan;15(1):7-24. doi: 10.1038/nrc3860. Review. PubMed PMID: 25533673; PubMed Central PMCID: PMC4384662. Castillo JJ, Iyengar M, Kuritzky B, Bishop KD. Isotype-specific inhibition of the phosphatidylinositol-3-kinase pathway in hematologic malignancies. Onco Targets Ther. 2014 Feb 21;7:333-42. doi: 10.2147/OTT.S34641. eCollection 2014. Review. PubMed PMID: 24591840; PubMed Central PMCID: PMC3937185.
TAE684	Zdzalik D, Dymek B, Grygielewicz P, Gunerka P, Bujak A, Lamparska-Przybysz M, Wieczorek M, Dzwonek K. Activating mutations in ALK kinase domain confer resistance to structurally unrelated ALK inhibitors in NPM-ALK-positive anaplastic large-cell lymphoma. J Cancer Res Clin Oncol. 2014 Apr;140(4):589-98. doi: 10.1007/s00432-014-1589-3. Epub 2014 Feb 8. PubMed PMID: 24509625; PubMed Central PMCID: PMC3949014.
CERITINIB	Ceritinib gains FDA approval for lung cancer. Cancer Discov. 2014 Jul;4(7):753-4. doi: 10.1158/2159-8290.CD-NB2014-074. Epub 2014 May 22. PubMed PMID: 25002599.
GSK1838705A	Sabbatini P, Korenchuk S, Rowand JL, Groy A, Liu Q, Leperi D, Atkins C, Dumble M, Yang J, Anderson K, Kruger RG, Gontarek RR, Maksimchuk KR, Suravajjala S, Lapierre RR, Shotwell JB, Wilson JW, Chamberlain SD, Rabindran SK, Kumar R. GSK1838705A inhibits the insulin-like growth factor-1 receptor and anaplastic lymphoma kinase and shows antitumor activity in experimental models of human cancers. Mol Cancer Ther. 2009 Oct;8(10):2811-20. doi: 10.1158/1535-7163.MCT-09-0423. PubMed PMID: 19825801.
ALECTINIB	Gadgeel SM, Gandhi L, Riely GJ, Chiappori AA, West HL, Azada MC, Morcos PN, Lee RM, Garcia L, Yu L, Boisserie F, Di Laurenzio L, Golding S, Sato J, Yokoyama S, Tanaka T, Ou SH. Safety and activity of alectinib against systemic disease and brain metastases in patients with crizotinib-resistant ALK-rearranged non-small-cell lung cancer (AF-002JG): results from the dose-finding portion of a phase 1/2 study. Lancet Oncol. 2014 Sep;15(10):1119-28. doi: 10.1016/S1470-2045(14)70362-6. Epub 2014 Aug 18. PubMed PMID: 25153538. Zdzalik D, Dymek B, Grygielewicz P, Gunerka P, Bujak A, Lamparska-Przybysz M, Wieczorek M, Dzwonek K. Activating mutations in ALK kinase domain confer resistance to structurally unrelated ALK inhibitors in NPM-ALK-positive anaplastic large-cell lymphoma. J Cancer Res Clin Oncol. 2014 Apr;140(4):589-98. doi: 10.1007/s00432-014-1589-3. Epub 2014 Feb 8. PubMed PMID: 24509625; PubMed Central PMCID: PMC3949014.
BRIGATINIB	Katayama R, Khan TM, Benes C, Lifshits E, Ebi H, Rivera VM, Shakespeare WC, Iafrate AJ, Engelman JA, Shaw AT. Therapeutic strategies to overcome crizotinib resistance in non-small cell lung cancers harboring the fusion oncogene EML4-ALK. Proc Natl Acad Sci U S A. 2011 May 3;108(18):7535-40. doi: 10.1073/pnas.1019559108. Epub 2011 Apr 18. PubMed PMID: 21502504; PubMed Central PMCID: PMC3088626.
OLARATUMAB	Chiorean EG, Sweeney C, Youssoufian H, Qin A, Dontabhaktuni A, Loizos N, Nippgen J, Amato R. A phase I study of olaratumab, an anti-platelet-derived growth factor receptor alpha (PDGFR) monoclonal antibody, in patients with advanced solid tumors. Cancer Chemother Pharmacol. 2014 Mar;73(3):595-604. doi: 10.1007/s00280-014-2389-9. Epub 2014 Jan 23. PubMed PMID: 24452395. William D. Tap, Robin L Jones, Bartosz Chmielowski, Anthony D. Elias, Douglas Adkins, Brian Andrew Van Tine, Mark Agulnik, Matthew M. Cooney, Michael B. Livingston, Gregory K. Pennock, Amy Qin, Ashwin Shahir, Robert L. Ilaria, Ilaria Conti, Jan Cosaert, Gary K. Schwartz. A randomized phase Ib/II study evaluating the safety and efficacy of olaratumab (IMC-3G3), a human anti-platelet-derived growth factor (PDGFR) monoclonal antibody, with or without doxorubicin (Dox), in advanced soft tissue sarcoma (STS). DOI: 10.1200/jco.2015.33.15_suppl.10501 Journal of Clinical Oncology 33, no. 15_suppl Andrick BJ, Gandhi A. Olaratumab: A Novel Platelet-Derived Growth Factor Receptor -Inhibitor for Advanced Soft Tissue Sarcoma. Ann Pharmacother. 2017 Aug 1:1060028017723935. doi: 10.1177/1060028017723935. [Epub ahead of print] PubMed PMID: 28778132. Tobias A, O'brien MP, Agulnik M. Olaratumab for advanced soft tissue sarcoma. Expert Rev Clin Pharmacol. 2017 Jul;10(7):699-705. doi: 10.1080/17512433.2017.1324295. Epub 2017 May 5. Review. PubMed PMID: 28447475.
TAS-102	Mayer RJ, Van Cutsem E, Falcone A, Yoshino T, Garcia-Carbonero R, Mizunuma N, Yamazaki K, Shimada Y, Tabernero J, Komatsu Y, Sobrero A, Boucher E, Peeters M, Tran B, Lenz HJ, Zaniboni A, Hochster H, Cleary JM, Prenen H, Benedetti F, Mizuguchi H, Makris L, Ito M, Ohtsu A; RECOURSE Study Group.. Randomized trial of TAS-102 for refractory metastatic colorectal cancer. N Engl J Med. 2015 May 14;372(20):1909-19. doi: 10.1056/NEJMoa1414325. PubMed PMID: 25970050.

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COMPOUND NAME	REFERENCES
VORINOSTAT	Steven G. DuBois, Meaghan Granger, Susan G. Groshen, Denice Tsao-Wei, Anasheh Shamirian, Scarlett Czarnecki, Fariba Goodarzian, Rachel Berkovich, Hiroyuki Shimada, Yael P. Mosse, Suzanne Shusterman, Susan Lerner Cohn, Kelly C. Goldsmith, Brian D. Weiss, Gregory A. Yanik, Clare Twist, Meredith Irwin, Julie R. Park, Araz Marachelian, Katherine K. Matthay; Dana-Farber/Boston Children's Cancer and Blood Disorders Center, Boston, MA; Cook Children's Medical Center, Fort Worth, TX; University of Southern California, Los Angeles, CA; Children's Hospital Los Angeles, Los Angeles, CA; Loma Linda University Children's Hospital, Riverside, CA; Children's Hospital Los Angeles, Keck School of Medicine, University of Southern California, Los Angeles, CA; Stanford University Medical Center, Stanford, CA; Children's Hospital of Philadelphia, Philadelphia, PA; Dana-Farber/Boston Childrens Cancer and Blood Disorders Center, Boston, MA; The University of Chicago Medicine, Chicago, IL; Emory University School of Medicine, Atlanta, GA; Cincinnati Children's Hospital Medical Center, Cincinnati, OH; Roswell Park Comprehensive Cancer Center, Buffalo, NY; The Hospital for Sick Children, Toronto, ON, Canada; Seattle Children's Hospital, Seattle, WA; University of California San Francisco, San Francisco, CA. Randomized phase II trial of MIBG versus MIBG/vincristine/irinotecan versus MIBG/vorinostat for relapsed/refractory neuroblastoma: A report from the New Approaches to Neuroblastoma Therapy Consortium. J Clin Oncol 38: 2020 (suppl; abstr 10500). doi: 10.1200 /JCO.2020.38.15_suppl.10500. Palmieri D, Lockman PR, Thomas FC, Hua E, Herring J, Hargrave E, Johnson M, Flores N, Qian Y, Vega-Valle E, Taskar KS, Rudraraju V, Mittapalli RK, Gaasch JA, Bohn KA, Thorsheim HR, Liewehr DJ, Davis S, Reilly JF, Walker R, Bronder JL, Feigenbaum L, Steinberg SM, Camphausen K, Meltzer PS, Richon VM, Smith QR, Steeg PS. Vorinostat inhibits brain metastatic colonization in a model of triple-negative breast cancer and induces DNA double-strand breaks. Clin Cancer Res. 2009 Oct 1;15(19):6148-57. doi: 10.1158/1078-0432.CCR-09-1039. Epub 2009 Sep 29. PubMed PMID: 19789319. Buglio D, Georgakis GV, Hanabuchi S, Arima K, Khaskhely NM, Liu YJ, Younes A. Vorinostat inhibits STAT6-mediated TH2 cytokine and TARC production and induces cell death in Hodgkin lymphoma cell lines. Blood. 2008 Aug 15;112(4):1424-33. doi: 10.1182/blood-2008-01-133769. Epub 2008 Oct 09. PubMed PMID: 18541724; PubMed Central PMCID: PMC2515130. Telford BJ, Chen A, Beetham H, Frick J, Brew TP, Gould CM, Single A, Godwin T, Simpson KJ, Guilford P. Synthetic Lethal Screens Identify Vulnerabilities in GPCR Signaling and Cytoskeletal Organization in E-Cadherin-Deficient Cells. Mol Cancer Ther. 2015 May;14(5):1213-23. doi: 10.1158/1535-7163.MCT-14-1092. Epub 2015 Mar 16. PubMed PMID: 25777964.
LUCITANIB	Bello E, Colella G, Scarlato V, Oliva P, Berndt A, Valbusa G, Serra SC, D'Incalci M, Cavalletti E, Giavazzi R, Damia G, Camboni G. E-3810 is a potent dual inhibitor of VEGFR and FGFR that exerts antitumor activity in multiple preclinical models. Cancer Res. 2011 Feb 15;71(4):1396-405. doi: 10.1158/0008-5472.CAN-10-2700. Epub 2011 Jan 6. PubMed PMID: 21212416. Roskoski R. The role of fibroblast growth factor receptor (FGFR) protein-tyrosine kinase inhibitors in the treatment of cancers including those of the urinary bladder. Pharmacol Res. 2020 01;151:104567. doi: 10.1016/j.phrs.2019.104567. Epub 2019 November 23. PubMed PMID: 31770593. H-Y. Zhao, Y. Zhang, Y-X. Ma, L. Zhang, J. Lin, S. Qin. A phase-Ib study of lucitanib (AL3810) in a cohort of patients with recurrent and metastatic nasopharyngeal carcinoma (NPC). Volume 31, Supplement 6, S1348, November 01, 2020 doi: 10.1016/j.annonc.2020.10.262 Mayer IA, Arteaga CL, Nanda R, Miller KD, Jhaveri K, Brufsky AM, Rugo H, Yardley DA, Vahdat LT, Sadeghi S, Audeh MW, Rolfe L, Litten J, Knox A, Raponi M, Tankersley C, Isaacson J, Wride K, Morganstern DE, Vogel C, Connolly RM, Gradishar WJ, Patel R, Pusztai L, Abu-Khalaf M. A phase 2 open-label study of lucitanib in patients (pts) with FGF aberrant metastatic breast cancer (MBC) [abstract]. In: Proceedings of the 2016 San Antonio Breast Cancer Symposium; 2016 Dec 6-10; San Antonio, TX. Philadelphia (PA): AACR; Cancer Res 2017;77(4 Suppl):Abstract nr P6-11-03.
ABIRATERONE	de Bono JS, Logothetis CJ, Molina A, Fizazi K, North S, Chu L, Chi KN, Jones RJ, Goodman OB, Saad F, Staffurth JN, Mainwaring P, Harland S, Flaig TW, Hutson TE, Cheng T, Patterson H, Hainsworth JD, Ryan CJ, Sternberg CN, Ellard SL, Fléchon A, Saleh M, Scholz M, Efstathiou E, Zivi A, Bianchini D, Loriot Y, Chieffo N, Kheoh T, Haqq CM, Scher HI, . Abiraterone and increased survival in metastatic prostate cancer. N Engl J Med. 2011 May 26;364(21):1995-2005. doi: 10.1056/NEJMoa1014618. PubMed PMID: 21612468; PubMed Central PMCID: PMC3471149. Ryan CJ, Smith MR, de Bono JS, Molina A, Logothetis CJ, de Souza P, Fizazi K, Mainwaring P, Piulats JM, Ng S, Carles J, Mulders PF, Basch E, Small EJ, Saad F, Schrijvers D, Van Poppel H, Mukherjee SD, Suttmann H, Gerritsen WR, Flaig TW, George DJ, Yu EY, Efstathiou E, Pantuck A, Winquist E, Higano CS, Taplin ME, Park Y, Kheoh T, Griffin T, Scher HI, Rathkopf DE; COU-AA-302 Investigators.. Abiraterone in metastatic prostate cancer without previous chemotherapy. N Engl J Med. 2013 Jan 10;368(2):138-48. doi: 10.1056/NEJMoa1209096. Erratum in: N Engl J Med. 2013 Feb 7;368(6):584. PubMed PMID: 23228172; PubMed Central PMCID: PMC3683570.
CERDULATINIB	Guo A, Lu P, Coffey G, Conley P, Pandey A, Wang YL. Dual SYK/JAK inhibition overcomes ibrutinib resistance in chronic lymphocytic leukemia: Cerdulatinib, but not ibrutinib, induces apoptosis of tumor cells protected by the microenvironment. Oncotarget. 2017 Feb 21;8(8):12953-12967. doi: 10.18632/oncotarget.14588. PubMed PMID: 28088788; PubMed Central PMCID: PMC5355069. Ma J, Xing W, Coffey G, Dresser K, Lu K, Guo A, Raca G, Pandey A, Conley P, Yu H, Wang YL. Cerdulatinib, a novel dual SYK/JAK kinase inhibitor, has broad anti-tumor activity in both ABC and GCB types of diffuse large B cell lymphoma. Oncotarget. 2015 Dec 22;6(41):43881-96. doi: 10.18632/oncotarget.6316. PubMed PMID: 26575169; PubMed Central PMCID: PMC4791274.

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COMPOUND NAME	REFERENCES
ANLOTINIB	Xie C, Wan X, Quan H, Zheng M, Fu L, Li Y, Lou L. Preclinical characterization of anlotinib, a highly potent and selective vascular endothelial growth factor receptor-2 inhibitor. Cancer Sci. 2018 Apr;109(4):1207-1219. doi: 10.1111/cas.13536. Epub 2018 Jul 25. PubMed PMID: 29446853; PubMed Central PMCID: PMC5891194. Y. Chi, M. Gao, Y. Zhang, F. Shi, Y. Cheng, Z. Guo, M. Ge, J. Qin, J. Zhang, Z. Li, X. Zhou, R. Huang, X. Chen, H. Liu, R. Cheng, Z. Xu, X. Zheng, D. Li, P. Tang. 265O - Anlotinib in locally advanced or metastatic radioiodine-refractory differentiated thyroid carcinoma: A randomized, double-blind, multicenter phase II trial. Annals of Oncology (2020) 31 (suppl_6): S1347-S1354. 10.1016/annonc/annonc360
TOFACITINIB	Meyer DM, Jesson MI, Li X, Elrick MM, Funckes-Shippy CL, Warner JD, Gross CJ, Dowty ME, Ramaiah SK, Hirsch JL, Saabye MJ, Barks JL, Kishore N, Morris DL. Anti-inflammatory activity and neutrophil reductions mediated by the JAK1/JAK3 inhibitor, CP-690,550, in rat adjuvant-induced arthritis. J Inflamm (Lond). 2010 Aug 11;7:41. doi: 10.1186/1476-9255-7-41. PubMed PMID: 20701804; PubMed Central PMCID: PMC2928212. Bouchekioua A, Scourzic L, de Wever O, Zhang Y, Cervera P, Aline-Fardin A, Mercher T, Gaulard P, Nyga R, Jeziorowska D, Douay L, Vainchenker W, Louache F, Gespach C, Solary E, Coppo P. JAK3 deregulation by activating mutations confers invasive growth advantage in extranodal nasal-type natural killer cell lymphoma. Leukemia. 2014 Feb;28(2):338-48. doi: 10.1038/leu.2013.157. Epub 2013 May 21. PubMed PMID: 23689514.
NAVITOCLAX	Tse C, Shoemaker AR, Adickes J, Anderson MG, Chen J, Jin S, Johnson EF, Marsh KC, Mitten MJ, Nimmer P, Roberts L, Tahir SK, Xiao Y, Yang X, Zhang H, Fesik S, Rosenberg SH, Elmore SW. ABT-263: a potent and orally bioavailable Bcl-2 family inhibitor. Cancer Res. 2008 May 01;68(9):3421-8. doi: 10.1158/0008-5472.CAN-07-5836. PubMed PMID: 18451170. de Vos S, Leonard JP, Friedberg JW, Zain J, Dunleavy K, Humerickhouse R, Hayslip J, Pesko J, Wilson WH. Safety and efficacy of navitoclax, a BCL-2 and BCL-XL inhibitor, in patients with relapsed or refractory lymphoid malignancies: results from a phase 2a study. Leuk Lymphoma. 2021 04;62(4):810-818. doi: 10.1080/10428194.2020.1845332. Epub 2020 November 25. PubMed PMID: 33236943.
BRIVANIB	Huynh H, Ngo VC, Fargnoli J, Ayers M, Soo KC, Koong HN, Thng CH, Ong HS, Chung A, Chow P, Pollock P, Byron S, Tran E. Brivanib alaninate, a dual inhibitor of vascular endothelial growth factor receptor and fibroblast growth factor receptor tyrosine kinases, induces growth inhibition in mouse models of human hepatocellular carcinoma. Clin Cancer Res. 2008 Oct 1;14(19):6146-53. doi: 10.1158/1078-0432.CCR-08-0509. PubMed PMID: 18829493. Cai ZW, Zhang Y, Borzilleri RM, Qian L, Barbosa S, Wei D, Zheng X, Wu L, Fan J, Shi Z, Wautlet BS, Mortillo S, Jeyaseelan R Sr, Kukral DW, Kamath A, Marathe P, D'Arienzo C, Derbin G, Barrish JC, Robl JA, Hunt JT, Lombardo LJ, Fargnoli J, Bhide RS. Discovery of brivanib alaninate ((S)-((R)-1-(4-(4-fluoro-2-methyl-1H-indol-5-yloxy)-5-methylpyrrolo[2,1-f][1,2,4] triazin-6-yloxy)propan-2-yl)2-aminopropanoate), a novel prodrug of dual vascular endothelial growth factor receptor-2 and fibroblast growth factor receptor-1 kinase inhibitor (BMS-540215). J Med Chem. 2008 Mar 27;51(6):1976-80. doi: 10.1021/jm7013309. Epub 2008 Feb 21. PubMed PMID: 18288793.
AZD4547	IBRAHIM, Tony, et al. Clinical development of FGFR3 inhibitors for the treatment of urothelial cancer. Bladder Cancer, 2019, 5.2: 87-102. Roskoski R. The role of fibroblast growth factor receptor (FGFR) protein-tyrosine kinase inhibitors in the treatment of cancers including those of the urinary bladder. Pharmacol Res. 2020 01;151:104567. doi: 10.1016/j.phrs.2019.104567. Epub 2019 November 23. PubMed PMID: 31770593. Liu L, Ye TH, Han YP, Song H, Zhang YK, Xia Y, Wang NY, Xiong Y, Song XJ, Zhu YX, Li de L, Zeng J, Ran K, Peng CT, Wei YQ, Yu LT. Reductions in myeloid-derived suppressor cells and lung metastases using AZD4547 treatment of a metastatic murine breast tumor model. Cell Physiol Biochem. 2014;33(3):633-45. doi: 10.1159/000358640. Epub 2014 Mar 4. PubMed PMID: 24642893.
LINIFANIB	Albert DH, Tapang P, Magoc TJ, Pease LJ, Reuter DR, Wei RQ, Li J, Guo J, Bousquet PF, Ghoreishi-Haack NS, Wang B, Bukofzer GT, Wang YC, Stavropoulos JA, Hartandi K, Niquette AL, Soni N, Johnson EF, McCall JO, Bouska JJ, Luo Y, Donawho CK, Dai Y, Marcotte PA, Glaser KB, Michaelides MR, Davidsen SK. Preclinical activity of ABT-869, a multitargeted receptor tyrosine kinase inhibitor. Mol Cancer Ther. 2006 Apr;5(4):995-1006. PubMed PMID: 16648571. Luo Y, Jiang F, Cole TB, Hradil VP, Reuter D, Chakravartty A, Albert DH, Davidsen SK, Cox BF, McKeegan EM, Fox GB. A novel multi-targeted tyrosine kinase inhibitor, linifanib (ABT-869), produces functional and structural changes in tumor vasculature in an orthotopic rat glioma model. Cancer Chemother Pharmacol. 2012 Apr;69(4):911-21. doi: 10.1007/s00280-011-1740-7. Epub 2011 November 12. PubMed PMID: 22080168.
SURUFATINIB	Jinghong Zhou, Jun Ni, Min Cheng, Na Yang, Junqing Liang, Liang Ge, Wei Zhang, Jianxing Tang, qiaoling Sun, Fu Li, Jia Hu, Dongxia Shi, Hongbo Chen, Jingwen Long, Junen Sun, Fang Yin, Xuelei Ge, Hong Jia, Feng Zhou, Yongxin ren, Weiguo Qing and Weiguo Su. Abstract 4187: Preclinical evaluation of sulfatinib, a novel angio-immuno kinase inhibitor targeting VEGFR, FGFR1 and CSF1R kinases. Cancer Res. July 1 2017 (77) (13 Supplement) 4187; DOI: 10.1158/1538-7445.AM2017-4187
LY2874455	Roskoski R. The role of fibroblast growth factor receptor (FGFR) protein-tyrosine kinase inhibitors in the treatment of cancers including those of the urinary bladder. Pharmacol Res. 2020 01;151:104567. doi: 10.1016/j.phrs.2019.104567. Epub 2019 November 23. PubMed PMID: 31770593.
KX01	Creedon H, Brunton VG. Src kinase inhibitors: promising cancer therapeutics? Crit Rev Oncog. 2012;17(2):145-59. Review. PubMed PMID: 22471705.
ROGARATINIB	Roskoski R. The role of fibroblast growth factor receptor (FGFR) protein-tyrosine kinase inhibitors in the treatment of cancers including those of the urinary bladder. Pharmacol Res. 2020 01;151:104567. doi: 10.1016/j.phrs.2019.104567. Epub 2019 November 23. PubMed PMID: 31770593. IBRAHIM, Tony, et al. Clinical development of FGFR3 inhibitors for the treatment of urothelial cancer. Bladder Cancer, 2019, 5.2: 87-102.

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COMPOUND NAME	REFERENCES
ODM-203	Holmström TH, Moilanen AM, Ikonen T, Björkman ML, Linnanen T, Wohlfahrt G, Karlsson S, Oksala R, Korjamo T, Samajdar S, Rajagopalan S, Chelur S, Narayanan K, Ramachandra RK, Mani J, Nair R, Gowda N, Anthony T, Dhodheri S, Mukherjee S, Ujjinamatada RK, Srinivas N, Ramachandra M, Kallio PJ. ODM-203, a Selective Inhibitor of FGFR and VEGFR, Shows Strong Antitumor Activity, and Induces Antitumor Immunity. Mol Cancer Ther. 2019 01;18 (1):28-38. doi: 10.1158/1535-7163.MCT-18-0204. Epub 2018 Apr 09. PubMed PMID: 30301864.
PEMIGATINIB	IBRAHIM, Tony, et al. Clinical development of FGFR3 inhibitors for the treatment of urothelial cancer. Bladder Cancer, 2019, 5.2: 87-102. Roskoski R. The role of fibroblast growth factor receptor (FGFR) protein-tyrosine kinase inhibitors in the treatment of cancers including those of the urinary bladder. Pharmacol Res. 2020 01;151:104567. doi: 10.1016/j.phrs.2019.104567. Epub 2019 November 23. PubMed PMID: 31770593.
TAS-120	Sootome H, Fujita H, Ito K, Ochiiwa H, Fujioka Y, Ito K, Miura A, Sagara T, Ito S, Ohsawa H, Otsuki S, Funabashi K, Yashiro M, Matsuo K, Yonekura K, Hirai H. Futibatinib Is a Novel Irreversible FGFR 1-4 Inhibitor That Shows Selective Antitumor Activity against FGFR-Deregulated Tumors. Cancer Res. 2020 11 15;80(22):4986-4997. doi: 10.1158/0008-5472.CAN-19-2568. Epub 2020 September 24. PubMed PMID: 32973082. Roskoski R. The role of fibroblast growth factor receptor (FGFR) protein-tyrosine kinase inhibitors in the treatment of cancers including those of the urinary bladder. Pharmacol Res. 2020 01;151:104567. doi: 10.1016/j.phrs.2019.104567. Epub 2019 November 23. PubMed PMID: 31770593.
Filgotinib	Shien K, Papadimitrakopoulou VA, Ruder D, Behrens C, Shen L, Kalhor N, Song J, Lee JJ, Wang J, Tang X, Herbst RS, Toyooka S, Girard L, Minna JD, Kurie JM, Wistuba II, Izzo JG. JAK1/STAT3 activation through a proinflammatory cytokine pathway leads to resistance to molecularly targeted therapy in non-small cell lung cancer. Mol Cancer Ther. 2017 Jul 20. pii: molcanther.0148.2016. doi: 10.1158/1535-7163.MCT-17-0148. [Epub ahead of print] PubMed PMID: 28729401.
PF-04965842	Degryse S, Cools J. JAK kinase inhibitors for the treatment of acute lymphoblastic leukemia. J Hematol Oncol. 2015 Jul 26;8:91. doi: 10.1186/s13045-015-0192-7. PubMed PMID: 26208852; PubMed Central PMCID: PMC4545857.
Itacitinib	Bose P, Abou Zahr A, Verstovsek S. Investigational Janus kinase inhibitors in development for myelofibrosis. Expert Opin Investig Drugs. 2017 Jun;26(6):723-734. doi: 10.1080/13543784.2017.1323871. Epub 2017 May 8. Review. PubMed PMID: 28441920.
CT 1578	Madan B, Goh KC, Hart S, William AD, Jayaraman R, Ethirajulu K, Dymock BW, Wood JM. SB1578, a novel inhibitor of JAK2, FLT3, and c-Fms for the treatment of rheumatoid arthritis. J Immunol. 2012 Oct 15;189(8):4123-34. doi: 10.4049/jimmunol.1200675. Epub 2012 Sep 7. PubMed PMID: 22962687.
AEG 41174	Lipka DB, Hoffmann LS, Heidel F, Markova B, Blum MC, Breitenbuecher F, Kasper S, Kindler T, Levine RL, Huber C, Fischer T. LS104, a non-ATP-competitive small-molecule inhibitor of JAK2, is potently inducing apoptosis in JAK2V617F-positive cells. Mol Cancer Ther. 2008 May;7(5):1176-84. doi: 10.1158/1535-7163.MCT-07-2215. PubMed PMID: 18483305.
R 348	Deuse T, Velotta JB, Hoyt G, Govaert JA, Taylor V, Masuda E, Herlaar E, Park G, Carroll D, Pelletier MP, Robbins RC, Schrepfer S. Novel immunosuppression: R348, a JAK3- and Syk-inhibitor attenuates acute cardiac allograft rejection. Transplantation. 2008 Mar 27;85(6):885-92. doi: 10.1097/TP.0b013e318166acc4. PubMed PMID: 18360272.
WHIP 131	Bhavsar SK, Singh Y, Sharma P, Khairnar V, Hosseinzadeh Z, Zhang S, Palmada M, Sabolic I, Koepsell H, Lang KS, Lang PA, Lang F. Expression of JAK3 Sensitive Na+ Coupled Glucose Carrier SGLT1 in Activated Cytotoxic T Lymphocytes. Cell Physiol Biochem. 2016;39(3):1209-28. doi: 10.1159/000447827. Epub 2016 Sep 5. PubMed PMID: 27595398.
AZM 475271	Gill AL, Verdonk M, Boyle RG, Taylor R. A comparison of physicochemical property profiles of marketed oral drugs and orally bioavailable anti-cancer protein kinase inhibitors in clinical development. Curr Top Med Chem. 2007;7 (14):1408-22. Review. PubMed PMID: 17692029.
KW 2449	Pratz KW, Cortes J, Roboz GJ, Rao N, Arowojolu O, Stine A, Shiotsu Y, Shudo A, Akinaga S, Small D, Karp JE, Levis M. A pharmacodynamic study of the FLT3 inhibitor KW-2449 yields insight into the basis for clinical response. Blood. 2009 Apr 23;113(17):3938-46. doi: 10.1182/blood-2008-09-177030. Epub 2008 Nov 24. PubMed PMID: 19029442; PubMed Central PMCID: PMC2673122.
ENTINOSTAT	Telford BJ, Chen A, Beetham H, Frick J, Brew TP, Gould CM, Single A, Godwin T, Simpson KJ, Guilford P. Synthetic Lethal Screens Identify Vulnerabilities in GPCR Signaling and Cytoskeletal Organization in E-Cadherin-Deficient Cells. Mol Cancer Ther. 2015 May;14(5):1213-23. doi: 10.1158/1535-7163.MCT-14-1092. Epub 2015 Mar 16. PubMed PMID: 25777964.
CCT3833	Saturno G, Lopes F, Girotti MR, Niculescu-Duvaz I, Niculescu-Duvaz D, Zambon A, et al. Abstract LB-212: Therapeutic efficacy of the paradox-breaking panRAF and SRC drug CCT3833/BAL3833 in KRAS-driven cancer models. Cancer Res. 2016 Jul 15;76(14 Supplement):LB-212-LB-212.
Debio1347	Nakanishi Y, Akiyama N, Tsukaguchi T, Fujii T, Sakata K, Sase H, Isobe T, Morikami K, Shindoh H, Mio T, Ebiike H, Taka N, Aoki Y, Ishii N. The fibroblast growth factor receptor genetic status as a potential predictor of the sensitivity to CH5183284/Debio 1347, a novel selective FGFR inhibitor. Mol Cancer Ther. 2014 Nov;13(11):2547-58. doi: 10.1158 /1535-7163.MCT-14-0248. Epub 2014 August 28. PubMed PMID: 25169980. Nakanishi Y, Mizuno H, Sase H, Fujii T, Sakata K, Akiyama N, Aoki Y, Aoki M, Ishii N. ERK Signal Suppression and Sensitivity to CH5183284/Debio 1347, a Selective FGFR Inhibitor. Mol Cancer Ther. 2015 Dec;14(12):2831-9. doi: 10.1158/1535-7163.MCT-15-0497. Epub 2015 Oct 5. PubMed PMID: 26438159.
SSR128129E	Ader I, Delmas C, Skuli N, Bonnet J, Schaeffer P, Bono F, Cohen-Jonathan-Moyal E, Toulas C. Preclinical evidence that SSR128129E--a novel small-molecule multi-fibroblast growth factor receptor blocker--radiosensitises human glioblastoma. Eur J Cancer. 2014 Sep;50(13):2351-9. doi: 10.1016/j.ejca.2014.05.012. Epub 2014 Jun 18. PubMed PMID: 24953334.

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

COMPOUND NAME	REFERENCES
XL228	King ER, Wong KK. Insulin-like growth factor: current concepts and new developments in cancer therapy. Recent Pat Anticancer Drug Discov. 2012 Jan;7(1):14-30. Review. PubMed PMID: 21875414; PubMed Central PMCID: PMC3724215.
XL019	Verstovsek, Srdan, Pardanani, Animesh D., Shah, Neil P., Sokol, Lubomir, Wadleigh, Martha, Gilliland, D. Gary, List, Alan F., Tefferi, Ayalew, Kantarjian, Hagop M., Bui, Lynne A., Clary, Douglas O. A Phase I Study of XL019, a Selective JAK2 Inhibitor, in Patients with Primary Myelofibrosis and Post-Polycythemia Vera/Essential Thrombocythemia Myelofibrosis. ASH Annual Meeting Abstracts 2007 110: 553
PACRITINIB	Hart S, Goh KC, Novotny-Diermayr V, Tan YC, Madan B, Amalini C, Ong LC, Kheng B, Cheong A, Zhou J, Chng WJ, Wood JM. Pacritinib (SB1518), a JAK2/FLT3 inhibitor for the treatment of acute myeloid leukemia. Blood Cancer J. 2011 Nov;1(11):e44. doi: 10.1038/bcj.2011.43. Epub 2011 Nov 11. PubMed PMID: 22829080; PubMed Central PMCID: PMC3256753.
BAFETINIB	Yokota A, Kimura S, Masuda S, Ashihara E, Kuroda J, Sato K, Kamitsuji Y, Kawata E, Deguchi Y, Urasaki Y, Terui Y, Ruthardt M, Ueda T, Hatake K, Inui K, Maekawa T. INNO-406, a novel BCR-ABL/Lyn dual tyrosine kinase inhibitor, suppresses the growth of Ph+ leukemia cells in the central nervous system, and cyclosporine A augments its in vivo activity. Blood. 2007 Jan 1;109(1):306-14. Epub 2006 Sep 5. PubMed PMID: 16954504.
INCB047986	Buchert M, Burns CJ, Ernst M. Targeting JAK kinase in solid tumors: emerging opportunities and challenges. Oncogene. 2016 Feb 25;35(8):939-51. doi: 10.1038/onc.2015.150. Epub 2015 May 18. Review. PubMed PMID: 25982279.
HGS1036	Harding TC, Long L, Palencia S, Zhang H, Sadra A, Hestir K, Patil N, Levin A, Hsu AW, Charych D, Brennan T, Zanghi J, Halenbeck R, Marshall SA, Qin M, Doberstein SK, Hollenbaugh D, Kavanaugh WM, Williams LT, Baker KP. Blockade of nonhormonal fibroblast growth factors by FP-1039 inhibits growth of multiple types of cancer. Sci Transl Med. 2013 Mar 27;5(178):178ra39. doi: 10.1126/scitranslmed.3005414. PubMed PMID: 23536011.
REBASTINIB	O'Hare T, Eide CA, Agarwal A, Adrian LT, Zabriskie MS, Mackenzie RJ, Latocha DH, Johnson KJ, You H, Luo J, Riddle SM, Marks BD, Vogel KW, Koop DR, Apgar J, Tyner JW, Deininger MW, Druker BJ. Threshold levels of ABL tyrosine kinase inhibitors retained in chronic myeloid leukemia cells determine their commitment to apoptosis. Cancer Res. 2013 Jun 1;73(11):3356-70. doi: 10.1158/0008-5472.CAN-12-3904. Epub 2013 Apr 10. PubMed PMID: 23576564; PubMed Central PMCID: PMC3674150.
MOMELOTINIB	Abubaker K, Luwor RB, Zhu H, McNally O, Quinn MA, Burns CJ, Thompson EW, Findlay JK, Ahmed N. Inhibition of the JAK2/STAT3 pathway in ovarian cancer results in the loss of cancer stem cell-like characteristics and a reduced tumor burden. BMC Cancer. 2014 May 6;14:317. doi: 10.1186/1471-2407-14-317. PubMed PMID: 24886434; PubMed Central PMCID: PMC4025194. Pardanani A, Laborde RR, Lasho TL, Finke C, Begna K, Al-Kali A, Hogan WJ, Litzow MR, Leontovich A, Kowalski M, Tefferi A. Safety and efficacy of CYT387, a JAK1 and JAK2 inhibitor, in myelofibrosis. Leukemia. 2013 Jun;27(6):1322-7. doi: 10.1038/leu.2013.71. Epub 2013 Mar 5. PubMed PMID: 23459451; PubMed Central PMCID: PMC3677140.
CRENOLANIB	Heinrich MC, Griffith D, McKinley A, Patterson J, Presnell A, Ramachandran A, Debiec-Rychter M. Crenolanib inhibits the drug-resistant PDGFRA D842V mutation associated with imatinib-resistant gastrointestinal stromal tumors. Clin Cancer Res. 2012 Aug 15;18(16):4375-84. doi: 10.1158/1078-0432.CCR-12-0625. Epub 2012 Jun 27. PubMed PMID: 22745105.
SARACATINIB	Creedon H, Brunton VG. Src kinase inhibitors: promising cancer therapeutics? Crit Rev Oncog. 2012;17(2):145-59. Review. PubMed PMID: 22471705. Nam HJ, Im SA, Oh DY, Elvin P, Kim HP, Yoon YK, Min A, Song SH, Han SW, Kim TY, Bang YJ. Antitumor activity of saracatinib (AZD0530), a c-Src/Abl kinase inhibitor, alone or in combination with chemotherapeutic agents in gastric cancer. Mol Cancer Ther. 2013 Jan;12(1):16-26. doi: 10.1158/1535-7163.MCT-12-0109. Epub 2012 Nov 9. PubMed PMID: 23144237.
ZM39923	Wang H, Wang Y, Jiang X, Wang Z, Zhong B, Fang Y. The molecular mechanism of curcumol on inducing cell growth arrest and apoptosis in Jurkat cells, a model of CD4 T cells. Int Immunopharmacol. 2014 Aug;21(2):375-82. doi: 10.1016/j.intimp.2014.05.021. Epub 2014 May 28. PubMed PMID: 24877754.
APATINIB	Tian S, Quan H, Xie C, Guo H, Lü F, Xu Y, Li J, Lou L. YN968D1 is a novel and selective inhibitor of vascular endothelial growth factor receptor-2 tyrosine kinase with potent activity in vitro and in vivo. Cancer Sci. 2011 Jul;102(7):1374-80. doi: 10.1111/j.1349-7006.2011.01939.x. Epub 2011 May 09. PubMed PMID: 21443688.
WHI-P154	Amin HM, Medeiros LJ, Ma Y, Feretzaki M, Das P, Leventaki V, Rassidakis GZ, O'Connor SL, McDonnell TJ, Lai R. Inhibition of JAK3 induces apoptosis and decreases anaplastic lymphoma kinase activity in anaplastic large cell lymphoma. Oncogene. 2003 Aug 21;22(35):5399-407. PubMed PMID: 12934099.
DECERNOTINIB	Farmer LJ, Ledeboer MW, Hoock T, Arnost MJ, Bethiel RS, Bennani YL, Black JJ, Brummel CL, Chakilam A, Dorsch WA, Fan B, Cochran JE, Halas S, Harrington EM, Hogan JK, Howe D, Huang H, Jacobs DH, Laitinen LM, Liao S, Mahajan S, Marone V, Martinez-Botella G, McCarthy P, Messersmith D, Namchuk M, Oh L, Penney MS, Pierce AC, Raybuck SA, Rugg A, Salituro FG, Saxena K, Shannon D, Shlyakter D, Swenson L, Tian SK, Town C, Wang J, Wang T, Wannamaker MW, Winquist RJ, Zuccola HJ. Discovery of VX-509 (Decernotinib): A Potent and Selective Janus Kinase 3 Inhibitor for the Treatment of Autoimmune Diseases. J Med Chem. 2015 Sep 24;58(18):7195-216. doi: 10.1021/acs.jmedchem.5b00301. Epub 2015 Sep 10. PubMed PMID: 26230873. Kyttaris VC. Kinase inhibitors: a new class of antirheumatic drugs. Drug Des Devel Ther. 2012;6:245-50. doi: 10.2147/DDDT.S25426. Epub 2012 Sep 21. Review. PubMed PMID: 23055694; PubMed Central PMCID: PMC3457674.
ORANTINIB	Machida S, Saga Y, Takei Y, Mizuno I, Takayama T, Kohno T, Konno R, Ohwada M, Suzuki M. Inhibition of peritoneal dissemination of ovarian cancer by tyrosine kinase receptor inhibitor SU6668 (TSU-68). Int J Cancer. 2005 Mar 20;114(2):224-9. PubMed PMID: 15551349.

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COMPOUND NAME	REFERENCES
PD173074	Taylor JG 6th, Cheuk AT, Tsang PS, Chung JY, Song YK, Desai K, Yu Y, Chen QR, Shah K, Youngblood V, Fang J, Kim SY, Yeung C, Helman LJ, Mendoza A, Ngo V, Staudt LM, Wei JS, Khanna C, Catchpoole D, Qualman SJ, Hewitt SM, Merlino G, Chanock SJ, Khan J. Identification of FGFR4-activating mutations in human rhabdomyosarcomas that promote metastasis in xenotransplanted models. J Clin Invest. 2009 Nov;119(11):3395-407. doi: 10.1172/JCI39703. Epub 2009 Oct 5. PubMed PMID: 19809159; PubMed Central PMCID: PMC2769177.
LY287445	Zhao G, Li WY, Chen D, Henry JR, Li HY, Chen Z, Zia-Ebrahimi M, Bloem L, Zhai Y, Huss K, Peng SB, McCann DJ. A novel, selective inhibitor of fibroblast growth factor receptors that shows a potent broad spectrum of antitumor activity in several tumor xenograft models. Mol Cancer Ther. 2011 Nov;10(11):2200-10. doi: 10.1158/1535-7163.MCT-11-0306. Epub 2011 Sep 7. PubMed PMID: 21900693.
ERDAFITINIB	Roskoski R. The role of fibroblast growth factor receptor (FGFR) protein-tyrosine kinase inhibitors in the treatment of cancers including those of the urinary bladder. Pharmacol Res. 2020 01;151:104567. doi: 10.1016/j.phrs.2019.104567. Epub 2019 November 23. PubMed PMID: 31770593. IBRAHIM, Tony, et al. Clinical development of FGFR3 inhibitors for the treatment of urothelial cancer. Bladder Cancer, 2019, 5.2: 87-102.
INFIGRATINIB	IBRAHIM, Tony, et al. Clinical development of FGFR3 inhibitors for the treatment of urothelial cancer. Bladder Cancer, 2019, 5.2: 87-102. Roskoski R. The role of fibroblast growth factor receptor (FGFR) protein-tyrosine kinase inhibitors in the treatment of cancers including those of the urinary bladder. Pharmacol Res. 2020 01;151:104567. doi: 10.1016/j.phrs.2019.104567. Epub 2019 November 23. PubMed PMID: 31770593.
IBRUTINIB	Byrd JC, Hillmen P, O'Brien S, Barrientos JC, Reddy NM, Coutre S, Tam CS, Mulligan SP, Jaeger U, Barr PM, Furman RR, Kipps TJ, Thornton P, Moreno C, Montillo M, Pagel JM, Burger JA, Woyach JA, Dai S, Vezan R, James DF, Brown JR. Long-term follow-up of the RESONATE phase 3 trial of ibrutinib vs ofatumumab. Blood. 2019 05 09;133(19):2031-2042. doi: 10.1182/blood-2018-08-870238. Epub 2019 Oct 06. PubMed PMID: 30842083; PubMed Central PMCID: PMC6509542. Burger JA, Barr PM, Robak T, Owen C, Ghia P, Tedeschi A, Bairey O, Hillmen P, Coutre SE, Devereux S, Grosicki S, McCarthy H, Simpson D, Offner F, Moreno C, Dai S, Lal I, Dean JP, Kipps TJ. Long-term efficacy and safety of first-line ibrutinib treatment for patients with CLL/SLL: 5 years of follow-up from the phase 3 RESONATE-2 study. Leukemia. 2020 03;34(3):787-798. doi: 10.1038/s41375-019-0602-x. Epub 2019 Jan 18. PubMed PMID: 31628428; PubMed Central PMCID: PMC7214263. Woyach JA, Ruppert AS, Heerema NA, Zhao W, Booth AM, Ding W, Bartlett NL, Brander DM, Barr PM, Rogers KA, Parikh SA, Coutre S, Hurria A, Brown JR, Lozanski G, Blachly JS, Ozer HG, Major-Elechi B, Fruth B, Nattam S, Larson RA, Erba H, Litzow M, Owen C, Kuzma C, Abramson JS, Little RF, Smith SE, Stone RM, Mandrekar SJ, Byrd JC. Ibrutinib Regimens versus Chemoimmunotherapy in Older Patients with Untreated CLL. N Engl J Med. 2018 12 27;379(26):2517-2528. doi: 10.1056/NEJMoa1812836. Epub 2018 Jan 01. PubMed PMID: 30501481; PubMed Central PMCID: PMC6325637.
DOVITINIB	André F, Bachelot T, Campone M, Dalenc F, Perez-Garcia JM, Hurvitz SA, Turner N, Rugo H, Smith JW, Deudon S, Shi M, Zhang Y, Kay A, Porta DG, Yovine A, Baselga J. Targeting FGFR with dovitinib (TKI258): preclinical and clinical data in breast cancer. Clin Cancer Res. 2013 Jul 1;19(13):3693-702. doi: 10.1158/1078-0432.CCR-13-0190. Epub 2013 May 8. PubMed PMID: 23658459. Wan X, Corn PG, Yang J, Palanisamy N, Starbuck MW, Efstathiou E, Tapia EM, Zurita AJ, Aparicio A, Ravoori MK, Vazquez ES, Robinson DR, Wu YM, Cao X, Iyer MK, McKeehan W, Kundra V, Wang F, Troncoso P, Chinnaiyan AM, Logothetis CJ, Navone NM. Prostate cancer cell-stromal cell crosstalk via FGFR1 mediates antitumor activity of dovitinib in bone metastases. Sci Transl Med. 2014 Sep 3;6(252):252ra122. doi: 10.1126/scitranslmed.3009332. PubMed PMID: 25186177. Milowsky MI, Dittrich C, Durán I, Jagdev S, Millard FE, Sweeney CJ, Bajorin D, Cerbone L, Quinn DI, Stadler WM, Rosenberg JE, Lochheed M, Sen P, Squires M, Shi M, Sternberg CN. Phase 2 trial of dovitinib in patients with progressive FGFR3-mutated or FGFR3 wild-type advanced urothelial carcinoma. Eur J Cancer. 2014 Dec;50(18):3145-52. doi: 10.1016/j.ejca.2014.10.013. Epub 2014 Oct 30. PubMed PMID: 25457633.
APALUTAMIDE	Rathkopf DE et al., Final results from ACIS, a randomized, placebo (PBO)-controlled double-blind phase 3 study of apalutamide (APA) and abiraterone acetate plus prednisone (AAP) versus AAP in patients (pts) with chemo-naive metastatic castration-resistant prostate cancer (mCRPC). J Clin Oncol. 2021;39(suppl 6):abstr 9. doi: 10.1200/JCO.2021.39.6_suppl.9. Smith MR, Antonarakis ES, Ryan CJ, Berry WR, Shore ND, Liu G, Alumkal JJ, Higano CS, Chow Maneval E, Bandekar R, de Boer CJ, Yu MK, Rathkopf DE. Phase 2 Study of the Safety and Antitumor Activity of Apalutamide (ARN-509), a Potent Androgen Receptor Antagonist, in the High-risk Nonmetastatic Castration-resistant Prostate Cancer Cohort. Eur Urol. 2016 Dec;70(6):963-970. doi: 10.1016/j.eururo.2016.04.023. PubMed PMID: 27160947. Chi KN, Chowdhury S, Bjartell A, Chung BH, Pereira de Santana Gomes AJ, Given R, Juárez A, Merseburger AS, Özgüroğlu M, Uemura H, Ye D, Brookman-May S, Mundle SD, McCarthy SA, Larsen JS, Sun W, Bevans KB, Zhang K, Bandyopadhyay N, Agarwal N. Apalutamide in Patients With Metastatic Castration-Sensitive Prostate Cancer: Final Survival Analysis of the Randomized, Double-Blind, Phase III TITAN Study. J Clin Oncol. 2021 Apr 29;:JCO2003488. doi: 10.1200/JCO.20.03488. Epub 2021 April 29. PubMed PMID: 33914595. Chi KN, Agarwal N, Bjartell A, Chung BH, Pereira de Santana Gomes AJ, Given R, Juárez Soto Á, Merseburger AS, Özgüroğlu M, Uemura H, Ye D, Deprince K, Naini V, Li J, Cheng S, Yu MK, Zhang K, Larsen JS, McCarthy S, Chowdhury S, . Apalutamide for Metastatic, Castration-Sensitive Prostate Cancer. N Engl J Med. 2019 07 04;381(1):13-24. doi: 10.1056/NEJMoa1903307. Epub 2019 Oct 31. PubMed PMID: 31150574.

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COMPOUND NAME	REFERENCES
ENFORTUMAB VEDOTIN	Rosenberg JE, O'Donnell PH, Balar AV, McGregor BA, Heath EI, Yu EY, Galsky MD, Hahn NM, Gartner EM, Pinelli JM, Liang SY, Melhem-Bertrandt A, Petrylak DP. Pivotal Trial of Enfortumab Vedotin in Urothelial Carcinoma After Platinum and Anti-Programmed Death 1/Programmed Death Ligand 1 Therapy. J Clin Oncol. 2019 Oct 10;37(29): 2592-2600. doi: 10.1200/JCO.19.01140. Epub 2019 Jul 29. PubMed PMID: 31356140; PubMed Central PMCID: PMC6784850. Powles T, Rosenberg JE, Sonpavde GP, Loriot Y, Durán I, Lee JL, Matsubara N, Vulsteke C, Castellano D, Wu C, Campbell M, Matsangou M, Petrylak DP. Enfortumab Vedotin in Previously Treated Advanced Urothelial Carcinoma. N Engl J Med. 2021 Feb 12;:. doi: 10.1056/NEJMoa2035807. Epub 2021 Feb 12. PubMed PMID: 33577729.
BLINATUMOMAB	Viardot A, Hess G, Bargou RC, Morley NJ, Gritti G, Goebeler ME, Iskander K, Cohan D, Zhang A, Franklin J, Coyle L. Durability of complete response after blinatumomab therapy for relapsed/refractory diffuse large B-cell lymphoma. Leuk Lymphoma. 2020 Jul 07;:1-4. doi: 10.1080/10428194.2020.1783442. Epub 2020 Aug 07. PubMed PMID: 32633177. Locatelli F, Zugmaier G, Rizzari C, Morris JD, Gruhn B, Klingebiel T, Parasole R, Linderkamp C, Flotho C, Petit A, Micalizzi C, Mergen N, Mohammad A, Kormany WN, Eckert C, Möricke A, Sartor M, Hrusak O, Peters C, Saha V, Vinti L, von Stackelberg A. Effect of Blinatumomab vs Chemotherapy on Event-Free Survival Among Children With High-risk First-Relapse B-Cell Acute Lymphoblastic Leukemia: A Randomized Clinical Trial. JAMA. 2021 03 02;325(9): 843-854. doi: 10.1001/jama.2021.0987. PubMed PMID: 33651091. Brown PA, Ji L, Xu X, Devidas M, Hogan LE, Borowitz MJ, Raetz EA, Zugmaier G, Sharon E, Bernhardt MB, Terezakis SA, Gore L, Whitlock JA, Pulsipher MA, Hunger SP, Loh ML. Effect of Postreinduction Therapy Consolidation With Blinatumomab vs Chemotherapy on Disease-Free Survival in Children, Adolescents, and Young Adults With First Relapse of B-Cell Acute Lymphoblastic Leukemia: A Randomized Clinical Trial. JAMA. 2021 03 02;325(9):833-842. doi: 10.1001/jama.2021.0669. PubMed PMID: 33651090.
ZIV-AFLIBERCEPT	Van Cutsem E, Tabernero J, Lakomy R, Prenen H, Prausová J, Macarulla T, Ruff P, van Hazel GA, Moiseyenko V, Ferry D, McKendrick J, Polikoff J, Tellier A, Castan R, Allegra C. Addition of aflibercept to fluorouracil, leucovorin, and irinotecan improves survival in a phase III randomized trial in patients with metastatic colorectal cancer previously treated with an oxaliplatin-based regimen. J Clin Oncol. 2012 Oct 1;30(28):3499-506. Epub 2012 Sep 4. PubMed PMID: 22949147. Coleman RL, Duska LR, Ramirez PT, Heymach JV, Kamat AA, Modesitt SC, Schmeler KM, Iyer RB, Garcia ME, Miller DL, Jackson EF, Ng CS, Kundra V, Jaffe R, Sood AK. Phase 1-2 study of docetaxel plus aflibercept in patients with recurrent ovarian, primary peritoneal, or fallopian tube cancer. Lancet Oncol. 2011 Nov;12(12):1109-17. doi: 10.1016 /S1470-2045(11)70244-3. Epub 2011 Oct 10. PubMed PMID: 21992853; PubMed Central PMCID: PMC3444811.
CABAZITAXEL	Oudard S. TROPIC: Phase III trial of cabazitaxel for the treatment of metastatic castration-resistant prostate cancer. Future Oncol. 2011 Apr;7(4):497-506. doi: 10.2217/fon.11.23. PubMed PMID: 21463139. Bahl A, Oudard S, Tombal B, Ozgüroglu M, Hansen S, Kocak I, Gravis G, Devin J, Shen L, de Bono JS, Sartor AO; TROPIC Investigators.. Impact of cabazitaxel on 2-year survival and palliation of tumour-related pain in men with metastatic castration-resistant prostate cancer treated in the TROPIC trial. Ann Oncol. 2013 Sep;24(9):2402-8. doi: 10.1093/annonc/mdt194. PubMed PMID: 23723295; PubMed Central PMCID: PMC3755329. de Wit R, de Bono J, Sternberg CN, Fizazi K, Tombal B, Wülfing C, Kramer G, Eymard JC, Bamias A, Carles J, Iacovelli R, Melichar B, Sverrisdóttir Á, Theodore C, Feyerabend S, Helissey C, Ozatilgan A, Geffriaud-Ricouard C, Castellano D, . Cabazitaxel versus Abiraterone or Enzalutamide in Metastatic Prostate Cancer. N Engl J Med. 2019 12 26;381(26):2506-2518. doi: 10.1056/NEJMoa1911206. Epub 2019 Oct 30. PubMed PMID: 31566937.
RAMUCIRUMAB	Rouanne M, Loriot Y, Lebret T, Soria JC. Novel therapeutic targets in advanced urothelial carcinoma. Crit Rev Oncol Hematol. 2016 Feb;98:106-15. doi: 10.1016/j.critrevonc.2015.10.021. Epub 2015 Nov 9. Review. PubMed PMID: 26589398. Javle M, Smyth EC, Chau I. Ramucirumab: successfully targeting angiogenesis in gastric cancer. Clin Cancer Res. 2014 Dec 1;20(23):5875-81. doi: 10.1158/1078-0432.CCR-14-1071. Epub 2014 Oct 3. Review. PubMed PMID: 25281695; PubMed Central PMCID: PMC4252869. Tabernero J, Yoshino T, Cohn AL, Obermannova R, Bodoky G, Garcia-Carbonero R, Ciuleanu TE, Portnoy DC, Van Cutsem E, Grothey A, Prausová J, Garcia-Alfonso P, Yamazaki K, Clingan PR, Lonardi S, Kim TW, Simms L, Chang SC, Nasroulah F; RAISE Study Investigators. Ramucirumab versus placebo in combination with second-line FOLFIRI in patients with metastatic colorectal carcinoma that progressed during or after first-line therapy with bevacizumab, oxaliplatin, and a fluoropyrimidine (RAISE): a randomised, double-blind, multicentre, phase 3 study. Lancet Oncol. 2015 May;16(5):499-508. doi: 10.1016/S1470-2045(15)70127-0. Epub 2015 Apr 12. Erratum in: Lancet Oncol. 2015 Jun; 16(6):e262. PubMed PMID: 25877855.
CEDIRANIB	Ledermann JA, Embleton AC, Raja F, Perren TJ, Jayson GC, Rustin GJS, Kaye SB, Hirte H, Eisenhauer E, Vaughan M, Friedlander M, González-Martín A, Stark D, Clark E, Farrelly L, Swart AM, Cook A, Kaplan RS, Parmar MKB; ICON6 collaborators. Cediranib in patients with relapsed platinum-sensitive ovarian cancer (ICON6): a randomised, double-blind, placebo-controlled phase 3 trial. Lancet. 2016 Mar 12;387(10023):1066-1074. doi: 10.1016/S0140-6736(15) 01167-8. Erratum in: Lancet. 2016 Apr 23;387(10029):1722. PubMed PMID: 27025186.

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COMPOUND NAME	REFERENCES
OBINUTUZUMAB	Awasthi A, Ayello J, Van de Ven C, Elmacken M, Sabulski A, Barth MJ, Czuczman MS, Islam H, Klein C, Cairo MS. Obinutuzumab (GA101) compared to rituximab significantly enhances cell death and antibody-dependent cytotoxicity and improves overall survival against CD20(+) rituximab-sensitive/-resistant Burkitt lymphoma (BL) and precursor B-acute lymphoblastic leukaemia (pre-B-ALL): potential targeted therapy in patients with poor risk CD20 (+) BL and pre-B-ALL. Br J Haematol. 2015 Dec;171(5):763-75. doi: 10.1111/bjh.13764. Epub 2015 Oct 16. PubMed PMID: 26471982. Nadine Kutsch, Christian Pallasch, Thomas Decker, Holger Hebart, Kai Uwe Chow, Ullrich Graeven, Jens Kisro, Alexander Kroeber, Eugen Tausch, Clemens-Martin Wendtner, Michael J. Eckart, Stephan Stilgenbauer, Xi Huang, Juliane M. Jürgensmeier, Pankaj Bhargava, Michael Hallek, Barbara F. Eichhorst; A Prospective, Open-Label, Multicenter, Phase 2 Trial to Evaluate the Safety and Efficacy of the Combination of Tirabrutinib (ONO/GS-4059) and Idelalisib with and without Obinutuzumab in Patients with Relapsed/Refractory Chronic Lymphocytic Leukemia (CLL). Blood 2019; 134 (Supplement_1): 3047. doi: https://doi.org/10.1182/blood-2019-131025 Marcus R, Davies A, Ando K, Klapper W, Opat S, Owen C, Phillips E, Sangha R, Schlag R, Seymour JF, Townsend W, Trněný M, Wenger M, Fingerle-Rowson G, Rufibach K, Moore T, Herold M, Hiddemann W. Obinutuzumab for the First-Line Treatment of Follicular Lymphoma. N Engl J Med. 2017 Oct 5;377(14):1331-1344. doi: 10.1056 /NEJMoa1614598. PubMed PMID: 28976863.
BORTEZOMIB	Durie BGM, Hoering A, Sexton R, Abidi MH, Epstein J, Rajkumar SV, Dispenzieri A, Kahanic SP, Thakuri MC, Reu FJ, Reynolds CM, Orlowski RZ, Barlogie B. Longer term follow-up of the randomized phase III trial SWOG S0777: bortezomib, lenalidomide and dexamethasone vs. lenalidomide and dexamethasone in patients (Pts) with previously untreated multiple myeloma without an intent for immediate autologous stem cell transplant (ASCT). Blood Cancer J. 2020 May 11;10(5):53. doi: 10.1038/s41408-020-0311-8. Epub 2020 Aug 11. PubMed PMID: 32393732; PubMed Central PMCID: PMC7214419. Putzer D, Gabriel M, Kroiss A, Madleitner R, Eisterer W, Kendler D, Uprimny C, Bale RJ, Gastl G, Virgolini IJ. First experience with proteasome inhibitor treatment of radioiodine nonavid thyroid cancer using bortezomib. Clin Nucl Med. 2012 Jun;37(6):539-44. doi: 10.1097/RLU.0b013e31824c5f24. PubMed PMID: 22614183. Robak T, Huang H, Jin J, Zhu J, Liu T, Samoilova O, Pylypenko H, Verhoef G, Siritanaratkul N, Osmanov E, Alexeeva J, Pereira J, Drach J, Mayer J, Hong X, Okamoto R, Pei L, Rooney B, van de Velde H, Cavalli F; LYM-3002 Investigators. Bortezomib-based therapy for newly diagnosed mantle-cell lymphoma. N Engl J Med. 2015 Mar 5;372 (10):944-53. doi: 10.1056/NEJMoa1412096. PubMed PMID: 25738670.
DARATUMUMAB	Dimopoulos MA et al., Apollo: phase 3 randomized study of subcutaneous daratumumab plus pomalidomide and dexamethasone (D-Pd) versus pomalidomide and dexamethasone (Pd) alone in patients (pts) with relapsed /refractory multiple myeloma (RRMM). 62nd (ASH) Annual Meeting and Exposition. 2020. Session: 653. Abstract: 412. Paper: 135874. Voorhees PM, Kaufman JL, Laubach J, Sborov DW, Reeves B, Rodriguez C, Chari A, Silbermann R, Costa LJ, Anderson LD, Nathwani N, Shah N, Efebera YA, Holstein SA, Costello C, Jakubowiak A, Wildes TM, Orlowski RZ, Shain KH, Cowan AJ, Murphy S, Lutska Y, Pei H, Ukropec J, Vermeulen J, de Boer C, Hoehn D, Lin TS, Richardson PG. Daratumumab, lenalidomide, bortezomib, and dexamethasone for transplant-eligible newly diagnosed multiple myeloma: the GRIFFIN trial. Blood. 2020 08 20;136(8):936-945. doi: 10.1182/blood.2020005288. PubMed PMID: 32325490; PubMed Central PMCID: PMC7441167. Moreau P, Attal M, Hulin C, Arnulf B, Belhadj K, Benboubker L, Béné MC, Broijl A, Caillon H, Caillot D, Corre J, Delforge M, Dejoie T, Doyen C, Facon T, Sonntag C, Fontan J, Garderet L, Jie KS, Karlin L, Kuhnowski F, Lambert J, Leleu X, Lenain P, Macro M, Mathiot C, Orsini-Piocelle F, Perrot A, Stoppa AM, van de Donk NW, Wuilleme S, Zweegman S, Kolb B, Touzeau C, Roussel M, Tiab M, Marolleau JP, Meuleman N, Vekemans MC, Westerman M, Klein SK, Levin MD, Fermand JP, Escoffre-Barbe M, Eveillard JR, Garidi R, Ahmadi T, Zhuang S, Chiu C, Pei L, de Boer C, Smith E, Deraedt W, Kampfenkel T, Schecter J, Vermeulen J, Avet-Loiseau H, Sonneveld P. Bortezomib, thalidomide, and dexamethasone with or without daratumumab before and after autologous stem-cell transplantation for newly diagnosed multiple myeloma (CASSIOPEIA): a randomised, open-label, phase 3 study. Lancet. 2019 07 06;394(10192):29-38. doi: 10.1016/S0140-6736(19)31240-1. Epub 2019 Apr 03. PubMed PMID: 31171419.
RITUXIMAB	Véronique V, Anne A, Marta M, G A Amos GAA, Donald A DA, Keith K, Rafael F RF, Sarah S, Anne A, Catherine M CM, József J, Monika M, Bernarda B, Alan K AK, Rodney R RR, Andrew A, Peter C PC, Gilles G, Catherine C, Thomas G TG, . Rituximab for High-Risk, Mature B-Cell Non-Hodgkin's Lymphoma in Children. N Engl J Med. 2020 06 04; 382(23):2207-2219. doi: 10.1056/NEJMoa1915315. PubMed PMID: 32492302
DINUTUXIMAB	Ploessl C, Pan A, Maples KT, Lowe DK. Dinutuximab: An Anti-GD2 Monoclonal Antibody for High-Risk Neuroblastoma. Ann Pharmacother. 2016 May;50(5):416-22. doi: 10.1177/1060028016632013. Epub 2016 Feb 25. Review. PubMed PMID: 26917818. Yu AL, Gilman AL, Ozkaynak MF, London WB, Kreissman SG, Chen HX, Smith M, Anderson B, Villablanca JG, Matthay KK, Shimada H, Grupp SA, Seeger R, Reynolds CP, Buxton A, Reisfeld RA, Gillies SD, Cohn SL, Maris JM, Sondel PM; Children's Oncology Group. Anti-GD2 antibody with GM-CSF, interleukin-2, and isotretinoin for neuroblastoma. N Engl J Med. 2010 Sep 30;363(14):1324-34. doi: 10.1056/NEJMoa0911123. PubMed PMID: 20879881; PubMed Central PMCID: PMC3086629.
NAB-PACLITAXEL	Von Hoff DD, Ervin T, Arena FP, Chiorean EG, Infante J, Moore M, Seay T, Tjulandin SA, Ma WW, Saleh MN, Harris M, Reni M, Dowden S, Laheru D, Bahary N, Ramanathan RK, Tabernero J, Hidalgo M, Goldstein D, Van Cutsem E, Wei X, Iglesias J, Renschler MF. Increased survival in pancreatic cancer with nab-paclitaxel plus gemcitabine. N Engl J Med. 2013 Oct 31;369(18):1691-703. doi: 10.1056/NEJMoa1304369. Epub 2013 Oct 16. PubMed PMID: 24131140; PubMed Central PMCID: PMC4631139.

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COMPOUND NAME	REFERENCES
FOLFIRINOX	Conroy T, Desseigne F, Ychou M, Bouché O, Guimbaud R, Bécouarn Y, Adenis A, Raoul JL, Gourgou-Bourgade S, de la Fouchardière C, Bennouna J, Bachet JB, Khemissa-Akouz F, Péré-Vergé D, Delbaldo C, Assenat E, Chauffert B, Michel P, Montoto-Grillot C, Ducreux M; Groupe Tumeurs Digestives of Unicancer; PRODIGE Intergroup. FOLFIRINOX versus gemcitabine for metastatic pancreatic cancer. N Engl J Med. 2011 May 12;364(19):1817-25. doi: 10.1056/NEJMoa1011923. PubMed PMID: 21561347.
SELINEXOR	Grosicki S, Simonova M, Spicka I, Pour L, Kriachok I, Gavriatopoulou M, Pylypenko H, Auner HW, Leleu X, Doronin V, Usenko G, Bahlis NJ, Hajek R, Benjamin R, Dolai TK, Sinha DK, Venner CP, Garg M, Gironella M, Jurczyszyn A, Robak P, Galli M, Wallington-Beddoe C, Radinoff A, Salogub G, Stevens DA, Basu S, Liberati AM, Quach H, Goranova-Marinova VS, Bila J, Katodritou E, Oliynyk H, Korenkova S, Kumar J, Jagannath S, Moreau P, Levy M, White D, Gatt ME, Facon T, Mateos MV, Cavo M, Reece D, Anderson LD, Saint-Martin JR, Jeha J, Joshi AA, Chai Y, Li L, Peddagali V, Arazy M, Shah J, Shacham S, Kauffman MG, Dimopoulos MA, Richardson PG, Delimpasi S. Once-per-week selinexor, bortezomib, and dexamethasone versus twice-per-week bortezomib and dexamethasone in patients with multiple myeloma (BOSTON): a randomised, open-label, phase 3 trial. Lancet. 2020 Nov 14;396 (10262):1563-1573. doi: 10.1016/S0140-6736(20)32292-3. PubMed PMID: 33189178.
RIPRETINIB	Janku F, Abdul Razak AR, Chi P, Heinrich MC, von Mehren M, Jones RL, Ganjoo K, Trent J, Gelderblom H, Somaiah N, Hu S, Rosen O, Su Y, Ruiz-Soto R, Gordon M, George S. Switch Control Inhibition of KIT and PDGFRA in Patients With Advanced Gastrointestinal Stromal Tumor: A Phase I Study of Ripretinib. J Clin Oncol. 2020 Oct 01;38(28): 3294-3303. doi: 10.1200/JCO.20.00522. Epub 2020 Feb 17. PubMed PMID: 32804590; PubMed Central PMCID: PMC7526717. Blay JY, Serrano C, Heinrich MC, Zalcberg J, Bauer S, Gelderblom H, Schöffski P, Jones RL, Attia S, D'Amato G, Chi P, Reichardt P, Meade J, Shi K, Ruiz-Soto R, George S, von Mehren M. Ripretinib in patients with advanced gastrointestinal stromal tumours (INVICTUS): a double-blind, randomised, placebo-controlled, phase 3 trial. Lancet Oncol. 2020 Jun 05;:. doi: 10.1016/S1470-2045(20)30168-6. Epub 2020 Jun 05. PubMed PMID: 32511981.
TREBANANIB	Marth C, Vergote I, Scambia G, Oberaigner W, Clamp A, Berger R, Kurzeder C, Colombo N, Vuylsteke P, Lorusso D, Hall M, Renard V, Pignata S, Kristeleit R, Altintas S, Rustin G, Wenham RM, Mirza MR, Fong PC, Oza A, Monk BJ, Ma H, Vogl FD, Bach BA. ENGOT-ov-6/TRINOVA-2: Randomised, double-blind, phase 3 study of pegylated liposomal doxorubicin plus trebananib or placebo in women with recurrent partially platinum-sensitive or resistant ovarian cancer. Eur J Cancer. 2017 Jan;70:111-121. doi: 10.1016/j.ejca.2016.09.004. Epub 2016 Dec 1. PubMed PMID: 27914241. Monk BJ, Poveda A, Vergote I, Raspagliesi F, Fujiwara K, Bae DS, Oaknin A, Ray-Coquard I, Provencher DM, Karlan BY, Lhommé C, Richardson G, Rincón DG, Coleman RL, Herzog TJ, Marth C, Brize A, Fabbro M, Redondo A, Bamias A, Tassoudji M, Navale L, Warner DJ, Oza AM. Anti-angiopoietin therapy with trebananib for recurrent ovarian cancer (TRINOVA-1): a randomised, multicentre, double-blind, placebo-controlled phase 3 trial. Lancet Oncol. 2014 Jul;15(8):799-808. doi: 10.1016/S1470-2045(14)70244-X. Epub 2014 Jun 17. PubMed PMID: 24950985.
DENOSUMAB	Fizazi K, Carducci M, Smith M, Damião R, Brown J, Karsh L, Milecki P, Shore N, Rader M, Wang H, Jiang Q, Tadros S, Dansey R, Goessl C. Denosumab versus zoledronic acid for treatment of bone metastases in men with castration-resistant prostate cancer: a randomised, double-blind study. Lancet. 2011 Mar 5;377(9768):813-22. doi: 10.1016 /S0140-6736(10)62344-6. Epub 2011 Feb 25. PubMed PMID: 21353695; PubMed Central PMCID: PMC3090685.
RUCAPARIB	Coleman RL, Oza AM, Lorusso D, Aghajanian C, Oaknin A, Dean A, Colombo N, Weberpals JI, Clamp A, Scambia G, Leary A, Holloway RW, Gancedo MA, Fong PC, Goh JC, O'Malley DM, Armstrong DK, Garcia-Donas J, Swisher EM, Floquet A, Konecny GE, McNeish IA, Scott CL, Cameron T, Maloney L, Isaacson J, Goble S, Grace C, Harding TC, Raponi M, Sun J, Lin KK, Giordano H, Ledermann JA; ARIEL3 investigators. Rucaparib maintenance treatment for recurrent ovarian carcinoma after response to platinum therapy (ARIEL3): a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet. 2017 Oct 28;390(10106):1949-1961. doi: 10.1016/S0140-6736(17)32440-6. Epub 2017 Sep 12. Erratum in: Lancet. 2017 Oct 28;390(10106):1948. PubMed PMID: 28916367; PubMed Central PMCID: PMC5901715.
BELANTAMAB MAFODOTIN	Lonial S, Lee HC, Badros A, Trudel S, Nooka AK, Chari A, Abdallah AO, Callander N, Lendvai N, Sborov D, Suvannasankha A, Weisel K, Karlin L, Libby E, Arnulf B, Facon T, Hulin C, Kortüm KM, Rodríguez-Otero P, Usmani SZ, Hari P, Baz R, Quach H, Moreau P, Voorhees PM, Gupta I, Hoos A, Zhi E, Baron J, Piontek T, Lewis E, Jewell RC, Dettman EJ, Popat R, Esposti SD, Opalinska J, Richardson P, Cohen AD. Belantamab mafodotin for relapsed or refractory multiple myeloma (DREAMM-2): a two-arm, randomised, open-label, phase 2 study. Lancet Oncol. 2020 Feb;21(2):207-221. doi: 10.1016/S1470-2045(19)30788-0. Epub 2019 Dec 16. PubMed PMID: 31859245.
ORTERONEL	Saad F, Fizazi K, Jinga V, Efstathiou E, Fong PC, Hart LL, Jones R, McDermott R, Wirth M, Suzuki K, MacLean DB, Wang L, Akaza H, Nelson J, Scher HI, Dreicer R, Webb IJ, de Wit R; ELM-PC 4 investigators.. Orteronel plus prednisone in patients with chemotherapy-naive metastatic castration-resistant prostate cancer (ELM-PC 4): a double-blind, multicentre, phase 3, randomised, placebo-controlled trial. Lancet Oncol. 2015 Mar;16(3):338-48. doi: 10.1016/S1470-2045(15)70027-6. PubMed PMID: 25701170.
TISOTUMAB VEDOTIN	Coleman RL, Lorusso D, Gennigens C, González-Martín A, Randall L, Cibula D, Lund B, Woelber L, Pignata S, Forget F, Redondo A, Vindeløv SD, Chen M, Harris JR, Smith M, Nicacio LV, Teng MSL, Laenen A, Rangwala R, Manso L, Mirza M, Monk BJ, Vergote I, . Efficacy and safety of tisotumab vedotin in previously treated recurrent or metastatic cervical cancer (innovaTV 204/GOG-3023/ENGOT-cx6): a multicentre, open-label, single-arm, phase 2 study. Lancet Oncol. 2021 Apr 09;:. doi: 10.1016/S1470-2045(21)00056-5. Epub 2021 April 09. PubMed PMID: 33845034.
TALIMOGENE LAHERPAREPVEC	Chesney J, Puzanov I, Collichio F, Singh P, Milhem MM, Glaspy J, Hamid O, Ross M, Friedlander P, Garbe C, Logan TF, Hauschild A, Lebbé C, Chen L, Kim JJ, Gansert J, Andtbacka RHI, Kaufman HL. Randomized, Open-Label Phase II Study Evaluating the Efficacy and Safety of Talimogene Laherparepvec in Combination With Ipilimumab Versus Ipilimumab Alone in Patients With Advanced, Unresectable Melanoma. J Clin Oncol. 2018 06 10;36(17):1658-1667. doi: 10.1200/JCO.2017.73.7379. Epub 2017 Aug 05. PubMed PMID: 28981385; PubMed Central PMCID: PMC6075852.
BELINOSTAT	O'Connor OA, Horwitz S, Masszi T, Van Hoof A, Brown P, Doorduijn J, Hess G, Jurczak W, Knoblauch P, Chawla S, Bhat G, Choi MR, Walewski J, Savage K, Foss F, Allen LF, Shustov A. Belinostat in Patients With Relapsed or Refractory Peripheral T-Cell Lymphoma: Results of the Pivotal Phase II BELIEF (CLN-19) Study. J Clin Oncol. 2015 Aug 10;33(23):2492-9. doi: 10.1200/JCO.2014.59.2782. Epub 2015 Oct 22. PubMed PMID: 26101246; PubMed Central PMCID: PMC5087312.

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COMPOUND NAME	REFERENCES
LENALIDOMIDE	Nowakowski GS, Hong F, Scott DW, Macon WR, King RL, Habermann TM, Wagner-Johnston N, Casulo C, Wade JL, Nagargoje GG, Reynolds CM, Cohen JB, Khan N, Amengual JE, Richards KL, Little RF, Leonard JP, Friedberg JW, Kostakoglu L, Kahl BS, Witzig TE. Addition of Lenalidomide to R-CHOP Improves Outcomes in Newly Diagnosed Diffuse Large B-Cell Lymphoma in a Randomized Phase II US Intergroup Study ECOG-ACRIN E1412. J Clin Oncol. 2021 Feb 08;:JCO2001375. doi: 10.1200/JCO.20.01375. Epub 2021 Feb 08. PubMed PMID: 33555941.
GLASDEGIB	Michael Heuser, Tadeusz Robak, Pau Montesinos, Brian Leber, Walter M. Fiedler, Daniel Aaron Pollyea, Andrew Brown, Ashleigh O'Connell, Wendy Ma, Geoffrey Chan, Jorge E. Cortes. Glasdegib (GLAS) plus low-dose cytarabine (LDAC) in AML or MDS: BRIGHT AML 1003 final report and four-year overall survival (OS) follow-up. Journal of Clinical Oncology 2020 38:15_suppl, 7509-7509. doi: 10.1200/JCO.2020.38.15_suppl.7509 Cortes JE, Heidel FH, Hellmann A, Fiedler W, Smith BD, Robak T, Montesinos P, Pollyea DA, DesJardins P, Ottmann O, Ma WW, Shaik MN, Laird AD, Zeremski M, O'Connell A, Chan G, Heuser M. Randomized comparison of low dose cytarabine with or without glasdegib in patients with newly diagnosed acute myeloid leukemia or high-risk myelodysplastic syndrome. Leukemia. 2019 02;33(2):379-389. doi: 10.1038/s41375-018-0312-9. Epub 2018 Aug 16. PubMed PMID: 30555165; PubMed Central PMCID: PMC6365492.
IXAZOMIB	Meletios A. Dimopoulos, Ivan Spicka, Hang Quach, Albert Oriol, Roman Hajek, Mamta Garg, Meral Beksac, Sara Bringhen, Eirini Katodritou, Wee Joo Chng, Xavier Leleu, Shinsuke Iida, Maria-Victoria Mateos, Gareth Morgan, Alexander Vorog, Richard Labotka, Bingxia Wang, Antonio Palumbo, Sagar Lonial;. Ixazomib vs placebo maintenance for newly diagnosed multiple myeloma (NDMM) patients not undergoing autologous stem cell transplant (ASCT): The phase III TOURMALINE-MM4 trial. J Clin Oncol 38: 2020 (suppl; abstr 8527). doi: 10.1200 /JCO.2020.38.15_suppl.8527. Kumar SK, Berdeja JG, Niesvizky R, Lonial S, Laubach JP, Hamadani M, Stewart AK, Hari P, Roy V, Vescio R, Kaufman JL, Berg D, Liao E, Rajkumar SV, Richardson PG. Ixazomib, lenalidomide, and dexamethasone in patients with newly diagnosed multiple myeloma: long-term follow-up including ixazomib maintenance. Leukemia. 2019 Jul; 33(7):1736-1746. doi: 10.1038/s41375-019-0384-1. Epub 2019 Jan 29. PubMed PMID: 30696949; PubMed Central PMCID: PMC6755968.
ACALABRUTINIB	Byrd JC, Wierda WG, Schuh A, Devereux S, Chaves JM, Brown JR, Hillmen P, Martin P, Awan FT, Stephens DM, Ghia P, Barrientos J, Pagel JM, Woyach JA, Burke K, Covey T, Gulrajani M, Hamdy A, Izumi R, Frigault MM, Patel P, Rothbaum W, Wang MH, O'Brien S, Furman RR. Acalabrutinib monotherapy in patients with relapsed/refractory chronic lymphocytic leukemia: updated phase 2 results. Blood. 2020 04 09;135(15):1204-1213. doi: 10.1182/blood. 2018884940. PubMed PMID: 31876911; PubMed Central PMCID: PMC7146022.
BRENTUXIMAB VEDOTIN	Straus DJ, Długosz-Danecka M, Alekseev S, Illés Á, Picardi M, Lech-Maranda E, Feldman T, Smolewski P, Savage KJ, Bartlett NL, Walewski J, Ramchandren R, Zinzani PL, Hutchings M, Connors JM, Radford J, Munoz J, Kim WS, Advani R, Ansell SM, Younes A, Miao H, Liu R, Fenton K, Forero-Torres A, Gallamini A. Brentuximab vedotin with chemotherapy for stage III/IV classical Hodgkin lymphoma: 3-year update of the ECHELON-1 study. Blood. 2020 03 05;135(10):735-742. doi: 10.1182/blood.2019003127. PubMed PMID: 31945149.
TAMOXIFEN	Lee WL, Yen MS, Chao KC, Yuan CC, Ng HT, Chao HT, Lee FK, Wang PH. Hormone therapy for patients with advanced or recurrent endometrial cancer. J Chin Med Assoc. 2014 May;77(5):221-6. doi: 10.1016/j.jcma. 2014.02.007. Epub 2014 Mar 30. Review. PubMed PMID: 24694672. Tropé C, Marth C, Kaern J. Tamoxifen in the treatment of recurrent ovarian carcinoma. Eur J Cancer. 2000 Sep;36 Suppl 4:S59-61. PubMed PMID: 11056321.
NICLOSAMIDE	Osada T, Chen M, Yang XY, Spasojevic I, Vandeusen JB, Hsu D, Clary BM, Clay TM, Chen W, Morse MA, Lyerly HK. Antihelminth compound niclosamide downregulates Wnt signaling and elicits antitumor responses in tumors with activating APC mutations. Cancer Res. 2011 Jun 15;71(12):4172-82. doi: 10.1158/0008-5472.CAN-10-3978. Epub 2011 Apr 29. PubMed PMID: 21531761; PubMed Central PMCID: PMC3117125.
IPILIMUMAB	Quinn DI, Shore ND, Egawa S, Gerritsen WR, Fizazi K. Immunotherapy for castration-resistant prostate cancer: Progress and new paradigms. Urol Oncol. 2015 May;33(5):245-60. doi: 10.1016/j.urolonc.2014.10.009. Epub 2015 Jan 7. Review. PubMed PMID: 25575714. Madan RA, Gulley JL, Kantoff PW. Demystifying immunotherapy in prostate cancer: understanding current and future treatment strategies. Cancer J. 2013 Jan-Feb;19(1):50-8. doi: 10.1097/PPO.0b013e31828160a9. PubMed PMID: 23337757; PubMed Central PMCID: PMC3556901.
silmitasertib	Nitta, R. T., Bolin, S., Luo, E., Solow-Codero, D. E., Samghabadi, P., Purzner, T., ... & Li, G. (2019). Casein kinase 2 inhibition sensitizes medulloblastoma to temozolomide. Oncogene, 1-13. Purzner T, Purzner J, Buckstaff T, Cozza G, Gholamin S, Rusert JM, Hartl TA, Sanders J, Conley N, Ge X, Langan M, Ramaswamy V, Ellis L, Litzenburger U, Bolin S, Theruvath J, Nitta R, Qi L, Li XN, Li G, Taylor MD, Wechsler-Reya RJ, Pinna LA, Cho YJ, Fuller MT, Elias JE, Scott MP. Developmental phosphoproteomics identifies the kinase CK2 as a driver of Hedgehog signaling and a therapeutic target in medulloblastoma. Sci Signal. 2018 Sep 11;11(547). pii: eaau5147. doi: 10.1126/scisignal.aau5147. PubMed PMID: 30206138; PubMed Central PMCID: PMC6475502.
AICAR	Bost F, Decoux-Poullot AG, Tanti JF, Clavel S. Energy disruptors: rising stars in anticancer therapy? Oncogenesis. 2016 Jan 18;5:e188. doi: 10.1038/oncsis.2015.46. Review. PubMed PMID: 26779810; PubMed Central PMCID: PMC4728676.
ELTANEXOR	Eltanexor (KPT-8602), a Second-Generation Selective Inhibitor of Nuclear Export (SINE) Compound, in Patients with Higher-Risk Myelodysplastic Syndrome. Sangmin Lee, MD, Bhavana Bhatnagar, DO, Sanjay R Mohan, MD MSCI, William T. Senapedis, Jr., Erkan Baloglu, PhD, Hongwei Wang, MD, Jatin J. Shah, MD, Sharon Shacham, PhD MBA, Michael G. Kauffman, MD PhD. Blood (2019) 134 (Supplement_1): 2997. doi: 10.1182/blood-2019-124136
DINUTUXIMAB BETA	LADENSTEIN, Ruth Lydia, et al. Immunotherapy with anti-GD2 antibody ch14. 18/CHO±IL2 within the HR-NBL1 /SIOPEN trial to improve outcome of high-risk neuroblastoma patients compared to historical controls. 2018.

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COMPOUND NAME	REFERENCES
PERIFOSINE	Kushner BH, Cheung NV, Modak S, Becher OJ, Basu EM, Roberts SS, Kramer K, Dunkel IJ. A phase I/Ib trial targeting the Pi3k/Akt pathway using perifosine: Long-term progression-free survival of patients with resistant neuroblastoma. Int J Cancer. 2017 Jan 15;140(2):480-484. doi: 10.1002/ijc.30440. Epub 2016 Jun 30. PubMed PMID: 27649927; PubMed Central PMCID: PMC5118186.
LETROZOLE	Yazigi R, Rodríguez T, Buckel E, Wash A. Ovarian granulosa cell tumour and letrozole: A case report. J Obstet Gynaecol. 2016;36(1):122-3. doi: 10.3109/01443615.2015.1036411. Epub 2015 Oct 2. PubMed PMID: 26431345. Schwartz M, Huang GS. Retreatment with aromatase inhibitor therapy in the management of granulosa cell tumor. Gynecol Oncol Rep. 2015 Dec 28;15:20-1. doi: 10.1016/j.gore.2015.12.004. eCollection 2016 Jan. PubMed PMID: 26937482; PubMed Central PMCID: PMC4750011. van Meurs HS, van der Velden J, Buist MR, van Driel WJ, Kenter GG, van Lonkhuijzen LR. Evaluation of response to hormone therapy in patients with measurable adult granulosa cell tumors of the ovary. Acta Obstet Gynecol Scand. 2015 Nov;94(11):1269-75. doi: 10.1111/aogs.12720. Epub 2015 Sep 15. PubMed PMID: 26230362.
RIGOSERTIB	Shyamala C SC, Steven M SM, Rosalie R, Erin P EP, Michael E ME, Patrick S PS, James F JF, Lewis R LR. A phase 1/2 study of rigosertib in patients with myelodysplastic syndromes (MDS) and MDS progressed to acute myeloid leukemia. Leuk Res. 2018 01;64:10-16. pii: S0145-2126(17)30584-2. Epub 2017 Jun 11. PubMed PMID: 29144985
NUTLIN-3A	Bill KL, Garnett J, Meaux I, Ma X, Creighton CJ, Bolshakov S, Barriere C, Debussche L, Lazar AJ, Prudner BC, Casadei L, Braggio D, Lopez G, Zewdu A, Bid H, Lev D, Pollock RE. SAR405838: A Novel and Potent Inhibitor of the MDM2:p53 Axis for the Treatment of Dedifferentiated Liposarcoma. Clin Cancer Res. 2016 Mar 1;22(5):1150-60. doi: 10.1158/1078-0432.CCR-15-1522. Epub 2015 Oct 16. PubMed PMID: 26475335; PubMed Central PMCID: PMC4775372.
FUZULOPARIB	Li N, Zhang Y, Wang J, et al. Fuzuloparib maintenance therapy in patients with platinum-sensitive, relapsed ovarian cancer: A multicenter, randomized, double-blind, placebo-controlled, phase III trial. Presented at: 2021 Society of Gynecologic Oncology Virtual Annual Meeting on Womens Cancer. Abstract 11557.
FLUVASTATIN	Li Y, He X, Ding Y, Chen H, Sun L. Statin uses and mortality in colorectal cancer patients: An updated systematic review and meta-analysis. Cancer Med. 2019 Jun;8(6):3305-3313. doi: 10.1002/cam4.2151. Epub 2019 May 8. PubMed PMID: 31069997; PubMed Central PMCID: PMC6558478.
ATORVASTATIN	Li Y, He X, Ding Y, Chen H, Sun L. Statin uses and mortality in colorectal cancer patients: An updated systematic review and meta-analysis. Cancer Med. 2019 Jun;8(6):3305-3313. doi: 10.1002/cam4.2151. Epub 2019 May 8. PubMed PMID: 31069997; PubMed Central PMCID: PMC6558478.
OCTREOTIDE	Li Y, He X, Ding Y, Chen H, Sun L. Statin uses and mortality in colorectal cancer patients: An updated systematic review and meta-analysis. Cancer Med. 2019 Jun;8(6):3305-3313. doi: 10.1002/cam4.2151. Epub 2019 May 8. PubMed PMID: 31069997; PubMed Central PMCID: PMC6558478.
PENTOSTATIN	Li Y, He X, Ding Y, Chen H, Sun L. Statin uses and mortality in colorectal cancer patients: An updated systematic review and meta-analysis. Cancer Med. 2019 Jun;8(6):3305-3313. doi: 10.1002/cam4.2151. Epub 2019 May 8. PubMed PMID: 31069997; PubMed Central PMCID: PMC6558478.
RILUZOLE	Dolfi SC, Medina DJ, Kareddula A, Paratala B, Rose A, Dhami J, Chen S, Ganesan S, Mackay G, Vazquez A, Hirshfield KM. Riluzole exerts distinct antitumor effects from a metabotropic glutamate receptor 1-specific inhibitor on breast cancer cells. Oncotarget. 2017 Jul 4;8(27):44639-44653. doi: 10.18632/oncotarget.17961. PubMed PMID: 28591718; PubMed Central PMCID: PMC5546507.
Metarrestin	Kanis MJ, Qiang W, Pineda M, Maniar KP, Kim JJ. A small molecule inhibitor of the perinucleolar compartment, ML246, attenuates growth and spread of ovarian cancer. Gynecol Oncol Res Pract. 2018;5:7. doi: 10.1186/s40661-018-0064-2. Epub 2018 Jul 02. PubMed PMID: 30305911; PubMed Central PMCID: PMC6167785.
MEDI-573	Zhong H, Fazenbaker C, Breen S, Chen C, Huang J, Morehouse C, Yao Y, Hollingsworth RE. MEDI-573, alone or in combination with mammalian target of rapamycin inhibitors, targets the insulin-like growth factor pathway in sarcomas. Mol Cancer Ther. 2014 Nov;13(11):2662-73. doi: 10.1158/1535-7163.MCT-14-0144. Epub 2014 Sep 5. Erratum in: Mol Cancer Ther. 2015 Mar;14(3):844. PubMed PMID: 25193511.
ARV-110	Taavi Neklesa, Lawrence B Snyder, Ryan R Willard, Nicholas Vitale, Jennifer Pizzano, Deborah A Gordon, Mark Bookbinder, Jennifer Macaluso, Hanqing Dong, Caterina Ferraro, Gan Wang, Jing Wang, Craig M Crews, John Houston, Andrew P Crew, and Ian Taylor. ARV-110: An oral androgen receptor PROTAC degrader for prostate cancer. Journal of Clinical Oncology 37, no. 7_suppl (March 01, 2019) 259-259. doi: 10.1200/JCO.2019.37.7_suppl.259
NAXITAMAB	Jaume Mora, Godfrey Chi-Fung Chan, Daniel A. Morgenstern, Karsten Nysom, Melissa K Bear, Lene Worsaae Dalby, Steen Lisby, Brian H. Kushner; Pediatric Cancer Center Barcelona, Hospital Sant Joan de Déu, Barcelona, Spain; Queen Mary Hospital, University of Hong Kong, Pokfulam, China; Hospital for Sick Children, Toronto, ON, Canada; Rigshospitalet, Copenhagen, Denmark; Riley Hospital for Children, Indianapolis, IN; Y-mAbs Therapeutics A/S, Hoersholm, Denmark; Memorial Sloan Kettering Cancer Center, New York, NY. Naxitamab, a new generation anti-GD2 monoclonal antibody (mAb) for treatment of relapsed/refractory high-risk neuroblastoma (HR-NB). J Clin Oncol 38: 2020 (suppl; abstr 10543). doi: 10.1200/JCO.2020.38.15_suppl.10543.
HER2-BBz-CAR T cells	Nellan, Anandani, Christopher Rota, Robbie Majzner, Cynthia M. Lester-McCully, Andrea M. Griesinger, Jean M. Mulcahy Levy, Nicholas K. Foreman, Katherine E. Warren, and Daniel W. Lee. "Durable regression of Medulloblastoma after regional and intravenous delivery of anti-HER2 chimeric antigen receptor T cells." Journal for immunotherapy of cancer 6, no. 1 (2018): 30.
CILTACABTAGENE AUTOLEUCEL	Fan F (Xiaohu), Zhao W, Liu J, He A, Chen Y, Cao X, et al. Durable remissions with BCMA-specific chimeric antigen receptor (CAR)-modified T cells in patients with refractory/relapsed multiple myeloma. JCO. 2017 Jun 13;35 (18_suppl):LBA3001-LBA3001.
TRILACICLIB	O'Shaughnessy J et al., PD1-06. Trilaciclib improves overall survival when given with gemcitabine/carboplatin in patients with metastatic triple-negative breast cancer: Final analysis of a randomized phase 2 trial. 2020 San Antonio Breast Cancer Symposium. Abstract PD1-06.

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COMPOUND NAME	REFERENCES
TRABECTEDIN	Preusser M, Spiegl-Kreinecker S, Lötsch D, Wöhrer A, Schmook M, Dieckmann K, Saringer W, Marosi C, Berger W. Trabectedin has promising antineoplastic activity in high-grade meningioma. Cancer. 2012 Oct 15;118(20):5038-49. doi: 10.1002/cncr.27460. Epub 2012 Dec 05. PubMed PMID: 22392434.
DAROLUTAMIDE	Aragon-Ching JB. Darolutamide: a novel androgen-signaling agent in nonmetastatic castration-resistant prostate cancer. Asian J Androl. 2020 Jan-Feb;22(1):76-78. doi: 10.4103/aja.aja_52_19. PubMed PMID: 31249268; PubMed Central PMCID: PMC6958984.
ZOLEDRONIC ACID	Conry RM, Rodriguez MG, Pressey JG. Zoledronic acid in metastatic osteosarcoma: encouraging progression free survival in four consecutive patients. Clin Sarcoma Res. 2016 Apr 28;6:6. doi: 10.1186/s13569-016-0046-2. eCollection 2016. PubMed PMID: 27127605; PubMed Central PMCID: PMC4848872.
CD30 CAR T-cells	Hong LK, Chen Y, Smith CC, Montgomery SA, Vincent BG, Dotti G, Savoldo B. CD30-Redirected Chimeric Antigen Receptor T Cells Target CD30+ and CD30- Embryonal Carcinoma via Antigen-Dependent and Fas/FasL Interactions. Cancer Immunol Res. 2018 10;6(10):1274-1287. doi: 10.1158/2326-6066.CIR-18-0065. Epub 2018 Aug 07. PubMed PMID: 30087115.
FOLFOX	Jin CH, Wang AH, Chen JM, Li RX, Liu XM, Wang GP, Xing LQ. Observation of curative efficacy and prognosis following combination chemotherapy with celecoxib in the treatment of advanced colorectal cancer. J Int Med Res. 2011;39(6):2129-40. PubMed PMID: 22289528.
PROPRANOLOL	Pasquier E, André N, Street J, Chougule A, Rekhi B, Ghosh J, Philip DSJ, Meurer M, MacKenzie KL, Kavallaris M, Banavali SD. Effective Management of Advanced Angiosarcoma by the Synergistic Combination of Propranolol and Vinblastine-based Metronomic Chemotherapy: A Bench to Bedside Study. EBioMedicine. 2016 Apr;6:87-95. doi: 10.1016/j.ebiom.2016.02.026. Epub 2016 Feb 17. PubMed PMID: 27211551; PubMed Central PMCID: PMC4856748.
PRACINOSTAT	Chen J, Li N, Liu B, Ling J, Yang W, Pang X, Li T. Pracinostat (SB939), a histone deacetylase inhibitor, suppresses breast cancer metastasis and growth by inactivating the IL-6/STAT3 signalling pathways. Life Sci. 2020 May 01;248:117469. doi: 10.1016/j.lfs.2020.117469. Epub 2020 February 25. PubMed PMID: 32109485.
MIDOSTAURIN	Yoshikawa N, Nakamura K, Yamaguchi Y, Kagota S, Shinozuka K, Kunitomo M. Effect of PKC412, a selective inhibitor of protein kinase C, on lung metastasis in mice injected with B16 melanoma cells. Life Sci. 2003 Feb 7;72(12):1377-87. PubMed PMID: 12527035.
NEO1132	Ryan KR, Giles F, Morgan GJ. Targeting both BET and CBP/EP300 proteins with the novel dual inhibitors NEO2734 and NEO1132 leads to anti-tumor activity in Multiple Myeloma. Eur J Haematol. 2020 Sep 30;:. doi: 10.1111/ejh.13525. Epub 2020 Oct 30. PubMed PMID: 32997383.
MIBG	Riad R, Kotb M, Omar W, Zaher A, Khalafalla K, Fawzy M, El-Wakil M, Ebeid E. Role of 131-I MIBG Therapy in the Treatment of Advanced Neuroblastoma. J Egypt Natl Canc Inst. 2009 Mar;21(1):51-8. PubMed PMID: 20601971.
ETOPOSIDE	Tweddle DA, Malcolm AJ, Bown N, Pearson AD, Lunec J. Evidence for the development of p53 mutations after cytotoxic therapy in a neuroblastoma cell line. Cancer Res. 2001 Jan 1;61(1):8-13. PubMed PMID: 11196202. Chamberlain MC. Salvage chemotherapy for recurrent spinal cord ependymona. Cancer. 2002 Sep 1;95(5):997-1002. PubMed PMID: 12209682.
CARBOPLATIN	http://www.ncbi.nlm.nih.gov/pubmed/29426293 Tweddle DA, Malcolm AJ, Bown N, Pearson AD, Lunec J. Evidence for the development of p53 mutations after cytotoxic therapy in a neuroblastoma cell line. Cancer Res. 2001 Jan 1;61(1):8-13. PubMed PMID: 11196202. Fouladi M, Gururangan S, Moghrabi A, Phillips P, Gronewold L, Wallace D, Sanford RA, Gajjar A, Kun LE, Heideman R. Carboplatin-based primary chemotherapy for infants and young children with CNS tumors. Cancer. 2009 Jul 15;115(14):3243-53. doi: 10.1002/cncr.24362. PubMed PMID: 19484793; PubMed Central PMCID: PMC4307774. Sugiyama T, Kamura T, Kigawa J, Terakawa N, Kikuchi Y, Kita T, Suzuki M, Sato I, Taguchi K. Clinical characteristics of clear cell carcinoma of the ovary: a distinct histologic type with poor prognosis and resistance to platinum-based chemotherapy. Cancer. 2000 Jun 1;88(11):2584-9. PubMed PMID: 10861437.
TRASTUZUMAB	Moroni M, Stella M, Pedrazzoli P, Pirovano M, Boveri E, Veronese S. c.428T > C (p.V143A) homozygous mutation in TP53 gene as a possible mechanism of resistance to trastuzumab therapy in gastric cancer. Acta Oncol. 2016 Nov;55(11):1373-1375. Epub 2016 Aug 31. PubMed PMID: 27579625.
MELPHALAN	Tweddle DA, Malcolm AJ, Bown N, Pearson AD, Lunec J. Evidence for the development of p53 mutations after cytotoxic therapy in a neuroblastoma cell line. Cancer Res. 2001 Jan 1;61(1):8-13. PubMed PMID: 11196202.
FK866	Thakur BK, Dittrich T, Chandra P, Becker A, Kuehnau W, Klusmann JH, Reinhardt D, Welte K. Involvement of p53 in the cytotoxic activity of the NAMPT inhibitor FK866 in myeloid leukemic cells. Int J Cancer. 2013 Feb 15;132(4):766-74. doi: 10.1002/ijc.27726. PubMed PMID: 22815158; PubMed Central PMCID: PMC3562481.
BUPARLISIB	Thorpe LM, Yuzugullu H, Zhao JJ. PI3K in cancer: divergent roles of isoforms, modes of activation and therapeutic targeting. Nat Rev Cancer. 2015 Jan;15(1):7-24. doi: 10.1038/nrc3860. Review. PubMed PMID: 25533673; PubMed Central PMCID: PMC4384662. Kirstein MM, Boukouris AE, Pothiraju D, Buitrago-Molina LE, Marhenke S, Schütt J, Orlik J, Kühnel F, Hegermann J, Manns MP, Vogel A. Activity of the mTOR inhibitor RAD001, the dual mTOR and PI3-kinase inhibitor BEZ235 and the PI3-kinase inhibitor BKM120 in hepatocellular carcinoma. Liver Int. 2013 May;33(5):780-93. doi: 10.1111/liv.12126. Epub 2013 Mar 15. PubMed PMID: 23489999. Soulières D, Licitra L, Mesía R, Remenár É, Li SH, Karpenko A, Chol M, Wang YA, Solovieff N, Bourdeau L, Sellami D, Faivre S. Molecular Alterations and Buparlisib Efficacy in Patients with Squamous Cell Carcinoma of the Head and Neck: Biomarker Analysis from BERIL-1. Clin Cancer Res. 2018 Jun 1;24(11):2505-2516. doi: 10.1158/1078-0432.CCR-17-2644. Epub 2018 Feb 28. PMID: 29490986.

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COMPOUND NAME	REFERENCES
PATUPILONE	Seagle BL, Yang CP, Eng KH, Dandapani M, Odunsi-Akanji O, Goldberg GL, Odunsi K, Horwitz SB, Shahabi S. TP53 hot spot mutations in ovarian cancer: selective resistance to microtubule stabilizers in vitro and differential survival outcomes from The Cancer Genome Atlas. Gynecol Oncol. 2015 Jul;138(1):159-64. doi: 10.1016/j.ygyno.2015.04.039. Epub 2015 May 6. PubMed PMID: 25958320; PubMed Central PMCID: PMC5303002.
DOXORUBICIN	Chang FL, Lai MD. Various forms of mutant p53 confer sensitivity to cisplatin and doxorubicin in bladder cancer cells. J Urol. 2001 Jul;166(1):304-10. PubMed PMID: 11435891. Capponcelli S, Pedrini E, Cerone MA, Corti V, Fontanesi S, Alessio M, Bachi A, Soddu S, Ribatti D, Picci P, Helman LJ, Cantelli-Forti G, Sangiorgi L. Evaluation of the molecular mechanisms involved in the gain of function of a Li-Fraumeni TP53 mutation. Hum Mutat. 2005 Aug;26(2):94-103. PubMed PMID: 15977174. Anasuya Pal, Laura Gonzalez-Malerva, Seron Eaton, Mayra Guzman, Donald Chow, Hongwei Yin, Jin Park, Karen Anderson, Joshua LaBaer. Functional genomics of TP53 mutations and its impact in breast cancer progression. Proceedings of the Thirty-Seventh Annual CTRC-AACR San Antonio Breast Cancer Symposium: 2014 Dec 9-13; San Antonio, TX. Philadelphia (PA): AACR; Cancer Res 2015;75(9 Suppl):Abstract nr P4-05-07. doi: 10.1158/1538-7445.SABCS14-P4-05-07 Hosain SB, Khiste SK, Uddin MB, Vorubindi V, Ingram C, Zhang S, Hill RA, Gu X, Liu YY. Inhibition of glucosylceramide synthase eliminates the oncogenic function of p53 R273H mutant in the epithelial-mesenchymal transition and induced pluripotency of colon cancer cells. Oncotarget. 2016 Sep 13;7(37):60575-60592. doi: 10.18632/oncotarget.11169. PubMed PMID: 27517620; PubMed Central PMCID: PMC5312403. Tweddle DA, Malcolm AJ, Bown N, Pearson AD, Lunec J. Evidence for the development of p53 mutations after cytotoxic therapy in a neuroblastoma cell line. Cancer Res. 2001 Jan 1;61(1):8-13. PubMed PMID: 11196202.
S49076	Clémenson C, Chargari C, Liu W, Mondini M, Ferté C, Burbridge MF, Cattan V, Jacquet-Bescond A, Deutsch E. The MET/AXL/FGFR Inhibitor S49076 Impairs Aurora B Activity and Improves the Antitumor Efficacy of Radiotherapy. Mol Cancer Ther. 2017 Oct;16(10):2107-2119. doi: 10.1158/1535-7163.MCT-17-0112. Epub 2017 Jun 15. PubMed PMID: 28619752.
VOXTALISIB	Thorpe LM, Yuzugullu H, Zhao JJ. PI3K in cancer: divergent roles of isoforms, modes of activation and therapeutic targeting. Nat Rev Cancer. 2015 Jan;15(1):7-24. doi: 10.1038/nrc3860. Review. PubMed PMID: 25533673; PubMed Central PMCID: PMC4384662. Papadopoulos KP, Egile C, Ruiz-Soto R, Jiang J, Shi W, Bentzien F, Rasco D, Abrisqueta P, Vose JM, Tabernero J. Efficacy, safety, pharmacokinetics and pharmacodynamics of SAR245409 (XL765), an orally administered PI3K /mTOR inhibitor: a phase 1 expansion cohort in patients with relapsed or refractory lymphoma. Leuk Lymphoma. 2014 Oct 10:1-32. [Epub ahead of print] PubMed PMID: 25300944.
DACTOLISIB	Gan ZY, Fitter S, Vandyke K, To LB, Zannettino AC, Martin SK. The effect of the dual PI3K and mTOR inhibitor BEZ235 on tumour growth and osteolytic bone disease in multiple myeloma. Eur J Haematol. 2014 Sep 2. doi: 10.1111/ejh.12436. [Epub ahead of print] PubMed PMID: 25179233. Thorpe LM, Yuzugullu H, Zhao JJ. PI3K in cancer: divergent roles of isoforms, modes of activation and therapeutic targeting. Nat Rev Cancer. 2015 Jan;15(1):7-24. doi: 10.1038/nrc3860. Review. PubMed PMID: 25533673; PubMed Central PMCID: PMC4384662. Serra V, Markman B, Scaltriti M, Eichhorn PJ, Valero V, Guzman M, Botero ML, Llonch E, Atzori F, Di Cosimo S, Maira M, Garcia-Echeverria C, Parra JL, Arribas J, Baselga J. NVP-BEZ235, a dual PI3K/mTOR inhibitor, prevents PI3K signaling and inhibits the growth of cancer cells with activating PI3K mutations. Cancer Res. 2008 Oct 01;68(19):8022-30. doi: 10.1158/0008-5472.CAN-08-1385. PubMed PMID: 18829560. Chen D, Lin X, Zhang C, Liu Z, Chen Z, Li Z, Wang J, Li B, Hu Y, Dong B, Shen L, Ji J, Gao J, Zhang X. Dual PI3K /mTOR inhibitor BEZ235 as a promising therapeutic strategy against paclitaxel-resistant gastric cancer via targeting PI3K/Akt/mTOR pathway. Cell Death Dis. 2018 Jan 26;9(2):123. doi: 10.1038/s41419-017-0132-2. PubMed PMID: 29374144.
PWT33597	Thorpe LM, Yuzugullu H, Zhao JJ. PI3K in cancer: divergent roles of isoforms, modes of activation and therapeutic targeting. Nat Rev Cancer. 2015 Jan;15(1):7-24. doi: 10.1038/nrc3860. Review. PubMed PMID: 25533673; PubMed Central PMCID: PMC4384662.
OMIPALISIB	Thorpe LM, Yuzugullu H, Zhao JJ. PI3K in cancer: divergent roles of isoforms, modes of activation and therapeutic targeting. Nat Rev Cancer. 2015 Jan;15(1):7-24. doi: 10.1038/nrc3860. Review. PubMed PMID: 25533673; PubMed Central PMCID: PMC4384662. Rewcastle GW, Kolekar S, Buchanan CM, Gamage SA, Giddens AC, Tsang KY, Kendall JD, Singh R, Lee WJ, Smith GC, Han W, Matthews DJ, Denny WA, Shepherd PR, Jamieson SMF. Biological characterization of SN32976, a selective inhibitor of PI3K and mTOR with preferential activity to PI3K, in comparison to established pan PI3K inhibitors. Oncotarget. 2017 May 9. doi: 10.18632/oncotarget.17730. [Epub ahead of print] PubMed PMID: 28537878. Albawardi A, Al Ayyan M, Al Bashir M, Souid AK, Almarzooqi S. In vitro assessment of antitumor activities of the PI3K /mTOR inhibitor GSK2126458. Cancer Cell Int. 2014 Sep 24;14(1):90. doi: 10.1186/s12935-014-0090-z. eCollection 2014. PubMed PMID: 25298748; PubMed Central PMCID: PMC4189195. Hassett M, Sternberg A, Roepe PD. Inhibition of Human Class I vs Class III Phosphatidylinositol 3'-Kinases. Biochemistry. 2017 Jul 18. doi: 10.1021/acs.biochem.7b00413. [Epub ahead of print] PubMed PMID: 28719179.

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COMPOUND NAME	REFERENCES
SF1126	Thorpe LM, Yuzugullu H, Zhao JJ. PI3K in cancer: divergent roles of isoforms, modes of activation and therapeutic targeting. Nat Rev Cancer. 2015 Jan;15(1):7-24. doi: 10.1038/nrc3860. Review. PubMed PMID: 25533673; PubMed Central PMCID: PMC4384662. Singh AR, Joshi S, Burgoyne AM, Sicklick JK, Ikeda S, Kono Y, Garlich JR, Morales GA, Durden DL. Single Agent and Synergistic Activity of the "First-in-Class" Dual PI3K/BRD4 Inhibitor SF1126 with Sorafenib in Hepatocellular Carcinoma. Mol Cancer Ther. 2016 Nov;15(11):2553-2562. Epub 2016 Aug 5. PubMed PMID: 27496136; PubMed Central PMCID: PMC5278767.
GEDATOLISIB	Thorpe LM, Yuzugullu H, Zhao JJ. PI3K in cancer: divergent roles of isoforms, modes of activation and therapeutic targeting. Nat Rev Cancer. 2015 Jan;15(1):7-24. doi: 10.1038/nrc3860. Review. PubMed PMID: 25533673; PubMed Central PMCID: PMC4384662. Zhu Y, Shah K. Multiple lesions in receptor tyrosine kinase pathway determine glioblastoma response to pan-ERBB inhibitor PF-00299804 and PI3K/mTOR dual inhibitor PF-05212384. Cancer Biol Ther. 2014 Jun 1;15(6):815-22. doi: 10.4161/cbt.28585. Epub 2014 Mar 21. PubMed PMID: 24658109; PubMed Central PMCID: PMC4049797. Del Campo JM, Birrer M, Davis C, Fujiwara K, Gollerkeri A, Gore M, Houk B, Lau S, Poveda A, González-Martín A, Muller C, Muro K, Pierce K, Suzuki M, Vermette J, Oza A. A randomized phase II non-comparative study of PF-04691502 and gedatolisib (PF-05212384) in patients with recurrent endometrial cancer. Gynecol Oncol. 2016 Jul;142(1):62-9. doi: 10.1016/j.ygyno.2016.04.019. Epub 2016 Apr 24. PubMed PMID: 27103175.
PF-04691502	Thorpe LM, Yuzugullu H, Zhao JJ. PI3K in cancer: divergent roles of isoforms, modes of activation and therapeutic targeting. Nat Rev Cancer. 2015 Jan;15(1):7-24. doi: 10.1038/nrc3860. Review. PubMed PMID: 25533673; PubMed Central PMCID: PMC4384662. Del Campo JM, Birrer M, Davis C, Fujiwara K, Gollerkeri A, Gore M, Houk B, Lau S, Poveda A, González-Martín A, Muller C, Muro K, Pierce K, Suzuki M, Vermette J, Oza A. A randomized phase II non-comparative study of PF-04691502 and gedatolisib (PF-05212384) in patients with recurrent endometrial cancer. Gynecol Oncol. 2016 Jul;142(1):62-9. doi: 10.1016/j.ygyno.2016.04.019. Epub 2016 Apr 24. PubMed PMID: 27103175. Fang DD, Zhang CC, Gu Y, Jani JP, Cao J, Tsaparikos K, Yuan J, Thiel M, Jackson-Fisher A, Zong Q, Lappin PB, Hayashi T, Schwab RB, Wong A, John-Baptiste A, Bagrodia S, Los G, Bender S, Christensen J, Vanarsdale T. Antitumor Efficacy of the Dual PI3K/mTOR Inhibitor PF-04691502 in a Human Xenograft Tumor Model Derived from Colorectal Cancer Stem Cells Harboring a PIK3CA Mutation. PLoS One. 2013 Jun 27;8(6):e67258. Print 2013. PubMed PMID: 23826249; PubMed Central PMCID: PMC3695076. Britten CD, Adjei AA, Millham R, Houk BE, Borzillo G, Pierce K, Wainberg ZA, LoRusso PM. Phase I study of PF-04691502, a small-molecule, oral, dual inhibitor of PI3K and mTOR, in patients with advanced cancer. Invest New Drugs. 2014 Jun;32(3):510-7. doi: 10.1007/s10637-013-0062-5. Epub 2014 Jan 7. Erratum in: Invest New Drugs. 2014 Jun;32(3):575. PubMed PMID: 24395457.
APITOLISIB	Powles T, Lackner MR, Oudard S, Escudier B, Ralph C, Brown JE, Hawkins RE, Castellano D, Rini BI, Staehler MD, Ravaud A, Lin W, O'Keeffe B, Wang Y, Lu S, Spoerke JM, Huw LY, Byrtek M, Zhu R, Ware JA, Motzer RJ. Randomized Open-Label Phase II Trial of Apitolisib (GDC-0980), a Novel Inhibitor of the PI3K/Mammalian Target of Rapamycin Pathway, Versus Everolimus in Patients With Metastatic Renal Cell Carcinoma. J Clin Oncol. 2016 May 10;34(14):1660-8. doi: 10.1200/JCO.2015.64.8808. Epub 2016 Mar 7. PubMed PMID: 26951309. Thorpe LM, Yuzugullu H, Zhao JJ. PI3K in cancer: divergent roles of isoforms, modes of activation and therapeutic targeting. Nat Rev Cancer. 2015 Jan;15(1):7-24. doi: 10.1038/nrc3860. Review. PubMed PMID: 25533673; PubMed Central PMCID: PMC4384662. Tang JY, Tu D, Zhang H, Xiong WJ, Xu MZ, Wang XJ, Tang QH, Chen B, Xu M. GDC-0980-induced apoptosis is enhanced by autophagy inhibition in human pancreatic cancer cells. Biochem Biophys Res Commun. 2014 Oct 5. pii: S0006-291X(14)01752-5. doi: 10.1016/j.bbrc.2014.09.115. [Epub ahead of print] PubMed PMID: 25285629. Makker V, Recio FO, Ma L, Matulonis UA, Lauchle JO, Parmar H, Gilbert HN, Ware JA, Zhu R, Lu S, Huw LY, Wang Y, Koeppen H, Spoerke JM, Lackner MR, Aghajanian CA. A multicenter, single-arm, open-label, phase 2 study of apitolisib (GDC-0980) for the treatment of recurrent or persistent endometrial carcinoma (MAGGIE study). Cancer. 2016 Sep 7. doi: 10.1002/cncr.30286. [Epub ahead of print] PubMed PMID: 27603005.
DS-7423	Kashiyama T, Oda K, Ikeda Y, Shiose Y, Hirota Y, Inaba K, Makii C, Kurikawa R, Miyasaka A, Koso T, Fukuda T, Tanikawa M, Shoji K, Sone K, Arimoto T, Wada-Hiraike O, Kawana K, Nakagawa S, Matsuda K, McCormick F, Aburatani H, Yano T, Osuga Y, Fujii T. Antitumor activity and induction of TP53-dependent apoptosis toward ovarian clear cell adenocarcinoma by the dual PI3K/mTOR inhibitor DS-7423. PLoS One. 2014 Feb 4;9(2):e87220. doi: 10.1371/journal.pone.0087220. eCollection 2014. PubMed PMID: 24504419; PubMed Central PMCID: PMC3913610. Thorpe LM, Yuzugullu H, Zhao JJ. PI3K in cancer: divergent roles of isoforms, modes of activation and therapeutic targeting. Nat Rev Cancer. 2015 Jan;15(1):7-24. doi: 10.1038/nrc3860. Review. PubMed PMID: 25533673; PubMed Central PMCID: PMC4384662. Oda K, Ikeda Y, Kashiyama T, Miyasaka A, Inaba K, Fukuda T, Asada K, Sone K, Wada-Hiraike O, Kawana K, Osuga Y, Fujii T. Characterization of TP53 and PI3K signaling pathways as molecular targets in gynecologic malignancies. J Obstet Gynaecol Res. 2016 Jul;42(7):757-62. doi: 10.1111/jog.13018. Epub 2016 Apr 20. Review. PubMed PMID: 27094348.

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COMPOUND NAME	REFERENCES
BGT226	Thorpe LM, Yuzugullu H, Zhao JJ. PI3K in cancer: divergent roles of isoforms, modes of activation and therapeutic targeting. Nat Rev Cancer. 2015 Jan;15(1):7-24. doi: 10.1038/nrc3860. Review. PubMed PMID: 25533673; PubMed Central PMCID: PMC4384662. Simioni C, Cani A, Martelli AM, Zauli G, Alameen AA, Ultimo S, Tabellini G, McCubrey JA, Capitani S, Neri LM. The novel dual PI3K/mTOR inhibitor NVP-BGT226 displays cytotoxic activity in both normoxic and hypoxic hepatocarcinoma cells. Oncotarget. 2015 Jul 10;6(19):17147-60. PubMed PMID: 26003166; PubMed Central PMCID: PMC4627298. Chang KY, Tsai SY, Wu CM, Yen CJ, Chuang BF, Chang JY. Novel phosphoinositide 3-kinase/mTOR dual inhibitor, NVP-BGT226, displays potent growth-inhibitory activity against human head and neck cancer cells in vitro and in vivo. Clin Cancer Res. 2011 Nov 15;17(22):7116-26. doi: 10.1158/1078-0432.CCR-11-0796. Epub 2011 Oct 5. PubMed PMID: 21976531.
CISPLATIN	Brachova P, Mueting SR, Carlson MJ, Goodheart MJ, Button AM, Mott SL, Dai D, Thiel KW, Devor EJ, Leslie KK. TP53 oncomorphic mutations predict resistance to platinum- and taxane-based standard chemotherapy in patients diagnosed with advanced serous ovarian carcinoma. Int J Oncol. 2015 Feb;46(2):607-18. doi: 10.3892/ijo.2014.2747. PubMed PMID: 25385265; PubMed Central PMCID: PMC4277253. Chang FL, Lai MD. Various forms of mutant p53 confer sensitivity to cisplatin and doxorubicin in bladder cancer cells. J Urol. 2001 Jul;166(1):304-10. PubMed PMID: 11435891. Li J, Yang L, Gaur S, Zhang K, Wu X, Yuan YC, Li H, Hu S, Weng Y, Yen Y. Mutants TP53 p.R273H and p.R273C but not p.R273G enhance cancer cell malignancy. Hum Mutat. 2014 May;35(5):575-84. doi: 10.1002/humu.22528. PubMed PMID: 24677579. Blandino G, Levine AJ, Oren M. Mutant p53 gain of function: differential effects of different p53 mutants on resistance of cultured cells to chemotherapy. Oncogene. 1999 Jan 14;18(2):477-85. PubMed PMID: 9927204. http://www.ncbi.nlm.nih.gov/pubmed/29426293
NIVOLUMAB	Wang C, Thudium KB, Han M, Wang XT, Huang H, Feingersh D, Garcia C, Wu Y, Kuhne M, Srinivasan M, Singh S, Wong S, Garner N, Leblanc H, Bunch RT, Blanset D, Selby MJ, Korman AJ. In vitro characterization of the anti-PD-1 antibody nivolumab, BMS-936558, and in vivo toxicology in non-human primates. Cancer Immunol Res. 2014 Sep;2(9):846-56. doi: 10.1158/2326-6066.CIR-14-0040. Epub 2014 May 28. PubMed PMID: 24872026. Echarri MJ, Lopez-Martin A, Hitt R. Targeted Therapy in Locally Advanced and Recurrent/Metastatic Head and Neck Squamous Cell Carcinoma (LA-R/M HNSCC). Cancers (Basel). 2016 Feb 26;8(3). pii: E27. doi: 10.3390/cancers8030027. Review. PubMed PMID: 26927178; PubMed Central PMCID: PMC4810111. Dean F. Bajorin, Johannes Alfred Witjes, Jürgen Gschwend, Michael Schenker, Begoña P. Valderrama, Yoshihiko Tomita, Aristotelis Bamias, Thierry Lebret, Shahrokh Shariat, Se Hoon Park, Dingwei Ye, Mads Agerbaek, Sandra Collette, Keziban Unsal-Kacmaz, Dimitrios Zardavas, Henry B. Koon, and Matt D. Galsky. First results from the phase 3 CheckMate 274 trial of adjuvant nivolumab vs placebo in patients who underwent radical surgery for high-risk muscle-invasive urothelial carcinoma (MIUC). Journal of Clinical Oncology. 2021;39(6_suppl):391-391. doi: 10.1200/JCO.2021.39.6_suppl.391. Hollebecque A, Meyer T, Moore KN, Machiels JPH, De Greve J, López-Picazo JM, Oaknin A, Kerger JN, Boni V, Evans TRJ, Kristeleit RS, Rao S, Soumaoro I, Cao ZA, Topalian SL. An open-label, multicohort, phase I/II study of nivolumab in patients with virus-associated tumors (CheckMate 358): Efficacy and safety in recurrent or metastatic (R/M) cervical, vaginal, and vulvar cancers. DOI: 10.1200/JCO.2017.35.15_suppl.5504 Journal of Clinical Oncology 35, no. 15_suppl (May 2017) 5504-5504. http://ascopubs.org/doi/abs/10.1200/JCO.2017.35.4_suppl.2
CHOP	Liu YY, Yao SN, Zhao Y, Yao ZH, Ma J, Xia QX, Fu K, Yang SJ. PTEN tumor suppressor plays less prognostic role than P53 tumor suppressor in diffuse large B-cell lymphoma. Leuk Lymphoma. 2010 Sep;51(9):1692-8. doi: 10.3109/10428194.2010.502584. PubMed PMID: 20807096. Young KH, Leroy K, Møller MB, Colleoni GW, Sánchez-Beato M, Kerbauy FR, Haioun C, Eickhoff JC, Young AH, Gaulard P, Piris MA, Oberley TD, Rehrauer WM, Kahl BS, Malter JS, Campo E, Delabie J, Gascoyne RD, Rosenwald A, Rimsza L, Huang J, Braziel RM, Jaffe ES, Wilson WH, Staudt LM, Vose JM, Chan WC, Weisenburger DD, Greiner TC. Structural profiles of TP53 gene mutations predict clinical outcome in diffuse large B-cell lymphoma: an international collaborative study. Blood. 2008 Oct 15;112(8):3088-98. doi: 10.1182/blood-2008-01-129783. Epub 2008 Feb 17. PubMed PMID: 18559976; PubMed Central PMCID: PMC2569165. Young KH, Weisenburger DD, Dave BJ, Smith L, Sanger W, Iqbal J, Campo E, Delabie J, Gascoyne RD, Ott G, Rimsza L, Müller-Hermelink HK, Jaffe ES, Rosenwald A, Staudt LM, Chan WC, Greiner TC. Mutations in the DNA-binding codons of TP53, which are associated with decreased expression of TRAILreceptor-2, predict for poor survival in diffuse large B-cell lymphoma. Blood. 2007 Dec 15;110(13):4396-405. doi: 10.1182/blood-2007-02-072082. Epub 2007 Feb 19. PubMed PMID: 17881637; PubMed Central PMCID: PMC2234786.

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COMPOUND NAME	REFERENCES
PANULISIB	Jalota-Badhwar A, Bhatia DR, Boreddy S, Joshi A, Venkatraman M, Desai N, Chaudhari S, Bose J, Kolla LS, Deore V, Yewalkar N, Kumar S, Sharma R, Damre A, More A, Sharma S, Agarwal VR. P7170: A Novel Molecule with Unique Profile of mTORC1/C2 and Activin Receptor-like Kinase 1 Inhibition Leading to Antitumor and Antiangiogenic Activity. Mol Cancer Ther. 2015 May;14(5):1095-106. doi: 10.1158/1535-7163.MCT-14-0486. Epub 2015 Feb 19. PubMed PMID: 25700704. Veena R. Agarwal, Asavari Joshi, Magesh Venkataraman, Dimple Bhatia, Julie Bose, Lakshmi Sireesha Kolla, Parkash Gill, and Somesh Sharma. P7170, a novel inhibitor of phosphoinositide 3-kinase (PI3K)-mammalian target of Rapamycin (mTOR) and activin receptor-like kinase 1 (ALK1) as a new therapeutic option for Kras mutated non small cell lung cancer (NSCLC). Proceedings of the 103rd Annual Meeting of the American Association for Cancer Research; 2012 Mar 31-Apr 4; Chicago, IL. Philadelphia (PA): AACR; Cancer Res 2012;72(8 Suppl):Abstract nr 3759. doi:1538-7445.AM2012-3759
COPANLISIB	Liu N, Rowley BR, Bull CO, Schneider C, Haegebarth A, Schatz CA, Fracasso PR, Wilkie DP, Hentemann M, Wilhelm SM, Scott WJ, Mumberg D, Ziegelbauer K. BAY 80-6946 is a highly selective intravenous PI3K inhibitor with potent p110 and p110 activities in tumor cell lines and xenograft models. Mol Cancer Ther. 2013 Nov;12(11):2319-30. doi: 10.1158/1535-7163.MCT-12-0993-T. Epub 2013 Oct 29. PubMed PMID: 24170767. Thorpe LM, Yuzugullu H, Zhao JJ. PI3K in cancer: divergent roles of isoforms, modes of activation and therapeutic targeting. Nat Rev Cancer. 2015 Jan;15(1):7-24. doi: 10.1038/nrc3860. Review. PubMed PMID: 25533673; PubMed Central PMCID: PMC4384662. Gerisch M, Schwarz T, Lang D, Rohde G, Reif S, Genvresse I, Reschke S, van der Mey D, Granvil C. Pharmacokinetics of intravenous pan-class I phosphatidylinositol 3-kinase (PI3K) inhibitor [(14)C]copanlisib (BAY 80-6946) in a mass balance study in healthy male volunteers. Cancer Chemother Pharmacol. 2017 Jul 11. doi: 10.1007/s00280-017-3383-9. [Epub ahead of print] PubMed PMID: 28714036. Dreyling M, Morschhauser F, Bouabdallah K, Bron D, Cunningham D, Assouline SE, Verhoef G, Linton K, Thieblemont C, Vitolo U, Hiemeyer F, Giurescu M, Garcia-Vargas J, Gorbatchevsky I, Liu L, Koechert K, Peña C, Neves M, Childs BH, Zinzani PL. Phase II study of copanlisib, a PI3K inhibitor, in relapsed or refractory, indolent or aggressive lymphoma. Ann Oncol. 2017 Sep 01;28(9):2169-2178. doi: 10.1093/annonc/mdx289. PubMed PMID: 28633365; PubMed Central PMCID: PMC5834070.
CH 5132799	Thorpe LM, Yuzugullu H, Zhao JJ. PI3K in cancer: divergent roles of isoforms, modes of activation and therapeutic targeting. Nat Rev Cancer. 2015 Jan;15(1):7-24. doi: 10.1038/nrc3860. Review. PubMed PMID: 25533673; PubMed Central PMCID: PMC4384662. Blagden S, Omlin A, Josephs D, Stavraka C, Zivi A, Pinato DJ, Anthoney A, Decordova S, Swales K, Riisnaes R, Pope L, Noguchi K, Shiokawa R, Inatani M, Prince J, Jones K, Twelves C, Spicer J, Banerji U. First-in-human study of CH5132799, an oral class I PI3K inhibitor, studying toxicity, pharmacokinetics, and pharmacodynamics, in patients with metastatic cancer. Clin Cancer Res. 2014 Dec 1;20(23):5908-17. doi: 10.1158/1078-0432.CCR-14-1315. Epub 2014 Sep 17. Erratum in: Clin Cancer Res. 2015 Feb 1;21(3):660. Olmin, Aurelius [corrected to Omlin, Aurelius]. PubMed PMID: 25231405; PubMed Central PMCID: PMC4254850.
SONOLISIB	Thorpe LM, Yuzugullu H, Zhao JJ. PI3K in cancer: divergent roles of isoforms, modes of activation and therapeutic targeting. Nat Rev Cancer. 2015 Jan;15(1):7-24. doi: 10.1038/nrc3860. Review. PubMed PMID: 25533673; PubMed Central PMCID: PMC4384662. Hong DS, Bowles DW, Falchook GS, Messersmith WA, George GC, O'Bryant CL, Vo AC, Klucher K, Herbst RS, Eckhardt SG, Peterson S, Hausman DF, Kurzrock R, Jimeno A. A multicenter phase I trial of PX-866, an oral irreversible phosphatidylinositol 3-kinase inhibitor, in patients with advanced solid tumors. Clin Cancer Res. 2012 Aug 1;18(15):4173-82. doi: 10.1158/1078-0432.CCR-12-0714. Epub 2012 Jun 12. PubMed PMID: 22693357.
PICTILISIB	Thorpe LM, Yuzugullu H, Zhao JJ. PI3K in cancer: divergent roles of isoforms, modes of activation and therapeutic targeting. Nat Rev Cancer. 2015 Jan;15(1):7-24. doi: 10.1038/nrc3860. Review. PubMed PMID: 25533673; PubMed Central PMCID: PMC4384662. Dogan T, Gnad F, Chan J, Phu L, Young A, Chen MJ, Doll S, Stokes MP, Belvin M, Friedman LS, Kirkpatrick DS, Hoeflich KP, Hatzivassiliou G. Role of the E3 ubiquitin ligase RNF157 as a novel downstream effector linking PI3K and MAPK signaling to the cell cycle. J Biol Chem. 2017 Jun 27. pii: jbc.M117.792754. doi: 10.1074/jbc.M117.792754. [Epub ahead of print] PubMed PMID: 28655764. Weigelt B, Warne PH, Lambros MB, Reis-Filho JS, Downward J. PI3K pathway dependencies in endometrioid endometrial cancer cell lines. Clin Cancer Res. 2013 Jul 1;19(13):3533-44. doi: 10.1158/1078-0432.CCR-12-3815. Epub 2013 May 14. PubMed PMID: 23674493; PubMed Central PMCID: PMC3700760.
ZSTK474	Thorpe LM, Yuzugullu H, Zhao JJ. PI3K in cancer: divergent roles of isoforms, modes of activation and therapeutic targeting. Nat Rev Cancer. 2015 Jan;15(1):7-24. doi: 10.1038/nrc3860. Review. PubMed PMID: 25533673; PubMed Central PMCID: PMC4384662. Zhao W, Guo W, Zhou Q, Ma SN, Wang R, Qiu Y, Jin M, Duan HQ, Kong D. In Vitro Antimetastatic Effect of Phosphatidylinositol 3-Kinase Inhibitor ZSTK474 on Prostate Cancer PC3 Cells. Int J Mol Sci. 2013 Jun 28;14(7):13577-91. doi: 10.3390/ijms140713577. PubMed PMID: 23812078; PubMed Central PMCID: PMC3742204.

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COMPOUND NAME	REFERENCES
PILARALISIB	Reynolds CP, Kang MH, Carol H, Lock R, Gorlick R, Kolb EA, Kurmasheva RT, Keir ST, Maris JM, Billups CA, Houghton PJ, Smith MA. Initial testing (stage 1) of the phosphatidylinositol 3' kinase inhibitor, SAR245408 (XL147) by the pediatric preclinical testing program. Pediatr Blood Cancer. 2013 May;60(5):791-8. doi: 10.1002/pbc.24301. Epub 2012 Sep 21. PubMed PMID: 23002019. Thorpe LM, Yuzugullu H, Zhao JJ. PI3K in cancer: divergent roles of isoforms, modes of activation and therapeutic targeting. Nat Rev Cancer. 2015 Jan;15(1):7-24. doi: 10.1038/nrc3860. Review. PubMed PMID: 25533673; PubMed Central PMCID: PMC4384662.
PI-103	Bagci-Onder T, Wakimoto H, Anderegg M, Cameron C, Shah K. A dual PI3K/mTOR inhibitor, PI-103, cooperates with stem cell-delivered TRAIL in experimental glioma models. Cancer Res. 2011 Jan 1;71(1):154-63. doi: 10.1158/0008-5472.CAN-10-1601. Epub 2010 Nov 17. PubMed PMID: 21084267.
VS-5584	Ning C, Liang M, Liu S, Wang G, Edwards H, Xia Y, Polin L, Dyson G, Taub JW, Mohammad RM, Azmi AS, Zhao L, Ge Y. Targeting ERK enhances the cytotoxic effect of the novel PI3K and mTOR dual inhibitor VS-5584 in preclinical models of pancreatic cancer. Oncotarget. 2017 Jul 4;8(27):44295-44311. doi: 10.18632/oncotarget.17869. PubMed PMID: 28574828. Hart S, Novotny-Diermayr V, Goh KC, Williams M, Tan YC, Ong LC, Cheong A, Ng BK, Amalini C, Madan B, Nagaraj H, Jayaraman R, Pasha KM, Ethirajulu K, Chng WJ, Mustafa N, Goh BC, Benes C, McDermott U, Garnett M, Dymock B, Wood JM. VS-5584, a novel and highly selective PI3K/mTOR kinase inhibitor for the treatment of cancer. Mol Cancer Ther. 2013 Feb;12(2):151-61. doi: 10.1158/1535-7163.MCT-12-0466. Epub 2012 Dec 27. PubMed PMID: 23270925; PubMed Central PMCID: PMC3588144.
PKI179	Venkatesan AM, Chen Z, dos Santos O, Dehnhardt C, Santos ED, Ayral-Kaloustian S, Mallon R, Hollander I, Feldberg L, Lucas J, Yu K, Chaudhary I, Mansour TS. PKI-179: an orally efficacious dual phosphatidylinositol-3-kinase (PI3K)/mammalian target of rapamycin (mTOR) inhibitor. Bioorg Med Chem Lett. 2010 Oct 1;20(19):5869-73. doi: 10.1016/j.bmcl.2010.07.104. Epub 2010 Jul 30. PubMed PMID: 20797855.
PEMBROLIZUMAB	Head L, Kiseljak-Vassiliades K, Clark TJ, Somerset H, King J, Raeburn C, Albuja-Cruz M, Weyant M, Cleveland J, Wierman ME, Leong S. Response to Immunotherapy in Combination With Mitotane in Patients With Metastatic Adrenocortical Cancer. J Endocr Soc. 2019 Oct 11;3(12):2295-2304. doi: 10.1210/js.2019-00305. eCollection 2019 Dec 1. PubMed PMID: 31745526; PubMed Central PMCID: PMC6853671. Echarri MJ, Lopez-Martin A, Hitt R. Targeted Therapy in Locally Advanced and Recurrent/Metastatic Head and Neck Squamous Cell Carcinoma (LA-R/M HNSCC). Cancers (Basel). 2016 Feb 26;8(3). pii: E27. doi: 10.3390/cancers8030027. Review. PubMed PMID: 26927178; PubMed Central PMCID: PMC4810111. Grob JJ, Gonzalez Mendoza R, Basset-Seguin N, et al. LBA72 Pembrolizumab for recurrent/metastatic cutaneous squamous cell carcinoma (cSCC): efficacy and safety results from the phase II KEYNOTE-629 study. Ann Oncol. 2019;30:(mdz394.069):v908. doi: 10.1093/annonc/mdz394.069 Sylvia Adams, Peter Schmid, Hope S. Rugo, Eric P. Winer, Delphine Loirat, Ahmad Awada, David W. Cescon, Hiroji Iwata, Mario Campone, Rita Nanda, Rina Hui, Giuseppe Curigliano, Deborah Toppmeyer, Joyce O'Shaughnessy, Sherene Loi, Shani Paluch-Shimon, Deborah Card, Jing Zhao, Vassiliki Karantza, Javier Cortes. Phase 2 study of pembrolizumab (pembro) monotherapy for previously treated metastatic triple-negative breast cancer (mTNBC): KEYNOTE-086 cohort A. DOI: 10.1200/JCO.2017.35.15_suppl.1008 Journal of Clinical Oncology 35, no. 15_suppl (May 20 2017) 1008-1008. Varga, Andrea, Sarina Anne Piha-Paul, Patrick Alexander Ott, Janice M. Mehnert, Dominique Berton-Rigaud, Elizabeth A. Johnson, Jonathan D. Cheng, Sammy Yuan, Eric H. Rubin, and Daniela E. Matei. "Antitumor activity and safety of pembrolizumab in patients (pts) with PD-L1 positive advanced ovarian cancer: Interim results from a phase Ib study." (2015): 5510-5510.

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COMPOUND NAME	REFERENCES
ATEZOLIZUMAB	Mizugaki H, Yamamoto N, Murakami H, Kenmotsu H, Fujiwara Y, Ishida Y, Kawakami T, Takahashi T. Phase I dose-finding study of monotherapy with atezolizumab, an engineered immunoglobulin monoclonal antibody targeting PD-L1, in Japanese patients with advanced solid tumors. Invest New Drugs. 2016 Oct;34(5):596-603. doi: 10.1007/s10637-016-0371-6. Epub 2016 Jul 1. PubMed PMID: 27363843; PubMed Central PMCID: PMC5007272. Balar AV, Galsky MD, Rosenberg JE, Powles T, Petrylak DP, Bellmunt J, Loriot Y, Necchi A, Hoffman-Censits J, Perez-Gracia JL, Dawson NA, van der Heijden MS, Dreicer R, Srinivas S, Retz MM, Joseph RW, Drakaki A, Vaishampayan UN, Sridhar SS, Quinn DI, Durán I, Shaffer DR, Eigl BJ, Grivas PD, Yu EY, Li S, Kadel EE 3rd, Boyd Z, Bourgon R, Hegde PS, Mariathasan S, Thåström A, Abidoye OO, Fine GD, Bajorin DF; IMvigor210 Study Group. Atezolizumab as first-line treatment in cisplatin-ineligible patients with locally advanced and metastatic urothelial carcinoma: a single-arm, multicentre, phase 2 trial. Lancet. 2017 Jan 7;389(10064):67-76. doi: 10.1016/S0140-6736(16)32455-2. Epub 2016 Dec 8. PubMed PMID: 27939400; PubMed Central PMCID: PMC5568632. Mittendorf EA, Zhang H, Barrios CH, Saji S, Jung KH, Hegg R, Koehler A, Sohn J, Iwata H, Telli ML, Ferrario C, Punie K, Penault-Llorca F, Patel S, Duc AN, Liste-Hermoso M, Maiya V, Molinero L, Chui SY, Harbeck N. Neoadjuvant atezolizumab in combination with sequential nab-paclitaxel and anthracycline-based chemotherapy versus placebo and chemotherapy in patients with early-stage triple-negative breast cancer (IMpassion031): a randomised, double-blind, phase 3 trial. Lancet. 2020 Sep 18;:. doi: 10.1016/S0140-6736(20)31953-X. Epub 2020 Sep 18. PubMed PMID: 32966830. Rosenberg JE, Hoffman-Censits J, Powles T, van der Heijden MS, Balar AV, Necchi A, Dawson N, O'Donnell PH, Balmanoukian A, Loriot Y, Srinivas S, Retz MM, Grivas P, Joseph RW, Galsky MD, Fleming MT, Petrylak DP, Perez-Gracia JL, Burris HA, Castellano D, Canil C, Bellmunt J, Bajorin D, Nickles D, Bourgon R, Frampton GM, Cui N, Mariathasan S, Abidoye O, Fine GD, Dreicer R. Atezolizumab in patients with locally advanced and metastatic urothelial carcinoma who have progressed following treatment with platinum-based chemotherapy: a single-arm, multicentre, phase 2 trial. Lancet. 2016 May 7;387(10031):1909-20. doi: 10.1016/S0140-6736(16)00561-4. Epub 2016 Mar 4. PubMed PMID: 26952546; PubMed Central PMCID: PMC5480242. Galsky MD, Arija JÁA, Bamias A, Davis ID, De Santis M, Kikuchi E, Garcia-Del-Muro X, De Giorgi U, Mencinger M, Izumi K, Panni S, Gumus M, Özgüroğlu M, Kalebasty AR, Park SH, Alekseev B, Schutz FA, Li JR, Ye D, Vogelzang NJ, Bernhard S, Tayama D, Mariathasan S, Mecke A, Thåström A, Grande E, . Atezolizumab with or without chemotherapy in metastatic urothelial cancer (IMvigor130): a multicentre, randomised, placebo-controlled phase 3 trial. Lancet. 2020 05 16;395(10236):1547-1557. doi: 10.1016/S0140-6736(20)30230-0. PubMed PMID: 32416780.
SITRAVATINIB	Patwardhan PP, Ivy KS, Musi E, de Stanchina E, Schwartz GK. Significant blockade of multiple receptor tyrosine kinases by MGCD516 (Sitravatinib), a novel small molecule inhibitor, shows potent anti-tumor activity in preclinical models of sarcoma. Oncotarget. 2016 Jan 26;7(4):4093-109. doi: 10.18632/oncotarget.6547. PubMed PMID: 26675259; PubMed Central PMCID: PMC4826192.
MK-2461	Inoue K, Ohtsuka H, Tachikawa M, Motoi F, Shijo M, Douchi D, Kawasaki S, Kawaguchi K, Masuda K, Fukase K, Naitoh T, Katayose Y, Egawa S, Unno M, Terasaki T. MK2461, a Multitargeted Kinase Inhibitor, Suppresses the Progression of Pancreatic Cancer by Disrupting the Interaction Between Pancreatic Cancer Cells and Stellate Cells. Pancreas. 2017 Apr;46(4):557-566. doi: 10.1097/MPA.0000000000000778. PubMed PMID: 28196027. Katz JD, Jewell JP, Guerin DJ, Lim J, Dinsmore CJ, Deshmukh SV, Pan BS, Marshall CG, Lu W, Altman MD, Dahlberg WK, Davis L, Falcone D, Gabarda AE, Hang G, Hatch H, Holmes R, Kunii K, Lumb KJ, Lutterbach B, Mathvink R, Nazef N, Patel SB, Qu X, Reilly JF, Rickert KW, Rosenstein C, Soisson SM, Spencer KB, Szewczak AA, Walker D, Wang W, Young J, Zeng Q. Discovery of a 5H-benzo[4,5]cyclohepta[1,2-b]pyridin-5-one (MK-2461) inhibitor of c-Met kinase for the treatment of cancer. J Med Chem. 2011 Jun 23;54(12):4092-108. doi: 10.1021/jm200112k. Epub 2011 May 24. PubMed PMID: 21608528.
DANUSERTIB	Meulenbeld HJ, Mathijssen RH, Verweij J, de Wit R, de Jonge MJ. Danusertib, an aurora kinase inhibitor. Expert Opin Investig Drugs. 2012 Mar;21(3):383-93. doi: 10.1517/13543784.2012.652303. Epub 2012 Jan 13. Review. PubMed PMID: 22242557. Calvo, et al. First-in-human phase I study of LY2780301, an oral P70S6K/AKT inhibitor, in patients with refractory solid tumors. J Clin Oncol. 2012;30(Suppl):Abstr 3005.
MASITINIB	Dubreuil P, Letard S, Ciufolini M, Gros L, Humbert M, Castéran N, Borge L, Hajem B, Lermet A, Sippl W, Voisset E, Arock M, Auclair C, Leventhal PS, Mansfield CD, Moussy A, Hermine O. Masitinib (AB1010), a potent and selective tyrosine kinase inhibitor targeting KIT. PLoS One. 2009 Sep 30;4(9):e7258. doi: 10.1371/journal.pone.0007258. PubMed PMID: 19789626; PubMed Central PMCID: PMC2746281. Christiane R. Maroun1, Helene Ste-Croix1, Normand Beaulieu1, Claire Bonfils1, Marielle Fournel1, Isabelle Dupont1, Christian Lemoyne1, James Wand1, and Jeffrey M. Besterman1. Potent preclinical anti-tumor activity of MGCD265, an oral Met/VEGFR multitargeted kinase inhibitor in clinical development, in combination with taxanes. Proceedings of the 102nd Annual Meeting of the American Association for Cancer Research; 2011 Apr 2-6; Orlando, FL. Philadelphia (PA): AACR; Cancer Res 2011;71(8 Suppl):Abstract nr 3610. doi:10.1158/1538-7445.AM2011-3610.

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COMPOUND NAME	REFERENCES
CABOZANTINIB	Yakes FM, Chen J, Tan J, Yamaguchi K, Shi Y, Yu P, Qian F, Chu F, Bentzien F, Cancilla B, Orf J, You A, Laird AD, Engst S, Lee L, Lesch J, Chou YC, Joly AH. Cabozantinib (XL184), a novel MET and VEGFR2 inhibitor, simultaneously suppresses metastasis, angiogenesis, and tumor growth. Mol Cancer Ther. 2011 Dec;10(12):2298-308. doi: 10.1158/1535-7163.MCT-11-0264. Epub 2011 Sep 16. PubMed PMID: 21926191. Mulligan LM. RET revisited: expanding the oncogenic portfolio. Nat Rev Cancer. 2014 Mar;14(3):173-86. doi: 10.1038/nrc3680. Review. PubMed PMID: 24561444. Boxtel et al. A phase II study on the efficacy and toxicity of cabozantinib in recurrent/metastatic salivary gland cancer patients. Journal of Clinical Oncology. 38. 6529-6529. DOI: 10.1200/JCO.2020.38.15_suppl.6529 Italiano A, Penel N, Toulmonde M, et al. : Cabozantinib in patients with advanced osteosarcomas and Ewing sarcomas: a French Sarcoma Group (FSG)/US National Cancer Institute phase II collaborative study. Connective Tissue Oncology Society Annual Meeting Rome, Italy2018. Jennifer A. Chan, Jason Edward Faris, Janet E. Murphy, Lawrence Scott Blaszkowsky, Eunice Lee Kwak, Nadine Jackson McCleary, Charles S. Fuchs, Jeffrey A. Meyerhardt, Kimmie Ng, Andrew X. Zhu, Thomas Adam Abrams, Brian M. Wolpin, Sui Zhang, Amanda Reardon, Bridget Fitzpatrick, Matthew H. Kulke, and David P. Ryan; Phase II trial of cabozantinib in patients with carcinoid and pancreatic neuroendocrine tumors (pNET). Journal of Clinical Oncology 2017 35:4_suppl, 228-228
IPATASERTIB	Yan Y, Serra V, Prudkin L, Scaltriti M, Murli S, Rodríguez O, Guzman M, Sampath D, Nannini M, Xiao Y, Wagle MC, Wu JQ, Wongchenko M, Hampton G, Ramakrishnan V, Lackner MR, Saura C, Roda D, Cervantes A, Tabernero J, Patel P, Baselga J. Evaluation and clinical analyses of downstream targets of the Akt inhibitor GDC-0068. Clin Cancer Res. 2013 Dec 15;19(24):6976-86. doi: 10.1158/1078-0432.CCR-13-0978. Epub 2013 Oct 18. PubMed PMID: 24141624. Lin J, Sampath D, Nannini MA, Lee BB, Degtyarev M, Oeh J, Savage H, Guan Z, Hong R, Kassees R, Lee LB, Risom T, Gross S, Liederer BM, Koeppen H, Skelton NJ, Wallin JJ, Belvin M, Punnoose E, Friedman LS, Lin K. Targeting activated Akt with GDC-0068, a novel selective Akt inhibitor that is efficacious in multiple tumor models. Clin Cancer Res. 2013 Apr 1;19(7):1760-72. doi: 10.1158/1078-0432.CCR-12-3072. Epub 2013 Jan 3. PubMed PMID: 23287563. Kim SB, Dent R, Im SA, Espié M, Blau S, Tan AR, Isakoff SJ, Oliveira M, Saura C, Wongchenko MJ, Kapp AV, Chan WY, Singel SM, Maslyar DJ, Baselga J; LOTUS investigators. Ipatasertib plus paclitaxel versus placebo plus paclitaxel as first-line therapy for metastatic triple-negative breast cancer (LOTUS): a multicentre, randomised, double-blind, placebo-controlled, phase 2 trial. Lancet Oncol. 2017 Oct;18(10):1360-1372. doi: 10.1016/S1470-2045(17)30450-3. Epub 2017 Aug 8. PubMed PMID: 28800861; PubMed Central PMCID: PMC5626630.
PAXALISIB	Salphati L, Alicke B, Heffron TP, Shahidi-Latham S, Nishimura M, Cao T, Carano RA, Cheong J, Greve J, Koeppen H, Lau S, Lee LB, Nannini-Pepe M, Pang J, Plise EG, Quiason C, Rangell L, Zhang X, Gould SE, Phillips HS, Olivero AG. Brain Distribution and Efficacy of the Brain Penetrant PI3K Inhibitor GDC-0084 in Orthotopic Mouse Models of Human Glioblastoma. Drug Metab Dispos. 2016 Dec;44(12):1881-1889. Epub 2016 Sep 16. PubMed PMID: 27638506.
WX 037	Haagensen EJ, Thomas HD, Schmalix WA, Payne AC, Kevorkian L, Allen RA, Bevan P, Maxwell RJ, Newell DR. Enhanced anti-tumour activity of the combination of the novel MEK inhibitor WX-554 and the novel PI3K inhibitor WX-037. Cancer Chemother Pharmacol. 2016 Dec;78(6):1269-1281. Epub 2016 Nov 11. PubMed PMID: 27837257; PubMed Central PMCID: PMC5114336.
TASELISIB	Thorpe LM, Yuzugullu H, Zhao JJ. PI3K in cancer: divergent roles of isoforms, modes of activation and therapeutic targeting. Nat Rev Cancer. 2015 Jan;15(1):7-24. doi: 10.1038/nrc3860. Review. PubMed PMID: 25533673; PubMed Central PMCID: PMC4384662.
MLN1117	Thorpe LM, Yuzugullu H, Zhao JJ. PI3K in cancer: divergent roles of isoforms, modes of activation and therapeutic targeting. Nat Rev Cancer. 2015 Jan;15(1):7-24. doi: 10.1038/nrc3860. Review. PubMed PMID: 25533673; PubMed Central PMCID: PMC4384662.
ALPELISIB	Thorpe LM, Yuzugullu H, Zhao JJ. PI3K in cancer: divergent roles of isoforms, modes of activation and therapeutic targeting. Nat Rev Cancer. 2015 Jan;15(1):7-24. doi: 10.1038/nrc3860. Review. PubMed PMID: 25533673; PubMed Central PMCID: PMC4384662. Gobin B, Huin MB, Lamoureux F, Ory B, Charrier C, Lanel R, Battaglia S, Redini F, Lezot F, Blanchard F, Heymann D. BYL719, a new -specific PI3K inhibitor: Single administration and in combination with conventional chemotherapy for the treatment of osteosarcoma. Int J Cancer. 2014 Jun 24. doi: 10.1002/ijc.29040. [Epub ahead of print] PubMed PMID: 24961790.
GSK1059615	Carnero A. Novel inhibitors of the PI3K family. Expert Opin Investig Drugs. 2009 Sep;18(9):1265-77. doi: 10.1517/13543780903066798. Review. PubMed PMID: 19589091. Joel Greshock, Kurtis Bachman, Kurt Auger, Christopher Moy, Jeffrey Jackson, Barbara Weber, and Richard Wooster. In vitro sensitivity data suggests targeting several tumor types and molecular subtypes with the PI3K inhibitor GSK1059615 could maximize response rates in early clinical trials. AACR International Conference: Molecular Diagnostics in Cancer Therapeutic Development-- Sep 22-25, 2008; Philadelphia, PA. Clin Cancer Res October 1, 2008 14; B37.

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COMPOUND NAME	REFERENCES
MK2206	Yap TA, Yan L, Patnaik A, Fearen I, Olmos D, Papadopoulos K, Baird RD, Delgado L, Taylor A, Lupinacci L, Riisnaes R, Pope LL, Heaton SP, Thomas G, Garrett MD, Sullivan DM, de Bono JS, Tolcher AW. First-in-man clinical trial of the oral pan-AKT inhibitor MK-2206 in patients with advanced solid tumors. J Clin Oncol. 2011 Dec 10;29(35):4688-95. doi: 10.1200/JCO.2011.35.5263. Epub 2011 Oct 24. PubMed PMID: 22025163. Molife LR, Yan L, Vitfell-Rasmussen J, Zernhelt AM, Sullivan DM, Cassier PA, Chen E, Biondo A, Tetteh E, Siu LL, Patnaik A, Papadopoulos KP, de Bono JS, Tolcher AW, Minton S. Phase 1 trial of the oral AKT inhibitor MK-2206 plus carboplatin/paclitaxel, docetaxel, or erlotinib in patients with advanced solid tumors. J Hematol Oncol. 2014 Jan 3;7:1. doi: 10.1186/1756-8722-7-1. PubMed PMID: 24387695; PubMed Central PMCID: PMC3884022.
MSC 2363318A	Machl A, Wilker EW, Tian H, Liu X, Schroeder P, Clark A, Huck BR. M2698 is a potent dual-inhibitor of p70S6K and Akt that affects tumor growth in mouse models of cancer and crosses the blood-brain barrier. Am J Cancer Res. 2016;6(4):806-18. Epub 2016 Feb 15. PubMed PMID: 27186432; PubMed Central PMCID: PMC4859885. Mundi PS, Sachdev J, McCourt C, Kalinsky K. AKT in cancer: new molecular insights and advances in drug development. Br J Clin Pharmacol. 2016 Oct;82(4):943-56. doi: 10.1111/bcp.13021. Epub 2016 Jun 27. Review. PubMed PMID: 27232857; PubMed Central PMCID: PMC5137819.
SR13668	Kummar S, Doroshow JH. Phase 0 trials: expediting the development of chemoprevention agents. Cancer Prev Res (Phila). 2011 Mar;4(3):288-92. doi: 10.1158/1940-6207.CAPR-11-0013. PubMed PMID: 21372025; PubMed Central PMCID: PMC3077921. Jong L, Chao W-R, Amin K, et al. SR13668: a novel indole derived inhibitor of phospho-Akt potently suppresses tumor growth in various murine xenograft models [abstract 3684]. Proc Amer Assoc Cancer Res 2004;45.
GSK2141795	Lassen A, Atefi M, Robert L, Wong DJ, Cerniglia M, Comin-Anduix B, Ribas A. Effects of AKT inhibitor therapy in response and resistance to BRAF inhibition in melanoma. Mol Cancer. 2014 Apr 16;13:83. doi: 10.1186/1476-4598-13-83. PubMed PMID: 24735930; PubMed Central PMCID: PMC4021505.
AFURESERTIB	Spencer A, Yoon SS, Harrison SJ, Morris SR, Smith DA, Brigandi RA, Gauvin J, Kumar R, Opalinska JB, Chen C. Novel AKT inhibitor afuresertib shows favorable safety, pharmacokinetics, and clinical activity in multiple myeloma: Phase 1 study results. Blood. 2014 Jul 29. pii: blood-2014-03-559963. [Epub ahead of print] PubMed PMID: 25075128.
BAY1125976	Politz O, Siegel F, Bärfacker L, Bömer U, Hägebarth A, Scott WJ, Michels M, Ince S, Neuhaus R, Meyer K, Fernández-Montalván AE, Liu N, von Nussbaum F, Mumberg D, Ziegelbauer K. BAY 1125976, a selective allosteric AKT1/2 inhibitor, exhibits high efficacy on AKT signaling-dependent tumor growth in mouse models. Int J Cancer. 2017 Jan 15;140(2):449-459. doi: 10.1002/ijc.30457. Epub 2016 Oct 20. PubMed PMID: 27699769.
CAPIVASERTIB	Toren P, Kim S, Cordonnier T, Crafter C, Davies BR, Fazli L, Gleave ME, Zoubeidi A. Combination AZD5363 with Enzalutamide Significantly Delays Enzalutamide-resistant Prostate Cancer in Preclinical Models. Eur Urol. 2014 Aug 20. pii: S0302-2838(14)00748-9. doi: 10.1016/j.eururo.2014.08.006. [Epub ahead of print] PubMed PMID: 25151012.
AT13148	Yap TA, Walton MI, Grimshaw KM, Te Poele RH, Eve PD, Valenti MR, de Haven Brandon AK, Martins V, Zetterlund A, Heaton SP, Heinzmann K, Jones PS, Feltell RE, Reule M, Woodhead SJ, Davies TG, Lyons JF, Raynaud FI, Eccles SA, Workman P, Thompson NT, Garrett MD. AT13148 is a novel, oral multi-AGC kinase inhibitor with potent pharmacodynamic and antitumor activity. Clin Cancer Res. 2012 Jul 15;18(14):3912-23. doi: 10.1158/1078-0432.CCR-11-3313. Epub 2012 Jul 10. PubMed PMID: 22781553.
ARQ 092	Slomovitz BM, Coleman RL. The PI3K/AKT/mTOR pathway as a therapeutic target in endometrial cancer. Clin Cancer Res. 2012 Nov 1;18(21):5856-64. doi: 10.1158/1078-0432.CCR-12-0662. Epub 2012 Oct 18. Review. PubMed PMID: 23082003.
SC-66	Rashmi R, DeSelm C, Helms C, Bowcock A, Rogers BE, Rader J, Grigsby PW, Schwarz JK. AKT inhibitors promote cell death in cervical cancer through disruption of mTOR signaling and glucose uptake. PLoS One. 2014 Apr 4;9(4):e92948. doi: 10.1371/journal.pone.0092948. eCollection 2014. PubMed PMID: 24705275; PubMed Central PMCID: PMC3976291.
TRICIRIBINE	Evangelisti C, Ricci F, Tazzari P, Chiarini F, Battistelli M, Falcieri E, Ognibene A, Pagliaro P, Cocco L, McCubrey JA, Martelli AM. Preclinical testing of the Akt inhibitor triciribine in T-cell acute lymphoblastic leukemia. J Cell Physiol. 2011 Mar;226(3):822-31. doi: 10.1002/jcp.22407. PubMed PMID: 20857426.
GSK690693	Dana S. Levy, Jason A. Kahana, Rakesh Kumar. AKT inhibitor, GSK690693, induces growth inhibition and apoptosis in acute lymphoblastic leukemia cell lines. BloodFeb 2009,113(8)1723-1729;DOI: 10.1182/blood-2008-02-137737
AVELUMAB	Andrea B. Apolo, John Allan Ellerton, Jeffrey R. Infante, Manish Agrawal, Michael S. Gordon, Raid Aljumaily, Carolyn D. Britten, Luc Yves Dirix, Keun-Wook Lee, Matthew H. Taylor, Patrick Schöffski, Ding Wang, Alain Ravaud, Arnold Gelb, Junyuan Xiong, Galit Rosen, Manish R. Patel. Updated efficacy and safety of avelumab in metastatic urothelial carcinoma (mUC): Pooled analysis from 2 cohorts of the phase 1b Javelin solid tumor study. Journal of Clinical Oncology 2017 35:15_suppl, 4528-4528. Powles T, Park SH, Voog E, Caserta C, Valderrama BP, Gurney H, Kalofonos H, Radulović S, Demey W, Ullén A, Loriot Y, Sridhar SS, Tsuchiya N, Kopyltsov E, Sternberg CN, Bellmunt J, Aragon-Ching JB, Petrylak DP, Laliberte R, Wang J, Huang B, Davis C, Fowst C, Costa N, Blake-Haskins JA, di Pietro A, Grivas P. Avelumab Maintenance Therapy for Advanced or Metastatic Urothelial Carcinoma. N Engl J Med. 2020 Sep 18;:. doi: 10.1056/NEJMoa2002788. Epub 2020 Sep 18. PubMed PMID: 32945632.

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COMPOUND NAME	REFERENCES
TISLELIZUMAB	Jie Wang, Xinmin Yu, Shun Lu, Yanping Hu, Yuping Sun, Zhijie Wang, Jun Zhao, Yan Yu, Chunhong Hu, Kunyu Yang, Guosheng Feng, Kejing Ying, Wu Zhuang, Jianying Zhou, Jingxun Wu, Yanjie Wu, Xiao Lin, Liang Liang, and Nong Yang. Phase III study of tislelizumab plus chemotherapy vs chemotherapy alone as first-line (1L) treatment for advanced squamous non-small cell lung cancer (sq NSCLC). Journal of Clinical Oncology 38, no. 15_suppl (May 20, 2020) 9554-9554. doi: 10.1200/JCO.2020.38.15_suppl.9554 Song Y, Gao Q, Zhang H, Fan L, Zhou J, Zou D, Li W, Yang H, Liu T, Wang Q, Lv F, Guo H, Yang L, Elstrom R, Huang J, Novotny W, Wei V, Zhu J. Treatment of relapsed or refractory classical Hodgkin lymphoma with the anti-PD-1, tislelizumab: results of a phase 2, single-arm, multicenter study. Leukemia. 2020 02;34(2):533-542. doi: 10.1038/s41375-019-0545-2. Epub 2019 Sep 13. PubMed PMID: 31520078; PubMed Central PMCID: PMC7214259. Wang J, Lu S, Yu X, Hu Y, Sun Y, Wang Z, Zhao J, Yu Y, Hu C, Yang K, Feng G, Ying K, Zhuang W, Zhou J, Wu J, Leaw SJ, Zhang J, Lin X, Liang L, Yang N. Tislelizumab Plus Chemotherapy vs Chemotherapy Alone as First-line Treatment for Advanced Squamous Non-Small-Cell Lung Cancer: A Phase 3 Randomized Clinical Trial. JAMA Oncol. 2021 Apr 01;:. doi: 10.1001/jamaoncol.2021.0366. Epub 2021 Apr 01. PubMed PMID: 33792623.
camrelizumab	Qin S, Ren Z, Meng Z, Chen Z, Chai X, Xiong J, Bai Y, Yang L, Zhu H, Fang W, Lin X, Chen X, Li E, Wang L, Chen C, Zou J. Camrelizumab in patients with previously treated advanced hepatocellular carcinoma: a multicentre, open-label, parallel-group, randomised, phase 2 trial. Lancet Oncol. 2020 Apr;21(4):571-580. doi: 10.1016/S1470-2045(20)30011-5. Epub 2020 Feb 26. PubMed PMID: 32112738.
R-CHOP group	Stefancikova L, Moulis M, Fabian P, Vasova I, Zedek F, Ravcukova B, Muzik J, Kuglik P, Vranova V, Falkova I, Hrabalkova R, Smardova J. Prognostic impact of p53 aberrations for R-CHOP-treated patients with diffuse large B-cell lymphoma. Int J Oncol. 2011 Dec;39(6):1413-20. doi: 10.3892/ijo.2011.1170. Epub 2011 Feb 18. PubMed PMID: 21874232. Intlekofer AM, Joffe E, Batlevi CL, Hilden P, He J, Seshan VE, Zelenetz AD, Palomba ML, Moskowitz CH, Portlock C, Straus DJ, Noy A, Horwitz SM, Gerecitano JF, Moskowitz A, Hamlin P, Matasar MJ, Kumar A, van den Brink MR, Knapp KM, Pichardo JD, Nahas MK, Trabucco SE, Mughal T, Copeland AR, Papaemmanuil E, Moarii M, Levine RL, Dogan A, Miller VA, Younes A. Integrated DNA/RNA targeted genomic profiling of diffuse large B-cell lymphoma using a clinical assay. Blood Cancer J. 2018 06 12;8(6):60. doi: 10.1038/s41408-018-0089-0. Epub 2018 Feb 12. PubMed PMID: 29895903; PubMed Central PMCID: PMC5997645. Qin Y, Jiang S, Liu P, Yang J, Yang S, He X, Zhou S, Gui L, Lin J, Du X, Yi Y, Sun Y, Shi Y. Characteristics and Management of TP53-Mutated Diffuse Large B-Cell Lymphoma Patients. Cancer Manag Res. 2020;12:11515-11522. doi: 10.2147/CMAR.S269624. Epub 2020 Feb 10. PubMed PMID: 33204162; PubMed Central PMCID: PMC7666999. Rushton CK, Arthur SE, Alcaide M, Cheung M, Jiang A, Coyle KM, Cleary KLS, Thomas N, Hilton LK, Michaud N, Daigle S, Davidson J, Bushell K, Yu S, Rys RN, Jain M, Shepherd L, Marra MA, Kuruvilla J, Crump M, Mann K, Assouline S, Connors JM, Steidl C, Cragg MS, Scott DW, Johnson NA, Morin RD. Genetic and evolutionary patterns of treatment resistance in relapsed B-cell lymphoma. Blood Adv. 2020 07 14;4(13):2886-2898. doi: 10.1182/bloodadvances.2020001696. PubMed PMID: 32589730; PubMed Central PMCID: PMC7362366. Xu-Monette ZY, Wu L, Visco C, Tai YC, Tzankov A, Liu WM, Montes-Moreno S, Dybkaer K, Chiu A, Orazi A, Zu Y, Bhagat G, Richards KL, Hsi ED, Zhao XF, Choi WW, Zhao X, van Krieken JH, Huang Q, Huh J, Ai W, Ponzoni M, Ferreri AJ, Zhou F, Kahl BS, Winter JN, Xu W, Li J, Go RS, Li Y, Piris MA, Møller MB, Miranda RN, Abruzzo LV, Medeiros LJ, Young KH. Mutational profile and prognostic significance of TP53 in diffuse large B-cell lymphoma patients treated with R-CHOP: report from an International DLBCL Rituximab-CHOP Consortium Program Study. Blood. 2012 Nov 8;120(19):3986-96. doi: 10.1182/blood-2012-05-433334. Epub 2012 Sep 5. PubMed PMID: 22955915; PubMed Central PMCID: PMC3496956.
SUGEMALIMAB	C. Zhou, Z. Wang, Y. Sun, L. Cao, Z. Ma, R. Wu, Y. Yu, W. Yao, J. Chang, J. Chen, W. Zhuang, J. Cui, X. Chen, Y. Lu, H. Shen, P. Li, J. Wang, B. Sun, D. Lu, J. Yang. LBA4 - GEMSTONE-302: A phase III study of platinum-based chemotherapy (chemo) with placebo or CS1001, an anti-PDL1 antibody, for first-line (1L) advanced non-small cell lung cancer (NSCLC). Annals of Oncology (2020) 31 (suppl_6): S1386-S1406. 10.1016/annonc/annonc367
GEPTANOLIMAB	Yuankai Shi, Jianqiu Wu, Zhen Wang, Liling Zhang, Zhao Wang, Mingzhi Zhang, Hong Cen, Zhigang Peng, Yufu Li, Lei Fan, Ye Guo, Liping Ma, Jie Cui, Yuhuan Gao, Haiyan Yang, Hongyu Zhang, Lin Wang, Weihua Zhang, Huilai Zhang, Liping Xie, Ming Jiang, Hui Zhou, Yuerong Shuang, Hang Su, Xiaoyan Ke, Chuan Jin, Xin Du, Xin Du, Li Liu, Yaming Xi, Zheng Ge, Ru Feng, Yang Zhang, Shengyu Zhou, Fan Xie and Chao Gao. Abstract CT041: The efficacy and safety of Geptanolimab (GB226) in patients with relapsed/refractory peripheral T cell lymphoma (PTCL): A multicenter, open-label, single-arm, phase 2 trial. DOI: 10.1158/1538-7445.AM2020-CT041 Published August 2020
DOSTARLIMAB	OAKNIN, A., et al. Preliminary safety, efficacy, and pharmacokinetic/pharmacodynamic characterization from GARNET, a phase I/II clinical trial of the anti–PD-1 monoclonal antibody, TSR-042, in patients with recurrent or advanced MSI-h and MSS endometrial cancer. Gynecologic Oncology, 2019, 154: 17.
DURVALUMAB	Robin Kate Kelley, Bruno Sangro, William Proctor Harris, Masafumi Ikeda, Takuji Okusaka, Yoon-Koo Kang, Shukui Qin, Wai Meng David Tai, Ho Yeong Lim, Thomas Yau, Wei-Peng Yong, Ann-Lii Cheng, Antonio Gasbarrini, Filippo G. De Braud, Jordi Bruix, Mitesh J. Borad, Philip He, Alejandra Negro, Masatoshi Kudo, and Ghassan K. Abou-Alfa. Efficacy, tolerability, and biologic activity of a novel regimen of tremelimumab (T) in combination with durvalumab (D) for patients (pts) with advanced hepatocellular carcinoma (aHCC). Journal of Clinical Oncology 2020 38: 15_suppl, 4508-4508. doi: 10.1200/JCO.2020.38.15_suppl.4508 Patrick M. Forde, Zhuoxin Sun, Valsamo Anagnostou, Hedy L. Kindler, William T. Purcell, Bernardo H. L. Goulart, Arkadiusz Z. Dudek, Hossein Borghaei, Julie R. Brahmer, and Suresh S. Ramalingam. PrE0505: Phase II multicenter study of anti-PD-L1, durvalumab, in combination with cisplatin and pemetrexed for the first-line treatment of unresectable malignant pleural mesothelioma (MPM)—A PrECOG LLC study. Journal of Clinical Oncology. May 25, 2020;38(15_suppl):9003-9003. doi: 10.1200/JCO.2020.38.15_suppl.9003

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COMPOUND NAME	REFERENCES
SINTILIMAB	Yang Y, Wang Z, Fang J, Yu Q, Han B, Cang S, Chen G, Mei X, Yang Z, Ma R, Bi M, Ren X, Zhou J, Li B, Song Y, Feng J, Li J, He Z, Zhou R, Li W, Lu Y, Wang Y, Wang L, Yang N, Zhang Y, Yu Z, Zhao Y, Xie C, Cheng Y, Zhou H, Wang S, Zhu D, Zhang W, Zhang L. Efficacy and Safety of Sintilimab Plus Pemetrexed and Platinum as First-Line Treatment for Locally Advanced or Metastatic Nonsquamous NSCLC: a Randomized, Double-Blind, Phase 3 Study (Oncology pRogram by InnovENT anti-PD-1-11). J Thorac Oncol. 2020 Oct;15(10):1636-1646. doi: 10.1016/j.jtho.2020.07.014. Epub 2020 Oct 08. PubMed PMID: 32781263.
CEMIPLIMAB	A. Sezer, S. Kilickap, M. Gümüş, I. Bondarenko, M. Özgüroğlu, M. Gogishvili, H.M. Turk, İ. Çiçin, D. Bentsion, O. Gladkov, P. Clingan, V. Sriuranpong, N. Rizvi, S. Li, S. Lee, G. Gullo, I. Lowy, P. Rietschel. LBA52 EMPOWER-Lung 1: Phase III first-line (1L) cemiplimab monotherapy vs platinum-doublet chemotherapy (chemo) in advanced non-small cell lung cancer (NSCLC) with programmed cell death-ligand 1 (PD-L1) 50%. Annals of Oncology, Volume 31, S1182 - S1183. doi: 10.1016/j.annonc.2020.08.2285
TORIPALIMAB	Fu J, Wang F, Dong LH, Zhang J, Deng CL, Wang XL, Xie XY, Zhang J, Deng RX, Zhang LB, Wu H, Feng H, Chen B, Song HF. Preclinical evaluation of the efficacy, pharmacokinetics and immunogenicity of JS-001, a programmed cell death protein-1 (PD-1) monoclonal antibody. Acta Pharmacol Sin. 2017 May;38(5):710-718. doi: 10.1038/aps.2016.161. Epub 2017 Oct 20. PubMed PMID: 28317872; PubMed Central PMCID: PMC5457696.
ABBV-181	POWDERLY, J., et al. 438P Safety and efficacy of the PD-1 inhibitor ABBV-181 in patients with advanced solid tumors: Preliminary phase I results from study M15-891. Annals of Oncology, 2018, 29.suppl_8: mdy279. 425.
BINTRAFUSP ALFA	Lan Y, Zhang D, Xu C, Hance KW, Marelli B, Qi J, Yu H, Qin G, Sircar A, Hernández VM, Jenkins MH, Fontana RE, Deshpande A, Locke G, Sabzevari H, Radvanyi L, Lo KM. Enhanced preclinical antitumor activity of M7824, a bifunctional fusion protein simultaneously targeting PD-L1 and TGF-. Sci Transl Med. 2018 01 17;10(424):. doi: 10.1126/scitranslmed.aan5488. PubMed PMID: 29343622.
PACMILIMAB	Fiona Thistlethwaite, Aung Naing, Marta Gil-Martin, Patricia LoRusso, Manreet Randhawa, Ferry Eskens, Rachel E. Sanborn, Nataliya Volodymyrivna Uboha, Daniel C. Cho, Alexander I. Spira, Igor Bondarenko, Elizabeth Ruth Plummer, Javier Garcia-Corbacho, Iván Victoria, Javier Lavernia, Ignacio Melero, Elisabeth De Vries, William Garner, Hendrik-Tobias Arkenau, Johanna C. Bendell. PROCLAIM-CX-072: Analysis of patients with advanced solid tumors receiving long-term treatment with CX-072, a PD-L1 probody therapeutic, as a single agent or in combination with ipilimumab. Journal of Clinical Oncology 38, no. 15_suppl (May 20, 2020) 3005-3005. doi: 10.1200/JCO.2020.38.15_suppl.3005
MDX-1105	Brahmer JR, Tykodi SS, Chow LQ, Hwu WJ, Topalian SL, Hwu P, Drake CG, Camacho LH, Kauh J, Odunsi K, Pitot HC, Hamid O, Bhatia S, Martins R, Eaton K, Chen S, Salay TM, Alaparthy S, Grosso JF, Korman AJ, Parker SM, Agrawal S, Goldberg SM, Pardoll DM, Gupta A, Wigginton JM. Safety and activity of anti-PD-L1 antibody in patients with advanced cancer. N Engl J Med. 2012 Jun 28;366(26):2455-65. doi: 10.1056/NEJMoa1200694. Epub 2012 Jun 2. PubMed PMID: 22658128; PubMed Central PMCID: PMC3563263.
XL-092	Hsu J et al. XL092, A multi-targeted inhibitor of MET, VEGFR2, AXL and MER with an optimized pharmacokinetic profile. European Journal of Cancer.32nd EORTC-NCI-AACR Symposium on Molecular Targets and Cancer Therapeutics. Volume 138, S16. doi: 10.1016/S0959-8049(20)31107-2.
SAVOLITINIB	Gavine PR, Ren Y, Han L, Lv J, Fan S, Zhang W, Xu W, Liu YJ, Zhang T, Fu H, Yu Y, Wang H, Xu S, Zhou F, Su X, Yin X, Xie L, Wang L, Qing W, Jiao L, Su W, Wang QM. Volitinib, a potent and highly selective c-Met inhibitor, effectively blocks c-Met signaling and growth in c-MET amplified gastric cancer patient-derived tumor xenograft models. Mol Oncol. 2014 Sep 10. pii: S1574-7891(14)00210-5. doi: 10.1016/j.molonc.2014.08.015. [Epub ahead of print] PubMed PMID: 25248999.
FORETINIB	Zillhardt M, Park SM, Romero IL, Sawada K, Montag A, Krausz T, Yamada SD, Peter ME, Lengyel E. Foretinib (GSK1363089), an orally available multikinase inhibitor of c-Met and VEGFR-2, blocks proliferation, induces anoikis, and impairs ovarian cancer metastasis. Clin Cancer Res. 2011 Jun 15;17(12):4042-51. doi: 10.1158/1078-0432.CCR-10-3387. Epub 2011 May 6. PubMed PMID: 21551255; PubMed Central PMCID: PMC3169439. Qian F, Engst S, Yamaguchi K, Yu P, Won KA, Mock L, Lou T, Tan J, Li C, Tam D, Lougheed J, Yakes FM, Bentzien F, Xu W, Zaks T, Wooster R, Greshock J, Joly AH. Inhibition of tumor cell growth, invasion, and metastasis by EXEL-2880 (XL880, GSK1363089), a novel inhibitor of HGF and VEGF receptor tyrosine kinases. Cancer Res. 2009 Oct 15;69(20):8009-16. doi: 10.1158/0008-5472.CAN-08-4889. Epub 2009 October 06. PubMed PMID: 19808973.
CAPMATINIB	Liu X, Wang Q, Yang G, Marando C, Koblish HK, Hall LM, Fridman JS, Behshad E, Wynn R, Li Y, Boer J, Diamond S, He C, Xu M, Zhuo J, Yao W, Newton RC, Scherle PA. A novel kinase inhibitor, INCB28060, blocks c-MET-dependent signaling, neoplastic activities, and cross-talk with EGFR and HER-3. Clin Cancer Res. 2011 Nov 15;17(22):7127-38. doi: 10.1158/1078-0432.CCR-11-1157. Epub 2011 Sep 14. PubMed PMID: 21918175.
SGX523	Buchanan SG, Hendle J, Lee PS, Smith CR, Bounaud PY, Jessen KA, Tang CM, Huser NH, Felce JD, Froning KJ, Peterman MC, Aubol BE, Gessert SF, Sauder JM, Schwinn KD, Russell M, Rooney IA, Adams J, Leon BC, Do TH, Blaney JM, Sprengeler PA, Thompson DA, Smyth L, Pelletier LA, Atwell S, Holme K, Wasserman SR, Emtage S, Burley SK, Reich SH. SGX523 is an exquisitely selective, ATP-competitive inhibitor of the MET receptor tyrosine kinase with antitumor activity in vivo. Mol Cancer Ther. 2009 Dec;8(12):3181-90. doi: 10.1158/1535-7163.MCT-09-0477. Epub . PubMed PMID: 19934279.
SAR125844	Laurent Schio1, Conception Nemecek1, Antonio Ugolini1, Sylvie Wentzler1, Sandrine Grapinet1, Jean Khider1, Eva Albert1, Nathalie Dischamps1, Frédéric Gay1, Véronique Sonnefraud1, Eric Bacqué1, Mireille Kenigsberg1, Hélène Goulaouic1, Anne Dagallier2, François Vallée2, Fabrice Bonche3, and Christoph Lengauer1. SAR125844: a potent and selective ATP-competitive inhibitor of MET kinase. Proceedings of the 103rd Annual Meeting of the American Association for Cancer Research; 2012 Mar 31-Apr 4; Chicago, IL. Philadelphia (PA): AACR; Cancer Res 2012;72(8 Suppl):Abstract nr 2911. doi:1538-7445.AM2012-2911.
ONARTUZUMAB	Merchant M, Ma X, Maun HR, Zheng Z, Peng J, Romero M, Huang A, Yang NY, Nishimura M, Greve J, Santell L, Zhang YW, Su Y, Kaufman DW, Billeci KL, Mai E, Moffat B, Lim A, Duenas ET, Phillips HS, Xiang H, Young JC, Vande Woude GF, Dennis MS, Reilly DE, Schwall RH, Starovasnik MA, Lazarus RA, Yansura DG. Monovalent antibody design and mechanism of action of onartuzumab, a MET antagonist with anti-tumor activity as a therapeutic agent. Proc Natl Acad Sci U S A. 2013 Aug 6;110(32):E2987-96. doi: 10.1073/pnas.1302725110. Epub 2013 Jul 23. PubMed PMID: 23882082; PubMed Central PMCID: PMC3740879.

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COMPOUND NAME	REFERENCES
PF-04217903	Zou HY, Li Q, Lee JH, Arango ME, Burgess K, Qiu M, Engstrom LD, Yamazaki S, Parker M, Timofeevski S, Cui JJ, McTigue M, Los G, Bender SL, Smeal T, Christensen JG. Sensitivity of selected human tumor models to PF-04217903, a novel selective c-Met kinase inhibitor. Mol Cancer Ther. 2012 Apr;11(4):1036-47. doi: 10.1158/1535-7163.MCT-11-0839. Epub 2012 Mar 2. PubMed PMID: 22389468.
TEPOTINIB	Bladt F, Faden B, Friese-Hamim M, Knuehl C, Wilm C, Fittschen C, Grädler U, Meyring M, Dorsch D, Jaehrling F, Pehl U, Stieber F, Schadt O, Blaukat A. EMD 1214063 and EMD 1204831 constitute a new class of potent and highly selective c-Met inhibitors. Clin Cancer Res. 2013 Jun 1;19(11):2941-51. doi: 10.1158/1078-0432.CCR-12-3247. Epub 2013 Apr 3. PubMed PMID: 23553846.
EMD 1204831	Bladt F, Faden B, Friese-Hamim M, Knuehl C, Wilm C, Fittschen C, Grädler U, Meyring M, Dorsch D, Jaehrling F, Pehl U, Stieber F, Schadt O, Blaukat A. EMD 1214063 and EMD 1204831 constitute a new class of potent and highly selective c-Met inhibitors. Clin Cancer Res. 2013 Jun 1;19(11):2941-51. doi: 10.1158/1078-0432.CCR-12-3247. Epub 2013 Apr 3. PubMed PMID: 23553846.
GOLVATINIB	Wang W, Li Q, Takeuchi S, Yamada T, Koizumi H, Nakamura T, Matsumoto K, Mukaida N, Nishioka Y, Sone S, Nakagawa T, Uenaka T, Yano S. Met kinase inhibitor E7050 reverses three different mechanisms of hepatocyte growth factor-induced tyrosine kinase inhibitor resistance in EGFR mutant lung cancer. Clin Cancer Res. 2012 Mar 15;18(6):1663-71. doi: 10.1158/1078-0432.CCR-11-1171. Epub 2012 Feb 8. PubMed PMID: 22317763.
TIVANTINIB	Previdi S, Abbadessa G, Dalò F, France DS, Broggini M. Breast cancer-derived bone metastasis can be effectively reduced through specific c-MET inhibitor tivantinib (ARQ 197) and shRNA c-MET knockdown. Mol Cancer Ther. 2012 Jan;11(1):214-23. doi: 10.1158/1535-7163.MCT-11-0277. Epub 2011 Oct 25. PubMed PMID: 22027690.
AMG 337	Paul E. Hughes, Yajing Yang, Karen Rex, Yihong Zhang, Paula J. Kaplan-Lefko, Sean Caenepeel, Jodi Moriguchi, Martin Broome, Deborah Choquette, Robert Radinsky, Richard Kendall, Angela Coxon, and Isabelle Dussault. AMG 337, a novel, potent and selective MET kinase inhibitor, has robust growth inhibitory activity in MET-dependent cancer models. doi: 10.1158/1538-7445.AM2014-728 Cancer Res October 1, 2014 74; 728.
AMG 208	David S. Hong, Peter J. Rosen, A. Craig Lockhart, Siqing Fu, Filip Janku, Razelle Kurzrock, Rabia Khan, Benny Amore, Isaac Caudillo, Hongjie Deng, Yuying C. Hwang, Robert D. Loberg, Poornima Shubhakar, Stephen Zoog, Darrin M. Beaupre, Peter Lee; The University of Texas MD Anderson Cancer Center, Houston, TX; Tower Cancer Research Foundation, Beverly Hills, CA; Washington University School of Medicine, St. Louis, MO; Amgen Inc., Seattle, WA; Amgen Inc., Thousand Oaks, CA. First-in-human study of AMG 208, an oral MET inhibitor, in adult patients (pts) with advanced solid tumors. J Clin Oncol 31, 2013 (suppl 6; abstr 41)
RILOTUMUMAB	Burgess TL, Sun J, Meyer S, Tsuruda TS, Sun J, Elliott G, Chen Q, Haniu M, Barron WF, Juan T, Zhang K, Coxon A, Kendall RL. Biochemical characterization of AMG 102: a neutralizing, fully human monoclonal antibody to human and nonhuman primate hepatocyte growth factor. Mol Cancer Ther. 2010 Feb;9(2):400-9. doi: 10.1158/1535-7163.MCT-09-0824. Epub 2010 Feb 2. PubMed PMID: 20124448.
VANDETANIB	Carlomagno F, Vitagliano D, Guida T, Ciardiello F, Tortora G, Vecchio G, Ryan AJ, Fontanini G, Fusco A, Santoro M. ZD6474, an orally available inhibitor of KDR tyrosine kinase activity, efficiently blocks oncogenic RET kinases. Cancer Res. 2002 Dec 15;62(24):7284-90. PubMed PMID: 12499271. Sarkar S, Mazumdar A, Dash R, Sarkar D, Fisher PB, Mandal M. ZD6474, a dual tyrosine kinase inhibitor of EGFR and VEGFR-2, inhibits MAPK/ERK and AKT/PI3-K and induces apoptosis in breast cancer cells. Cancer Biol Ther. 2010 Apr 15;9(8):592-603. Epub 2010 Apr 4. PubMed PMID: 20139705. Mulligan LM. RET revisited: expanding the oncogenic portfolio. Nat Rev Cancer. 2014 Mar;14(3):173-86. doi: 10.1038/nrc3680. Review. PubMed PMID: 24561444. Fox E, Widemann BC, Chuk MK, Marcus L, Aikin A, Whitcomb PO, Merino MJ, Lodish M, Dombi E, Steinberg SM, Wells SA, Balis FM. Vandetanib in children and adolescents with multiple endocrine neoplasia type 2B associated medullary thyroid carcinoma. Clin Cancer Res. 2013 Aug 1;19(15):4239-48. doi: 10.1158/1078-0432.CCR-13-0071. Epub 2013 Jun 13. PubMed PMID: 23766359. Inoue K, Torimura T, Nakamura T, Iwamoto H, Masuda H, Abe M, Hashimoto O, Koga H, Ueno T, Yano H, Sata M. Vandetanib, an inhibitor of VEGF receptor-2 and EGF receptor, suppresses tumor development and improves prognosis of liver cancer in mice. Clin Cancer Res. 2012 Jul 15;18(14):3924-33. doi: 10.1158/1078-0432.CCR-11-2041. Epub 2012 May 18. PubMed PMID: 22611027.
CI-1040	Rinehart J, Adjei AA, Lorusso PM, Waterhouse D, Hecht JR, Natale RB, Hamid O, Varterasian M, Asbury P, Kaldjian EP, Gulyas S, Mitchell DY, Herrera R, Sebolt-Leopold JS, Meyer MB. Multicenter phase II study of the oral MEK inhibitor, CI-1040, in patients with advanced non-small-cell lung, breast, colon, and pancreatic cancer. J Clin Oncol. 2004 Nov 15;22(22):4456-62. Epub 2004 Oct 13. PubMed PMID: 15483017.
NECITUMUMAB	" Kuenen B, Witteveen PO, Ruijter R, Giaccone G, Dontabhaktuni A, Fox F, Katz T, Youssoufian H, Zhu J, Rowinsky EK, Voest EE. A phase I pharmacologic study of necitumumab (IMC-11F8), a fully human IgG1 monoclonal antibody directed against EGFR in patients with advanced solid malignancies. Clin Cancer Res. 2010 Mar 15;16(6):1915-23. doi: 10.1158/1078-0432.CCR-09-2425. Epub 2010 Mar 2. Erratum in: Clin Cancer Res. 2010 Sep 15;16(18):4681. Dosage error in article text. PubMed PMID: 20197484. " Garnock-Jones KP. Necitumumab: First Global Approval. Drugs. 2016 Feb;76(2):283-9. doi: 10.1007/s40265-015-0537-0. PubMed PMID: 26729188. Paz-Ares L, Socinski MA, Shahidi J, Hozak RR, Soldatenkova V, Kurek R, Varella-Garcia M, Thatcher N, Hirsch FR. Correlation of EGFR-expression with safety and efficacy outcomes in SQUIRE: a randomized, multicenter, open-label, phase III study of gemcitabine-cisplatin plus necitumumab versus gemcitabine-cisplatin alone in the first-line treatment of patients with stage IV squamous non-small-cell lung cancer. Ann Oncol. 2016 Aug;27(8):1573-9. doi: 10.1093/annonc/mdw214. Epub 2016 May 20. PubMed PMID: 27207107; PubMed Central PMCID: PMC4959928.

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COMPOUND NAME	REFERENCES
AFATINIB	" Yu HA, Riely GJ. Second-generation epidermal growth factor receptor tyrosine kinase inhibitors in lung cancers. J Natl Compr Canc Netw. 2013 Feb 1;11(2):161-9. PubMed PMID: 23411383; PubMed Central PMCID: PMC3673302." Eskens FA, Mom CH, Planting AS, Gietema JA, Amelsberg A, Huisman H, van Doorn L, Burger H, Stopfer P, Verweij J, de Vries EG. A phase I dose escalation study of BIBW 2992, an irreversible dual inhibitor of epidermal growth factor receptor 1 (EGFR) and 2 (HER2) tyrosine kinase in a 2-week on, 2-week off schedule in patients with advanced solid tumours. Br J Cancer. 2008 Jan 15;98(1):80-5. Epub 2007 Nov 20. PubMed PMID: 18026190; PubMed Central PMCID: PMC2359721. Li D, Ambrogio L, Shimamura T, Kubo S, Takahashi M, Chirieac LR, Padera RF, Shapiro GI, Baum A, Himmelsbach F, Rettig WJ, Meyerson M, Solca F, Greulich H, Wong KK. BIBW2992, an irreversible EGFR/HER2 inhibitor highly effective in preclinical lung cancer models. Oncogene. 2008 Aug 7;27(34):4702-11. doi: 10.1038/onc.2008.109. Epub 2008 Apr 14. PubMed PMID: 18408761; PubMed Central PMCID: PMC2748240. Echarri MJ, Lopez-Martin A, Hitt R. Targeted Therapy in Locally Advanced and Recurrent/Metastatic Head and Neck Squamous Cell Carcinoma (LA-R/M HNSCC). Cancers (Basel). 2016 Feb 26;8(3). pii: E27. doi: 10.3390/cancers8030027. Review. PubMed PMID: 26927178; PubMed Central PMCID: PMC4810111. Schuler M, Awada A, Harter P, Canon JL, Possinger K, Schmidt M, De Grève J, Neven P, Dirix L, Jonat W, Beckmann MW, Schütte J, Fasching PA, Gottschalk N, Besse-Hammer T, Fleischer F, Wind S, Uttenreuther-Fischer M, Piccart M, Harbeck N. A phase II trial to assess efficacy and safety of afatinib in extensively pretreated patients with HER2-negative metastatic breast cancer. Breast Cancer Res Treat. 2012 Aug;134(3):1149-59. doi: 10.1007/s10549-012-2126-1. Epub 2012 Jul 5. PubMed PMID: 22763464; PubMed Central PMCID: PMC3409367.
PETOSEMTAMAB	Abstract 32: Preclinical evaluation of MCLA-158: A bispecific antibody targeting LGR5 and EGFR using patient-derived colon carcinoma organoids
ZALUTUMUMAB	Saloura V, Cohen EE, Licitra L, Billan S, Dinis J, Lisby S, Gauler TC. An open-label single-arm, phase II trial of zalutumumab, a human monoclonal anti-EGFR antibody, in patients with platinum-refractory squamous cell carcinoma of the head and neck. Cancer Chemother Pharmacol. 2014 Jun;73(6):1227-39. doi: 10.1007/s00280-014-2459-z. Epub 2014 Apr 9. PubMed PMID: 24714973. Echarri MJ, Lopez-Martin A, Hitt R. Targeted Therapy in Locally Advanced and Recurrent/Metastatic Head and Neck Squamous Cell Carcinoma (LA-R/M HNSCC). Cancers (Basel). 2016 Feb 26;8(3). pii: E27. doi: 10.3390/cancers8030027. Review. PubMed PMID: 26927178; PubMed Central PMCID: PMC4810111.
DACOMITINIB	Ramalingam SS, Blackhall F, Krzakowski M, Barrios CH, Park K, Bover I, Seog Heo D, Rosell R, Talbot DC, Frank R, Letrent SP, Ruiz-Garcia A, Taylor I, Liang JQ, Campbell AK, O'Connell J, Boyer M. Randomized phase II study of dacomitinib (PF-00299804), an irreversible pan-human epidermal growth factor receptor inhibitor, versus erlotinib in patients with advanced non-small-cell lung cancer. J Clin Oncol. 2012 Sep 20;30(27):3337-44. doi: 10.1200/JCO.2011.40.9433. Epub 2012 Jul 2. PubMed PMID: 22753918. Echarri MJ, Lopez-Martin A, Hitt R. Targeted Therapy in Locally Advanced and Recurrent/Metastatic Head and Neck Squamous Cell Carcinoma (LA-R/M HNSCC). Cancers (Basel). 2016 Feb 26;8(3). pii: E27. doi: 10.3390/cancers8030027. Review. PubMed PMID: 26927178; PubMed Central PMCID: PMC4810111.
SIMOTINIB	He L, Li S, Xie F, Cheng Z, Ran L, Liu X, Yu P. LC-ESI-MS/MS determination of simotinib, a novel epidermal growth factor receptor tyrosine kinase inhibitor: application to a pharmacokinetic study. J Chromatogr B Analyt Technol Biomed Life Sci. 2014 Feb 1;947-948:168-72. doi: 10.1016/j.jchromb.2013.12.021. Epub 2013 Dec 27. PubMed PMID: 24440798.
MATUZUMAB	Schmiedel J, Blaukat A, Li S, Knöchel T, Ferguson KM. Matuzumab binding to EGFR prevents the conformational rearrangement required for dimerization. Cancer Cell. 2008 Apr;13(4):365-73. doi: 10.1016/j.ccr.2008.02.019. PubMed PMID: 18394559; PubMed Central PMCID: PMC2725356.
H 447	Fury MG, Lipton A, Smith KM, Winston CB, Pfister DG. A phase-I trial of the epidermal growth factor receptor directed bispecific antibody MDX-447 without and with recombinant human granulocyte-colony stimulating factor in patients with advanced solid tumors. Cancer Immunol Immunother. 2008 Feb;57(2):155-63. Epub 2007 Jun 30. PubMed PMID: 17602224.
IMGATUZUMAB	Gerdes CA, Nicolini VG, Herter S, van Puijenbroek E, Lang S, Roemmele M, Moessner E, Freytag O, Friess T, Ries CH, Bossenmaier B, Mueller HJ, Umaña P. GA201 (RG7160): a novel, humanized, glycoengineered anti-EGFR antibody with enhanced ADCC and superior in vivo efficacy compared with cetuximab. Clin Cancer Res. 2013 Mar 1;19(5):1126-38. doi: 10.1158/1078-0432.CCR-12-0989. Epub 2012 Dec 3. PubMed PMID: 23209031.
BIBX 1382	Solca FF, Baum A, Langkopf E, Dahmann G, Heider KH, Himmelsbach F, van Meel JC. Inhibition of epidermal growth factor receptor activity by two pyrimidopyrimidine derivatives. J Pharmacol Exp Ther. 2004 Nov;311(2):502-9. Epub 2004 Jun 15. PubMed PMID: 15199094.
PKI 166	Bruns CJ, Solorzano CC, Harbison MT, Ozawa S, Tsan R, Fan D, Abbruzzese J, Traxler P, Buchdunger E, Radinsky R, Fidler IJ. Blockade of the epidermal growth factor receptor signaling by a novel tyrosine kinase inhibitor leads to apoptosis of endothelial cells and therapy of human pancreatic carcinoma. Cancer Res. 2000 Jun 1;60(11):2926-35. PubMed PMID: 10850439.
XILIERTINIB	Ren Y, Zheng J, Fan S, Wang L, Cheng M, Shi D, Zhang W, Tang R, Yu Y, Jiao L, Ni J, Yang H, Cai H, Yin F, Chen Y, Zhou F, Zhang W, Qing W, Su W. Anti-tumor efficacy of theliatinib in esophageal cancer patient-derived xenografts models with epidermal growth factor receptor (EGFR) overexpression and gene amplification. Oncotarget. 2017 Apr 19. doi: 10.18632/oncotarget.17243. [Epub ahead of print] PubMed PMID: 28472779.
TESEVATINIB	Gendreau SB, Ventura R, Keast P, Laird AD, Yakes FM, Zhang W, Bentzien F, Cancilla B, Lutman J, Chu F, Jackman L, Shi Y, Yu P, Wang J, Aftab DT, Jaeger CT, Meyer SM, De Costa A, Engell K, Chen J, Martini JF, Joly AH. Inhibition of the T790M gatekeeper mutant of the epidermal growth factor receptor by EXEL-7647. Clin Cancer Res. 2007 Jun 15;13(12):3713-23. PubMed PMID: 17575237.

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COMPOUND NAME	REFERENCES
JNJ-26483327	Gijsen M, King P, Perera T, Parker PJ, Harris AL, Larijani B, Kong A. HER2 phosphorylation is maintained by a PKB negative feedback loop in response to anti-HER2 herceptin in breast cancer. PLoS Biol. 2010 Dec 21;8(12): e1000563. doi: 10.1371/journal.pbio.1000563. Erratum in: PLoS Biol. 2016 Mar;14(3):e1002414. PubMed PMID: 21203579; PubMed Central PMCID: PMC3006345. Konings IR, de Jonge MJ, Burger H, van der Gaast A, van Beijsterveldt LE, Winkler H, Verweij J, Yuan Z, Hellemans P, Eskens FA. Phase I and pharmacological study of the broad-spectrum tyrosine kinase inhibitor JNJ-26483327 in patients with advanced solid tumours. Br J Cancer. 2010 Sep 28;103(7):987-92. doi: 10.1038/sj.bjc.6605867. Epub 2010 Sep 7. PubMed PMID: 20823884; PubMed Central PMCID: PMC2965873.
EPERTINIB	Spicer J, Baird R, Suder A, Cresti N, Corbacho JG, Hogarth L, Frenkel E, Matsumoto S, Kawabata I, Donaldson K, Posner J, Sarker D, Jodrell D, Plummer R. Phase 1 dose-escalation study of S-222611, an oral reversible dual tyrosine kinase inhibitor of EGFR and HER2, in patients with solid tumours. Eur J Cancer. 2015 Jan;51(2):137-45. doi: 10.1016/j.ejca.2014.11.003. Epub 2014 Nov 27. PubMed PMID: 25434923.
NIMOTUZUMAB	"Huang Y, Yu T, Fu X, Chen J, Liu Y, Li C, Xia Y, Zhang Z, Li L. EGFR inhibition prevents in vitro tumor growth of salivary adenoid cystic carcinoma. BMC Cell Biol. 2013 Mar 9;14:13. doi: 10.1186/1471-2121-14-13. PubMed PMID: 23496982; PubMed Central PMCID: PMC3610144." " Su D, Jiao SC, Wang LJ, Shi WW, Long YY, Li J, Bai L. Efficacy of nimotuzumab plus gemcitabine usage as first-line treatment in patients with advanced pancreatic cancer. Tumour Biol. 2014 Mar;35(3):2313-8. doi: 10.1007/s13277-013-1306-x. Epub 2013 Oct 19. PubMed PMID: 24142531. " "Chen YJ, Chi CW, Su WC, Huang HL. Lapatinib induces autophagic cell death and inhibits growth of human hepatocellular carcinoma. Oncotarget. 2014 Jul 15;5(13):4845-54. PubMed PMID: 24947784; PubMed Central PMCID: PMC4148104."
MEHD7945A	Huang S, Li C, Armstrong EA, Peet CR, Saker J, Amler LC, Sliwkowski MX, Harari PM. Dual targeting of EGFR and HER3 with MEHD7945A overcomes acquired resistance to EGFR inhibitors and radiation. Cancer Res. 2013 Jan 15; 73(2):824-33. doi: 10.1158/0008-5472.CAN-12-1611. Epub 2012 Nov 20. PubMed PMID: 23172311.
OSIMERTINIB	Cross DA, Ashton SE, Ghiorghiu S, Eberlein C, Nebhan CA, Spitzler PJ, Orme JP, Finlay MR, Ward RA, Mellor MJ, Hughes G, Rahi A, Jacobs VN, Red Brewer M, Ichihara E, Sun J, Jin H, Ballard P, Al-Kadhimi K, Rowlinson R, Klinowska T, Richmond GH, Cantarini M, Kim DW, Ranson MR, Pao W. AZD9291, an irreversible EGFR TKI, overcomes T790M-mediated resistance to EGFR inhibitors in lung cancer. Cancer Discov. 2014 Sep;4(9):1046-61. doi: 10.1158/2159-8290.CD-14-0337. Epub 2014 Jun 3. PubMed PMID: 24893891.
TAK-285	Ishikawa T, Seto M, Banno H, Kawakita Y, Oorui M, Taniguchi T, Ohta Y, Tamura T, Nakayama A, Miki H, Kamiguchi H, Tanaka T, Habuka N, Sogabe S, Yano J, Aertgeerts K, Kamiyama K. Design and synthesis of novel human epidermal growth factor receptor 2 (HER2)/epidermal growth factor receptor (EGFR) dual inhibitors bearing a pyrrolo[3,2-d]pyrimidine scaffold. J Med Chem. 2011 Dec 8;54(23):8030-50. doi: 10.1021/jm2008634. Epub 2011 Nov 4. PubMed PMID: 22003817.
NERATINIB	Rabindran SK, Discafani CM, Rosfjord EC, Baxter M, Floyd MB, Golas J, Hallett WA, Johnson BD, Nilakantan R, Overbeek E, Reich MF, Shen R, Shi X, Tsou HR, Wang YF, Wissner A. Antitumor activity of HKI-272, an orally active, irreversible inhibitor of the HER-2 tyrosine kinase. Cancer Res. 2004 Jun 1;64(11):3958-65. PubMed PMID: 15173008. Li D, Ambrogio L, Shimamura T, Kubo S, Takahashi M, Chirieac LR, Padera RF, Shapiro GI, Baum A, Himmelsbach F, Rettig WJ, Meyerson M, Solca F, Greulich H, Wong KK. BIBW2992, an irreversible EGFR/HER2 inhibitor highly effective in preclinical lung cancer models. Oncogene. 2008 Aug 7;27(34):4702-11. doi: 10.1038/onc.2008.109. Epub 2008 Apr 14. PubMed PMID: 18408761; PubMed Central PMCID: PMC2748240.
PELITINIB	Li D, Ambrogio L, Shimamura T, Kubo S, Takahashi M, Chirieac LR, Padera RF, Shapiro GI, Baum A, Himmelsbach F, Rettig WJ, Meyerson M, Solca F, Greulich H, Wong KK. BIBW2992, an irreversible EGFR/HER2 inhibitor highly effective in preclinical lung cancer models. Oncogene. 2008 Aug 7;27(34):4702-11. doi: 10.1038/onc.2008.109. Epub 2008 Apr 14. PubMed PMID: 18408761; PubMed Central PMCID: PMC2748240.
CUDC-101	Cai X, Zhai HX, Wang J, Forrester J, Qu H, Yin L, Lai CJ, Bao R, Qian C. Discovery of 7-(4-(3-ethynylphenylamino)-7-methoxyquinazolin-6-yloxy)-N-hydroxyheptanamide (CUDc-101) as a potent multi-acting HDAC, EGFR, and HER2 inhibitor for the treatment of cancer. J Med Chem. 2010 Mar 11;53(5):2000-9. doi: 10.1021/jm901453q. PubMed PMID: 20143778.
SAPITINIB	"Barlaam B, Anderton J, Ballard P, Bradbury RH, Hennequin LF, Hickinson DM, Kettle JG, Kirk G, Klinowska T, Lambert-van der Brempt C, Trigwell C, Vincent J, Ogilvie D. Discovery of AZD8931, an Equipotent, Reversible Inhibitor of Signaling by EGFR, HER2, and HER3 Receptors. ACS Med Chem Lett. 2013 May 31;4(8):742-6. doi: 10.1021/ml400146c. eCollection 2013 Aug 8. PubMed PMID: 24900741; PubMed Central PMCID: PMC4027407. "
AV-412	Suzuki T, Fujii A, Ohya J, Nakamura H, Fujita F, Koike M, Fujita M. Antitumor activity of a dual epidermal growth factor receptor and ErbB2 kinase inhibitor MP-412 (AV-412) in mouse xenograft models. Cancer Sci. 2009 Aug;100 (8):1526-31. doi: 10.1111/j.1349-7006.2009.01197.x. Epub 2009 May 13. PubMed PMID: 19459856.
ALLITINIB	Silva-Oliveira RJ, Silva VA, Martinho O, Cruvinel-Carloni A, Melendez ME, Rosa MN, de Paula FE, de Souza Viana L, Carvalho AL, Reis RM. Cytotoxicity of allitinib, an irreversible anti-EGFR agent, in a large panel of human cancer-derived cell lines: KRAS mutation status as a predictive biomarker. Cell Oncol (Dordr). 2016 Jun;39(3):253-63. doi: 10.1007/s13402-016-0270-z. Epub 2016 Feb 26. PubMed PMID: 26920031.

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COMPOUND NAME	REFERENCES
AEE788	Traxler P, Allegrini PR, Brandt R, Brueggen J, Cozens R, Fabbro D, Grosios K, Lane HA, McSheehy P, Mestan J, Meyer T, Tang C, Wartmann M, Wood J, Caravatti G. AEE788: a dual family epidermal growth factor receptor/ErbB2 and vascular endothelial growth factor receptor tyrosine kinase inhibitor with antitumor and antiangiogenic activity. Cancer Res. 2004 Jul 15;64(14):4931-41. PubMed PMID: 15256466. "Meco D, Servidei T, Zannonit GF, Martinelli E, Prisco MG, Waure Cd, Riccardi R. Dual Inhibitor AEE78 Reduces Tumor Growth in Preclinical Models of Medulloblastoma. Transl Oncol. 2010 Oct;3(5):326-35. doi: 10.1593/tlo.10163. Epub 2014 Mar 5. PubMed PMID: 24670630." "Baselga J, Mita AC, Schöffski P, Dumez H, Rojo F, Tabernero J, DiLea C, Mietlowski W, Low C, Huang J, Dugan M, Parker K, Walk E, van Oosterom A, Martinelli E, Takimoto CH. Using pharmacokinetic and pharmacodynamic data in early decision making regarding drug development: a phase I clinical trial evaluating tyrosine kinase inhibitor, AEE788. Clin Cancer Res. 2012 Nov 15;18(22):6364-72. doi: 10.1158/1078-0432.CCR-12-1499. Epub 2012 Sep 26. PubMed PMID: 23014528."
GEFITINIB	Bell DW, Lynch TJ, Haserlat SM, Harris PL, Okimoto RA, Brannigan BW, Sgroi DC, Muir B, Riemenschneider MJ, Iacona RB, Krebs AD, Johnson DH, Giaccone G, Herbst RS, Manegold C, Fukuoka M, Kris MG, Baselga J, Ochs JS, Haber DA. Epidermal growth factor receptor mutations and gene amplification in non-small-cell lung cancer: molecular analysis of the IDEAL/INTACT gefitinib trials. J Clin Oncol. 2005 Nov 1;23(31):8081-92. Epub 2005 Oct 3. PubMed PMID: 16204011. Moasser MM, Basso A, Averbuch SD, Rosen N. The tyrosine kinase inhibitor ZD1839 ("Iressa") inhibits HER2-driven signaling and suppresses the growth of HER2-overexpressing tumor cells. Cancer Res. 2001 Oct 1;61(19):7184-8. PubMed PMID: 11585753. Oizumi S, Kobayashi K, Inoue A, Maemondo M, Sugawara S, Yoshizawa H, Isobe H, Harada M, Kinoshita I, Okinaga S, Kato T, Harada T, Gemma A, Saijo Y, Yokomizo Y, Morita S, Hagiwara K, Nukiwa T. Quality of life with gefitinib in patients with EGFR-mutated non-small cell lung cancer: quality of life analysis of North East Japan Study Group 002 Trial. Oncologist. 2012;17(6):863-70. doi: 10.1634/theoncologist.2011-0426. Epub 2012 May 11. PubMed PMID: 22581822; PubMed Central PMCID: PMC3380886. Arteaga CL, Johnson DH. Tyrosine kinase inhibitors-ZD1839 (Iressa). Curr Opin Oncol. 2001 Nov;13(6):491-8. Review. PubMed PMID: 11673690. Murray S, Bobos M, Angouridakis N, Nikolaou A, Linardou H, Razis E, Fountzilas G. Screening for EGFR Mutations in Patients with Head and Neck Cancer Treated with Gefitinib on a Compassionate-Use Program: A Hellenic Cooperative Oncology Group Study. J Oncol. 2010;2010:709678. doi: 10.1155/2010/709678. Epub 2011 Jan 3. PubMed PMID: 21274259; PubMed Central PMCID: PMC3022192.
CETUXIMAB	Zhang X, Xu J, Liu H, Yang L, Liang J, Xu N, Bai Y, Wang J, Shen L. Predictive biomarkers for the efficacy of cetuximab combined with cisplatin and capecitabine in advanced gastric or esophagogastric junction adenocarcinoma: a prospective multicenter phase 2 trial. Med Oncol. 2014 Oct;31(10):226. doi: 10.1007/s12032-014-0226-y. Epub 2014 Sep 19. PubMed PMID: 25234930. Kwon J, Yoon HJ, Kim JH, Lee TS, Song IH, Lee HW, Kang MC, Park JH. Cetuximab inhibits cisplatin-induced activation of EGFR signaling in esophageal squamous cell carcinoma. Oncol Rep. 2014 Sep;32(3):1188-92. doi: 10.3892/or.2014.3302. Epub 2014 Jul 3. PubMed PMID: 24993015. Hata A, Katakami N, Kitajima N. Successful cetuximab therapy after failure of panitumumab rechallenge in a patient with metastatic colorectal cancer: restoration of drug sensitivity after anti-EGFR monoclonal antibody-free interval. J Gastrointest Cancer. 2014 Dec;45(4):506-7. doi: 10.1007/s12029-014-9624-9. PubMed PMID: 24880984. Barni S, Ghilardi M, Borgonovo K, Cabiddu M, Zaniboni A, Petrelli F. Cetuximab/irinotecan-chemotherapy in KRAS wild-type pretreated metastatic colorectal cancer: a pooled analysis and review of literature. Rev Recent Clin Trials. 2013 Jun;8(2):101-9. Review. PubMed PMID: 23859115. Herrmann D, Seitz G, Warmann SW, Bonin M, Fuchs J, Armeanu-Ebinger S. Cetuximab promotes immunotoxicity against rhabdomyosarcoma in vitro. J Immunother. 2010 Apr;33(3):279-86. doi: 10.1097/CJI.0b013e3181c549b0. PubMed PMID: 20445348.

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PANITUMUMAB	Vanderbilt Medical Center, Nashville, TN; Kansas City Cancer Center, Overland Park, KS; Hematology Oncology Associates, Port S. Lucie, FL; Utah Cancer Specialists, Salt Lake City, UT; Tennessee Oncology, Nashville, TN; UCLA School of Medicine, Los Angeles, CA; Amgen, Inc., Thousand Oaks, CA. Panitumumab antitumor activity in patients (pts) with metastatic colorectal cancer (mCRC) expressing 10% epidermal growth factor receptor (EGFr). J Clin Oncol (Meeting Abstracts) June 2006 vol. 24 no. 18_suppl 3548. Stephenson JJ, Gregory C, Burris H, Larson T, Verma U, Cohn A, Crawford J, Cohen RB, Martin J, Lum P, Yang X, Amado RG. An open-label clinical trial evaluating safety and pharmacokinetics of two dosing schedules of panitumumab in patients with solid tumors. Clin Colorectal Cancer. 2009 Jan;8(1):29-37. doi: 10.3816/CCC.2009.n.005. PubMed PMID: 19203894. Yamaguchi T, Iwasa S, Nagashima K, Ikezawa N, Hamaguchi T, Shoji H, Honma Y, Takashima A, Okita N, Kato K, Yamada Y, Shimada Y. Comparison of Panitumumab Plus Irinotecan and Cetuximab Plus Irinotecan for KRAS Wild-type Metastatic Colorectal Cancer. Anticancer Res. 2016 Jul;36(7):3531-6. PubMed PMID: 27354619. Echarri MJ, Lopez-Martin A, Hitt R. Targeted Therapy in Locally Advanced and Recurrent/Metastatic Head and Neck Squamous Cell Carcinoma (LA-R/M HNSCC). Cancers (Basel). 2016 Feb 26;8(3). pii: E27. doi: 10.3390/cancers8030027. Review. PubMed PMID: 26927178; PubMed Central PMCID: PMC4810111. Ibrahim EM, Abouelkhair KM. Clinical outcome of panitumumab for metastatic colorectal cancer with wild-type KRAS status: a meta-analysis of randomized clinical trials. Med Oncol. 2011 Dec;28 Suppl 1:S310-7. doi: 10.1007/s12032-010-9760-4. Epub 2011 Jan 9. PubMed PMID: 21221853.
EVEROLIMUS	Ferolla P, Brizzi MP, Meyer T, Mansoor W, Mazieres J, Do Cao C, Léna H, Berruti A, Damiano V, Buikhuisen W, Grønbæk H, Lombard-Bohas C, Grohé C, Minotti V, Tiseo M, De Castro J, Reed N, Gislimberti G, Singh N, Stankovic M, Öberg K, Baudin E. Efficacy and safety of long-acting pasireotide or everolimus alone or in combination in patients with advanced carcinoids of the lung and thymus (LUNA): an open-label, multicentre, randomised, phase 2 trial. Lancet Oncol. 2017 12;18(12):1652-1664. doi: 10.1016/S1470-2045(17)30681-2. Epub 2017 Sep 23. PubMed PMID: 29074099. Ghobrial IM, Witzig TE, Gertz M, LaPlant B, Hayman S, Camoriano J, Lacy M, Bergsagel PL, Chuma S, DeAngelo D, Treon SP. Long-term results of the phase II trial of the oral mTOR inhibitor everolimus (RAD001) in relapsed or refractory Waldenstrom Macroglobulinemia. Am J Hematol. 2014 Mar;89(3):237-42. PubMed PMID: 24716234. Courtney KD, Manola JB, Elfiky AA, Ross R, Oh WK, Yap JT, Van den Abbeele AD, Ryan CW, Beer TM, Loda M, Priolo C, Kantoff P, Taplin ME. A phase I study of everolimus and docetaxel in patients with castration-resistant prostate cancer. Clin Genitourin Cancer. 2015 Apr;13(2):113-23. doi: 10.1016/j.clgc.2014.08.007. PubMed PMID: 25450031; PubMed Central PMCID: PMC4418946. Singh J, Novik Y, Stein S, Volm M, Meyers M, Smith J, Omene C, Speyer J, Schneider R, Jhaveri K, Formenti S, Kyriakou V, Joseph B, Goldberg JD, Li X, Adams S, Tiersten A. Phase 2 trial of everolimus and carboplatin combination in patients with triple negative metastatic breast cancer. Breast Cancer Res. 2014 Mar 31;16(2):R32. doi: 10.1186/bcr3634. PubMed PMID: 24684785; PubMed Central PMCID: PMC4053575. Motzer RJ, Escudier B, Oudard S, Hutson TE, Porta C, Bracarda S, Grünwald V, Thompson JA, Figlin RA, Hollaender N, Urbanowitz G, Berg WJ, Kay A, Lebwohl D, Ravaud A, . Efficacy of everolimus in advanced renal cell carcinoma: a double-blind, randomised, placebo-controlled phase III trial. Lancet. 2008 Aug 09;372(9637):449-56. doi: 10.1016/S0140-6736(08)61039-9. Epub 2008 Sep 22. PubMed PMID: 18653228.
BRILANESTRANT	Maura Dickler, Aditya Bardia, Ingrid Mayer, Eric Winer, Peter Rix, Jeff Hager, Meng Chen, Iris Chan, Edna Chow-Maneval, Carlos Arteaga, Jose Baselga. A first-in-human phase I study to evaluate the oral selective estrogen receptor degrader GDC-0810 (ARN-810) in postmenopausal women with estrogen receptor+ HER2-, advanced/metastatic breast cancer. [abstract]. In: Proceedings of the 106th Annual Meeting of the American Association for Cancer Research; 2015 Apr 18-22; Philadelphia, PA. Philadelphia (PA): AACR; Cancer Res 2015;75(15 Suppl):Abstract nr CT231. doi:10.1158/1538-7445.AM2015-CT231
ELACESTRANT	Bihani T, Patel HK, Arlt H, Tao N, Jiang H, Brown JL, Purandare DM, Hattersley G, Garner F. Elacestrant (RAD1901), a Selective Estrogen Receptor Degrader (SERD), Has Antitumor Activity in Multiple ER(+) Breast Cancer Patient-derived Xenograft Models. Clin Cancer Res. 2017 Aug 15;23(16):4793-4804. doi: 10.1158/1078-0432.CCR-16-2561. Epub 2017 May 4. PubMed PMID: 28473534.
BAZEDOXIFENE	Wardell SE, Ellis MJ, Alley HM, Eisele K, VanArsdale T, Dann SG, Arndt KT, Primeau T, Griffin E, Shao J, Crowder R, Lai JP, Norris JD, McDonnell DP, Li S. Efficacy of SERD/SERM Hybrid-CDK4/6 Inhibitor Combinations in Models of Endocrine Therapy-Resistant Breast Cancer. Clin Cancer Res. 2015 Nov 15;21(22):5121-5130. doi: 10.1158/1078-0432.CCR-15-0360. Epub 2015 May 19. PubMed PMID: 25991817; PubMed Central PMCID: PMC4644714.
SRN-927	Dickler MN, Villanueva R, Perez Fidalgo JA, Mayer IA, Boni V, Winer EP, Hamilton EP, Bellet M, Urruticoechea A, Gonzalez-Martin A, Cortes J, Martin M, Giltnane J, Gates M, Cheeti S, Fredrickson J, Wang X, Friedman LS, Spoerke JM, Metcalfe C, Liu L, Li R, Morley R, McCurry U, Chan IT, Mueller L, Milan S, Lauchle J, Humke EW, Bardia A. A first-in-human phase I study to evaluate the oral selective estrogen receptor degrader (SERD), GDC-0927, in postmenopausal women with estrogen receptor positive (ER+) HER2-negative metastatic breast cancer (BC) [abstract]. In: Proceedings of the 2017 San Antonio Breast Cancer Symposium; 2017 Dec 5-9; San Antonio, TX. Philadelphia (PA): AACR; Cancer Res 2018;78(4 Suppl):Abstract nr PD5-10.
AZD9496	Weir HM, Bradbury RH, Lawson M, Rabow AA, Buttar D, Callis RJ, Curwen JO, de Almeida C, Ballard P, Hulse M, Donald CS, Feron LJ, Karoutchi G, MacFaul P, Moss T, Norman RA, Pearson SE, Tonge M, Davies G, Walker GE, Wilson Z, Rowlinson R, Powell S, Sadler C, Richmond G, Ladd B, Pazolli E, Mazzola AM, D'Cruz C, De Savi C. AZD9496: An Oral Estrogen Receptor Inhibitor That Blocks the Growth of ER-Positive and ESR1-Mutant Breast Tumors in Preclinical Models. Cancer Res. 2016 Jun 1;76(11):3307-18. doi: 10.1158/0008-5472.CAN-15-2357. Epub 2016 Mar 28. PubMed PMID: 27020862.

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COMPOUND NAME	REFERENCES
LAPATINIB	Bello M, Saldaña-Rivero L, Correa-Basurto J, García B, Sánchez-Espinosa VA. Structural and energetic basis for the molecular recognition of dual synthetic vs. natural inhibitors of EGFR/HER2. Int J Biol Macromol. 2018 Jan 9;111:569-586. doi: 10.1016/j.ijbiomac.2017.12.162. [Epub ahead of print] PubMed PMID: 29329808. Johnston SR, Leary A. Lapatinib: a novel EGFR/HER2 tyrosine kinase inhibitor for cancer. Drugs Today (Barc). 2006 Jul;42(7):441-53. Review. PubMed PMID: 16894399. Xia W, Husain I, Liu L, Bacus S, Saini S, Spohn J, Pry K, Westlund R, Stein SH, Spector NL. Lapatinib antitumor activity is not dependent upon phosphatase and tensin homologue deleted on chromosome 10 in ErbB2-overexpressing breast cancers. Cancer Res. 2007 Feb 1;67(3):1170-5. PubMed PMID: 17283152. R. K. Ramanathan, C. P. Belani, D. A. Singh, M. Tanaka Jr, H. J. Lenz, Y. Yen, H. L. Kindler, S. Iqbal, J. Longmate, D. R. Gandara. Phase II study of lapatinib, a dual inhibitor of epidermal growth factor receptor (EGFR) tyrosine kinase 1 and 2 (Her2/Neu) in patients (pts) with advanced biliary tree cancer (BTC) or hepatocellular cancer (HCC). A California Consortium (CCC-P) Trial. DOI: 10.1200/jco.2006.24.18_suppl.4010 Journal of Clinical Oncology 24, no. 18_suppl.
AMIVANTAMAB	Yun J, Lee SH, Kim SY, Jeong SY, Kim JH, Pyo KH, Park CW, Heo SG, Yun MR, Lim S, Lim SM, Hong MH, Kim HR, Thayu M, Curtin JC, Knoblauch RE, Lorenzi MV, Roshak A, Cho BC. Antitumor Activity of Amivantamab (JNJ-61186372), an EGFR-MET Bispecific Antibody, in Diverse Models of EGFR Exon 20 Insertion-Driven NSCLC. Cancer Discov. 2020 Aug;10(8):1194-1209. doi: 10.1158/2159-8290.CD-20-0116. Epub 2020 Oct 15. PubMed PMID: 32414908.
CRIZOTINIB	Zhang Y, Farenholtz KE, Yang Y, Guessous F, Dipierro CG, Calvert VS, Deng J, Schiff D, Xin W, Lee JK, Purow B, Christensen J, Petricoin E, Abounader R. Hepatocyte growth factor sensitizes brain tumors to c-MET kinase inhibition. Clin Cancer Res. 2013 Mar 15;19(6):1433-44. doi: 10.1158/1078-0432.CCR-12-2832. Epub 2013 Feb 5. PubMed PMID: 23386689; PubMed Central PMCID: PMC3602223. Yu Y, Ou Q, Wu X, Bao H, Ding Y, Shao YW, Lu S. Concomitant resistance mechanisms to multiple tyrosine kinase inhibitors in ALK-positive non-small cell lung cancer. Lung Cancer. 2019 01;127:19-24. doi: 10.1016/j.lungcan.2018.11.024. Epub 2018 November 22. PubMed PMID: 30642546. Kron A, Alidousty C, Scheffler M, Merkelbach-Bruse S, Seidel D, Riedel R, Ihle MA, Michels S, Nogova L, Fassunke J, Heydt C, Kron F, Ueckeroth F, Serke M, Krüger S, Grohe C, Koschel D, Benedikter J, Kaminsky B, Schaaf B, Braess J, Sebastian M, Kambartel KO, Thomas R, Zander T, Schultheis AM, Büttner R, Wolf J. Impact of TP53 mutation status on systemic treatment outcome in ALK-rearranged non-small-cell lung cancer. Ann Oncol. 2018 10 01;29(10):2068-2075. doi: 10.1093/annonc/mdy333. PubMed PMID: 30165392; PubMed Central PMCID: PMC6225899. Forde PM, Rudin CM. Crizotinib in the treatment of non-small-cell lung cancer. Expert Opin Pharmacother. 2012 Jun;13(8):1195-201. doi: 10.1517/14656566.2012.688029. Review. PubMed PMID: 22594847. Shaw AT, Hsu PP, Awad MM, Engelman JA. Tyrosine kinase gene rearrangements in epithelial malignancies. Nat Rev Cancer. 2013 Nov;13(11):772-87. doi: 10.1038/nrc3612. Epub 2013 Oct 17. Review. PubMed PMID: 24132104; PubMed Central PMCID: PMC3902129.
TRETINOIN	Hölzel M, Huang S, Koster J, Ora I, Lakeman A, Caron H, Nijkamp W, Xie J, Callens T, Asgharzadeh S, Seeger RC, Messiaen L, Versteeg R, Bernards R. NF1 is a tumor suppressor in neuroblastoma that determines retinoic acid response and disease outcome. Cell. 2010 Jul 23;142(2):218-29. doi: 10.1016/j.cell.2010.06.004. PubMed PMID: 20655465; PubMed Central PMCID: PMC2913027.
ERLOTINIB	Kelley RK, Ko AH. Erlotinib in the treatment of advanced pancreatic cancer. Biologics. 2008 Mar;2(1):83-95. PubMed PMID: 19707431; PubMed Central PMCID: PMC2727779. Garassino MC, Martelli O, Broggini M, Farina G, Veronese S, Rulli E, Bianchi F, Bettini A, Longo F, Moscetti L, Tomirotti M, Marabese M, Ganzinelli M, Lauricella C, Labianca R, Floriani I, Giaccone G, Torri V, Scanni A, Marsoni S; TAILOR trialists. Erlotinib versus docetaxel as second-line treatment of patients with advanced non-small-cell lung cancer and wild-type EGFR tumours (TAILOR): a randomised controlled trial. Lancet Oncol. 2013 Sep;14(10):981-8. doi: 10.1016/S1470-2045(13)70310-3. Epub 2013 Jul 22. PubMed PMID: 23883922. Wyman, K., Kelley, M., Puzanov, I., Sanders, K., Hubbard, F., Krozely, P., ... & Sosman, J. A. Gordon AN, Finkler N, Edwards RP, Garcia AA, Crozier M, Irwin DH, Barrett E. Efficacy and safety of erlotinib HCl, an epidermal growth factor receptor (HER1/EGFR) tyrosine kinase inhibitor, in patients with advanced ovarian carcinoma: results from a phase II multicenter study. Int J Gynecol Cancer. 2005 Sep-Oct;15(5):785-92. PubMed PMID: 16174225. Dickler MN, Cobleigh MA, Miller KD, Klein PM, Winer EP. Efficacy and safety of erlotinib in patients with locally advanced or metastatic breast cancer. Breast Cancer Res Treat. 2009 May;115(1):115-21. doi: 10.1007/s10549-008-0055-9. Epub 2008 May 22. PubMed PMID: 18496750.

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COMPOUND NAME	REFERENCES
FULVESTRANT	McNeil CM, Sergio CM, Anderson LR, Inman CK, Eggleton SA, Murphy NC, Millar EK, Crea P, Kench JG, Alles MC, Gardiner-Garden M, Ormandy CJ, Butt AJ, Henshall SM, Musgrove EA, Sutherland RL. c-Myc overexpression and endocrine resistance in breast cancer. J Steroid Biochem Mol Biol. 2006 Dec;102(1-5):147-55. doi: 10.1016/j.jsbmb.2006.09.028. Epub 2006 Apr 18. PubMed PMID: 17052904. Razavi P, Chang MT, Xu G, Bandlamudi C, Ross DS, Vasan N, Cai Y, Bielski CM, Donoghue MTA, Jonsson P, Penson A, Shen R, Pareja F, Kundra R, Middha S, Cheng ML, Zehir A, Kandoth C, Patel R, Huberman K, Smyth LM, Jhaveri K, Modi S, Traina TA, Dang C, Zhang W, Weigelt B, Li BT, Ladanyi M, Hyman DM, Schultz N, Robson ME, Hudis C, Brogi E, Viale A, Norton L, Dickler MN, Berger MF, Iacobuzio-Donahue CA, Chandarlapaty S, Scaltriti M, Reis-Filho JS, Solit DB, Taylor BS, Baselga J. The Genomic Landscape of Endocrine-Resistant Advanced Breast Cancers. Cancer Cell. 2018 09 10;34(3):427-438.e6. doi: 10.1016/j.ccell.2018.08.008. PubMed PMID: 30205045; PubMed Central PMCID: PMC6327853.

BIOMARKERS AND DRIVERS	REFERENCES
NF1 loss presence	Bottillo I, Ahlquist T, Brekke H, Danielsen SA, van den Berg E, Mertens F, Lothe RA, Dallapiccola B. Germline and somatic NF1 mutations in sporadic and NF1-associated malignant peripheral nerve sheath tumours. J Pathol. 2009 Apr;217(5):693-701. doi: 10.1002/path.2494. PubMed PMID: 19142971. Tasian SK, Casas JA, Posocco D, Gandre-Babbe S, Gagne AL, Liang G, Loh ML, Weiss MJ, French DL, Chou ST. Mutation-specific signaling profiles and kinase inhibitor sensitivities of juvenile myelomonocytic leukemia revealed by induced pluripotent stem cells. Leukemia. 2018 Jun 8. doi: 10.1038/s41375-018-0169-y. [Epub ahead of print] PubMed PMID: 29884903. Fangusaro, Jason, Arzu Onar-Thomas, Tina Y. Poussaint, Shengjie Wu, Azra H. Ligon, Neal Lindeman, Anu Banerjee et al. "Lgg-08. A Phase Ii Prospective Study Of Selumetinib In Children With Recurrent Or Refractory Low-grade Glioma (lgg): A Pediatric Brain Tumor Consortium (pbtc) Study." Neuro-oncology 19, no. suppl_4 (2017): iv34-iv35. http://www.ncbi.nlm.nih.gov/pubmed/22573716 Rotow JK, Gui P, Wu W, Raymond VM, Lanman RB, Kaye FJ, Peled N, Fece de la Cruz F, Nadres B, Corcoran RB, Yeh I, Bastian BC, Starostik P, Newsom K, Olivas VR, Wolff AM, Fraser JS, Collisson EA, McCoach CE, Camidge DR, Pacheco J, Bazhenova L, Li T, Bivona TG, Blakely CM. Co-occurring Alterations in the RAS-MAPK Pathway Limit Response to MET Inhibitor Treatment in MET Exon 14 Skipping Mutation-Positive Lung Cancer. Clin Cancer Res. 2020 01 15;26(2):439-449. doi: 10.1158/1078-0432.CCR-19-1667. Epub 2019 September 23. PubMed PMID: 31548343; PubMed Central PMCID: PMC6980768.
MYC amplification presence	Emoto M, Oshima K, Ishiguro M, Iwasaki H, Kawarabayashi T, Kikuchi M. Establishment and characterization of a serous papillary adenocarcinoma cell line of the human ovary in a serum-free culture. Pathol Res Pract. 1999;195(4):237-42. PubMed PMID: 10337661. Lui GYL, Grandori C, Kemp CJ. CDK12: an emerging therapeutic target for cancer. J Clin Pathol. 2018 Nov;71(11):957-962. doi: 10.1136/jclinpath-2018-205356. Epub 2018 Aug 13. Review. PubMed PMID: 30104286; PubMed Central PMCID: PMC6242340. Saglam O, Tang Z, Tang G, Medeiros LJ, Toruner GA. KAT6A amplifications are associated with shorter progression-free survival and overall survival in patients with endometrial serous carcinoma. PLoS One. 2020;15(9):e0238477. doi: 10.1371/journal.pone.0238477. Epub 2020 Apr 02. PubMed PMID: 32877461; PubMed Central PMCID: PMC7467277. Lee KS, Kwak Y, Nam KH, Kim DW, Kang SB, Choe G, Kim WH, Lee HS. c-MYC Copy-Number Gain Is an Independent Prognostic Factor in Patients with Colorectal Cancer. PLoS One. 2015 Oct 1;10(10):e0139727. doi: 10.1371/journal.pone.0139727. eCollection 2015. PubMed PMID: 26426996; PubMed Central PMCID: PMC4591346. Gogas H, Kotoula V, Alexopoulou Z, Christodoulou C, Kostopoulos I, Bobos M, Raptou G, Charalambous E, Tsolaki E, Xanthakis I, Pentheroudakis G, Koutras A, Bafaloukos D, Papakostas P, Aravantinos G, Psyrri A, Petraki K, Kalogeras KT, Pectasides D, Fountzilas G. MYC copy gain, chromosomal instability and PI3K activation as potential markers of unfavourable outcome in trastuzumab-treated patients with metastatic breast cancer. J Transl Med. 2016 May 17;14(1):136. doi: 10.1186/s12967-016-0883-z. PubMed PMID: 27184134; PubMed Central PMCID: PMC4869295.
TP53-560-2A>T	NCBI ClinVar NCBI ClinVar Wellcome Sanger Institute IARC TP53 Database Wellcome Trust Sanger Institute
PIM1 amplification presence	Brasó-Maristany F, Filosto S, Catchpole S, Marlow R, Quist J, Francesch-Domenech E, Plumb DA, Zakka L, Gazinska P, Liccardi G, Meier P, Gris-Oliver A, Cheang MC, Perdrix-Rosell A, Shafat M, Noël E, Patel N, McEachern K, Scaltriti M, Castel P, Noor F, Buus R, Mathew S, Watkins J, Serra V, Marra P, Grigoriadis A, Tutt AN. PIM1 kinase regulates cell death, tumor growth and chemotherapy response in triple-negative breast cancer. Nat Med. 2016 11;22(11):1303-1313. doi: 10.1038/nm.4198. Epub 2016 October 24. PubMed PMID: 27775704; PubMed Central PMCID: PMC5552044.

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BIOMARKERS AND DRIVERS	REFERENCES
APC-R854K	Wellcome Trust Sanger Institute
	Wellcome Trust Sanger Institute
	Wellcome Trust Sanger Institute
	Wellcome Sanger Institute
	Wellcome Trust Sanger Institute
CDH1-R124C	Wellcome Trust Sanger Institute
	Wellcome Trust Sanger Institute
	Mi EZ, Mi EZ, di Pietro M, O'Donovan M, Hardwick RH, Richardson S, Ziauddeen H, Fletcher PC, Caldas C, Tischkowitz M, Ragunath K, Fitzgerald RC. Comparative study of endoscopic surveillance in hereditary diffuse gastric cancer according to CDH1 mutation status. Gastrointest Endosc. 2018 Feb;87(2):408-418. doi: 10.1016/j.gie.2017.06.028. Epub 2017 Jul 6. PubMed PMID: 28688938; PubMed Central PMCID: PMC5780354.
	https://cancer.sanger.ac.uk/cosmic/mutation/overview?id=6923295
	NCBI ClinVar
TNFRSF14-P167L	Wellcome Sanger Institute
	Wellcome Trust Sanger Institute
	Wellcome Trust Sanger Institute
	http://snpeffect.switchlab.org/mutation/TNR14_HUMAN/VAR_018955
	Eleni Kotsiou, Jessica Okosun, Caroline Besley, Sameena Iqbal, Janet Matthews, Jude Fitzgibbon, John G. Gribben, Jeffrey K. Davies; TNFRSF14 aberrations in follicular lymphoma increase clinically significant allogeneic T-cell responses. Blood 2016; 128 (1): 72–81. doi: 10.1182/blood-2015-10-679191
KLHL6-L258F	Wellcome Sanger Institute
	Wellcome Trust Sanger Institute
	Choi J, Lee K, Ingvarsdottir K, Bonasio R, Saraf A, Florens L, Washburn MP, Tadros S, Green MR, Busino L. Loss of KLHL6 promotes diffuse large B-cell lymphoma growth and survival by stabilizing the mRNA decay factor roquin2. Nat Cell Biol. 2018 05;20(5):586-596. doi: 10.1038/s41556-018-0084-5. Epub 2018 April 25. PubMed PMID: 29695787; PubMed Central PMCID: PMC5926793.
NOTCH2-R1332L	Wellcome Trust Sanger Institute
	NCBI ClinVar
	Leiden Open Variation Database
	Wellcome Sanger Institute
	Wellcome Sanger Institute
KDR-G671E	NCBI ClinVar Database

TARGET GENES	REFERENCES
CDK1 wild-type	Kang J, Sergio CM, Sutherland RL, Musgrove EA. Targeting cyclin-dependent kinase 1 (CDK1) but not CDK4/6 or CDK2 is selectively lethal to MYC-dependent human breast cancer cells. BMC Cancer. 2014 Jan 20;14:32. doi: 10.1186/1471-2407-14-32. PubMed PMID: 24444383; PubMed Central PMCID: PMC3903446.
	Bhattacharya S, Ray RM, Johnson LR. Cyclin-dependent kinases regulate apoptosis of intestinal epithelial cells. Apoptosis. 2014 Mar;19(3):451-66. doi: 10.1007/s10495-013-0942-3. PubMed PMID: 24242917; PubMed Central PMCID: PMC3945523.
	Telford BJ, Chen A, Beetham H, Frick J, Brew TP, Gould CM, Single A, Godwin T, Simpson KJ, Guilford P. Synthetic Lethal Screens Identify Vulnerabilities in GPCR Signaling and Cytoskeletal Organization in E-Cadherin-Deficient Cells. Mol Cancer Ther. 2015 May;14(5):1213-23. doi: 10.1158/1535-7163.MCT-14-1092. Epub 2015 Mar 16. PubMed PMID: 25777964.
	Goga A, Yang D, Tward AD, Morgan DO, Bishop JM. Inhibition of CDK1 as a potential therapy for tumors over-expressing MYC. Nat Med. 2007 Jul;13(7):820-7. Epub 2007 Jun 24. PubMed PMID: 17589519.

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TARGET GENES	REFERENCES
CHEK1 wild-type	Chen Z, Xiao Z, Gu WZ, Xue J, Bui MH, Kovar P, Li G, Wang G, Tao ZF, Tong Y, Lin NH, Sham HL, Wang JY, Sowin TJ, Rosenberg SH, Zhang H. Selective Chk1 inhibitors differentially sensitize p53-deficient cancer cells to cancer therapeutics. Int J Cancer. 2006 Dec 15;119(12):2784-94. PubMed PMID: 17019715. Dai Y, Chen S, Kmieciak M, Zhou L, Lin H, Pei XY, Grant S. The novel Chk1 inhibitor MK-8776 sensitizes human leukemia cells to HDAC inhibitors by targeting the intra-S checkpoint and DNA replication and repair. Mol Cancer Ther. 2013 Jun;12(6):878-89. doi: 10.1158/1535-7163.MCT-12-0902. PubMed PMID: 23536721; PubMed Central PMCID: PMC3681875. Koniaras K, Cuddihy AR, Christopoulos H, Hogg A, O'Connell MJ. Inhibition of Chk1-dependent G2 DNA damage checkpoint radiosensitizes p53 mutant human cells. Oncogene. 2001 Nov 8;20(51):7453-63. PubMed PMID: 11709716. Sen T, Tong P, Stewart CA, Cristea S, Valliani A, Shames DS, Redwood AB, Fan YH, Li L, Glisson BS, Minna JD, Sage J, Gibbons DL, Piwnica-Worms H, Heymach JV, Wang J, Byers LA. CHK1 Inhibition in Small-Cell Lung Cancer Produces Single-Agent Activity in Biomarker-Defined Disease Subsets and Combination Activity with Cisplatin or Olaparib. Cancer Res. 2017 Jul 15;77(14):3870-3884. doi: 10.1158/0008-5472.CAN-16-3409. Epub 2017 May 10. PubMed PMID: 28490518; PubMed Central PMCID: PMC5563854.
MAP2K1 wild-type	Andrea M. Gross, Pamela Wolters, Andrea Baldwin, Eva Dombi, Michael J. Fisher, Brian D. Weiss, AeRang Kim, Jaishri O'Neill Blakeley, Patricia Whitcomb, Marielle Holmblad, Staci Martin, Marie Claire Roderick, Scott M. Paul, Janet Therrien, Kara Heisey, Austin Doyle, Malcolm A. Smith, John Glod, Seth M. Steinberg, and Brigitte C. Widemann, SPRINT: Phase II study of the MEK 1/2 inhibitor selumetinib (AZD6244, ARRY-142886) in children with neurofibromatosis type 1 (NF1) and inoperable plexiform neurofibromas (PN). DOI: 10.1200/JCO.2018.36.15_suppl. 10503 Journal of Clinical Oncology 36, no. 15_suppl (May 2018) 10503-10503.
BRD4 wild-type	Delmore JE, Issa GC, Lemieux ME, Rahl PB, Shi J, Jacobs HM, Kastritis E, Gilpatrick T, Paranal RM, Qi J, Chesi M, Schinzel AC, McKeown MR, Heffernan TP, Vakoc CR, Bergsagel PL, Ghobrial IM, Richardson PG, Young RA, Hahn WC, Anderson KC, Kung AL, Bradner JE, Mitsiades CS. BET bromodomain inhibition as a therapeutic strategy to target c-Myc. Cell. 2011 Sep 16;146(6):904-17. doi: 10.1016/j.cell.2011.08.017. Epub 2011 Sep 1. PubMed PMID: 21889194; PubMed Central PMCID: PMC3187920.
CDK12 wild-type	Lui GYL, Grandori C, Kemp CJ. CDK12: an emerging therapeutic target for cancer. J Clin Pathol. 2018 Nov;71(11):957-962. doi: 10.1136/jclinpath-2018-205356. Epub 2018 Aug 13. Review. PubMed PMID: 30104286; PubMed Central PMCID: PMC6242340.
PIM1 wild-type	Brasó-Maristany F, Filosto S, Catchpole S, Marlow R, Quist J, Francesch-Domenech E, Plumb DA, Zakka L, Gazinska P, Liccardi G, Meier P, Gris-Oliver A, Cheang MC, Perdrix-Rosell A, Shafat M, Noël E, Patel N, McEachern K, Scaltriti M, Castel P, Noor F, Buus R, Mathew S, Watkins J, Serra V, Marra P, Grigoriadis A, Tutt AN. PIM1 kinase regulates cell death, tumor growth and chemotherapy response in triple-negative breast cancer. Nat Med. 2016 11;22(11):1303-1313. doi: 10.1038/nm.4198. Epub 2016 October 24. PubMed PMID: 27775704; PubMed Central PMCID: PMC5552044.
AURKB wild-type	Diaz RJ, Golbourn B, Shekarforoush M, Smith CA, Rutka JT. Aurora kinase B/C inhibition impairs malignant glioma growth in vivo. J Neurooncol. 2012 Jul;108(3):349-60. doi: 10.1007/s11060-012-0835-2. Epub 2012 Jun 01. PubMed PMID: 22382783. Telford BJ, Chen A, Beetham H, Frick J, Brew TP, Gould CM, Single A, Godwin T, Simpson KJ, Guilford P. Synthetic Lethal Screens Identify Vulnerabilities in GPCR Signaling and Cytoskeletal Organization in E-Cadherin-Deficient Cells. Mol Cancer Ther. 2015 May;14(5):1213-23. doi: 10.1158/1535-7163.MCT-14-1092. Epub 2015 Mar 16. PubMed PMID: 25777964. Li D, Lo W, Rudloff U. Merging perspectives: genotype-directed molecular therapy for hereditary diffuse gastric cancer (HDGC) and E-cadherin-EGFR crosstalk. Clin Transl Med. 2018 Feb 22;7(1):7. doi: 10.1186/s40169-018-0184-7. PubMed PMID: 29468433; PubMed Central PMCID: PMC5821620.
CDK2 wild-type	Bhattacharya S, Ray RM, Johnson LR. Cyclin-dependent kinases regulate apoptosis of intestinal epithelial cells. Apoptosis. 2014 Mar;19(3):451-66. doi: 10.1007/s10495-013-0942-3. PubMed PMID: 24242917; PubMed Central PMCID: PMC3945523. Telford BJ, Chen A, Beetham H, Frick J, Brew TP, Gould CM, Single A, Godwin T, Simpson KJ, Guilford P. Synthetic Lethal Screens Identify Vulnerabilities in GPCR Signaling and Cytoskeletal Organization in E-Cadherin-Deficient Cells. Mol Cancer Ther. 2015 May;14(5):1213-23. doi: 10.1158/1535-7163.MCT-14-1092. Epub 2015 Mar 16. PubMed PMID: 25777964.
WEE1 wild-type	Hirai H, Iwasawa Y, Okada M, Arai T, Nishibata T, Kobayashi M, Kimura T, Kaneko N, Ohtani J, Yamanaka K, Itadani H, Takahashi-Suzuki I, Fukasawa K, Oki H, Nambu T, Jiang J, Sakai T, Arakawa H, Sakamoto T, Sagara T, Yoshizumi T, Mizuarai S, Kotani H. Small-molecule inhibition of Wee1 kinase by MK-1775 selectively sensitizes p53-deficient tumor cells to DNA-damaging agents. Mol Cancer Ther. 2009 Nov;8(11):2992-3000. doi: 10.1158/1535-7163.MCT-09-0463. PubMed PMID: 19887545. Leijen S, van Geel RM, Pavlick AC, Tibes R, Rosen L, Razak AR, Lam R, Demuth T, Rose S, Lee MA, Freshwater T, Shumway S, Liang LW, Oza AM, Schellens JH, Shapiro GI. Phase I Study Evaluating WEE1 Inhibitor AZD1775 As Monotherapy and in Combination With Gemcitabine, Cisplatin, or Carboplatin in Patients With Advanced Solid Tumors. J Clin Oncol. 2016 Dec 20;34(36):4371-4380. doi: 10.1200/JCO.2016.67.5991. Epub 2016 Oct 31. PubMed PMID: 27601554.
ATR wild-type	Reaper PM, Griffiths MR, Long JM, Charrier JD, Maccormick S, Charlton PA, Golec JM, Pollard JR. Selective killing of ATM- or p53-deficient cancer cells through inhibition of ATR. Nat Chem Biol. 2011 Apr 13;7(7):428-30. doi: 10.1038/nchembio.573. PubMed PMID: 21490603.

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TARGET GENES	REFERENCES
CDK4 wild-type	Zou X, Ray D, Aziyu A, Christov K, Boiko AD, Gudkov AV, Kiyokawa H. Cdk4 disruption renders primary mouse cells resistant to oncogenic transformation, leading to Arf/p53-independent senescence. Genes Dev. 2002 Nov 15;16 (22):2923-34. PubMed PMID: 12435633; PubMed Central PMCID: PMC187486.
RARG wild-type	Larsson CA, Moyer SM, Liu B, Michel KA, Pant V, Yang P, Wong J, El-Naggar AK, Krahe R, Lozano G. Synergistic and additive effect of retinoic acid in circumventing resistance to p53 restoration. Proc Natl Acad Sci U S A. 2018 02 27; 115(9):2198-2203. doi: 10.1073/pnas.1719001115. Epub 2018 Oct 13. PubMed PMID: 29440484; PubMed Central PMCID: PMC5834709.
PLK1 wild-type	Degenhardt Y, Greshock J, Laquerre S, Gilmartin AG, Jing J, Richter M, Zhang X, Bleam M, Halsey W, Hughes A, Moy C, Liu-Sullivan N, Powers S, Bachman K, Jackson J, Weber B, Wooster R. Sensitivity of cancer cells to Plk1 inhibitor GSK461364A is associated with loss of p53 function and chromosome instability. Mol Cancer Ther. 2010 Jul;9(7):2079-89. doi: 10.1158/1535-7163.MCT-10-0095. Epub 2010 Jun 22. PubMed PMID: 20571075.
PRKDC wild-type	Sun Q, Guo Y, Liu X, Czauderna F, Carr MI, Zenke FT, Blaukat A, Vassilev LT. Therapeutic Implications of p53 Status on Cancer Cell Fate Following Exposure to Ionizing Radiation and the DNA-PK Inhibitor M3814. Mol Cancer Res. 2019 12;17(12):2457-2468. doi: 10.1158/1541-7786.MCR-19-0362. Epub 2019 Jul 24. PubMed PMID: 31551253.
CDK9 wild-type	Bhattacharya S, Ray RM, Johnson LR. Cyclin-dependent kinases regulate apoptosis of intestinal epithelial cells. Apoptosis. 2014 Mar;19(3):451-66. doi: 10.1007/s10495-013-0942-3. PubMed PMID: 24242917; PubMed Central PMCID: PMC3945523.
MTOR wild-type	Telford BJ, Chen A, Beetham H, Frick J, Brew TP, Gould CM, Single A, Godwin T, Simpson KJ, Guilford P. Synthetic Lethal Screens Identify Vulnerabilities in GPCR Signaling and Cytoskeletal Organization in E-Cadherin-Deficient Cells. Mol Cancer Ther. 2015 May;14(5):1213-23. doi: 10.1158/1535-7163.MCT-14-1092. Epub 2015 Mar 16. PubMed PMID: 25777964. Li D, Lo W, Rudloff U. Merging perspectives: genotype-directed molecular therapy for hereditary diffuse gastric cancer (HDGC) and E-cadherin-EGFR crosstalk. Clin Transl Med. 2018 Feb 22;7(1):7. doi: 10.1186/s40169-018-0184-7. PubMed PMID: 29468433; PubMed Central PMCID: PMC5821620. Johannessen CM, Reczek EE, James MF, Brems H, Legius E, Cichowski K. The NF1 tumor suppressor critically regulates TSC2 and mTOR. Proc Natl Acad Sci U S A. 2005 Jun 14;102(24):8573-8. Epub 2005 Jun 3. Erratum in: Proc Natl Acad Sci U S A. 2005 Nov 1;102(44):16119. PubMed PMID: 15937108; PubMed Central PMCID: PMC1142482. Johannessen CM, Johnson BW, Williams SM, Chan AW, Reczek EE, Lynch RC, Rioth MJ, McClatchey A, Ryeom S, Cichowski K. TORC1 is essential for NF1-associated malignancies. Curr Biol. 2008 Jan 8;18(1):56-62. doi: 10.1016/j.cub.2007.11.066. Epub 2007 Dec 27. PubMed PMID: 18164202. Martins MM, Zhou AY, Corella A, Horiuchi D, Yau C, Rakhshandehroo T, Gordan JD, Levin RS, Johnson J, Jascur J, Shales M, Sorrentino A, Cheah J, Clemons PA, Shamji AF, Schreiber SL, Krogan NJ, Shokat KM, McCormick F, Goga A, Bandyopadhyay S. Linking tumor mutations to drug responses via a quantitative chemical-genetic interaction map. Cancer Discov. 2015 02;5(2):154-67. doi: 10.1158/2159-8290.CD-14-0552. Epub 2014 Sep 12. PubMed PMID: 25501949; PubMed Central PMCID: PMC4407699.
COX2 wild-type	Cherukuri DP, Ishikawa TO, Chun P, Catapang A, Elashoff D, Grogan TR, Bugni J, Herschman HR. Targeted Cox2 gene deletion in intestinal epithelial cells decreases tumorigenesis in female, but not male, ApcMin/+ mice. Mol Oncol. 2014 Mar;8(2):169-77. doi: 10.1016/j.molonc.2013.10.009. Epub 2013 Nov 8. PubMed PMID: 24268915; PubMed Central PMCID: PMC3963510. Oshima M, Dinchuk JE, Kargman SL, Oshima H, Hancock B, Kwong E, Trzaskos JM, Evans JF, Taketo MM. Suppression of intestinal polyposis in Apc delta716 knockout mice by inhibition of cyclooxygenase 2 (COX-2). Cell. 1996 Nov 29;87(5):803-9. PubMed PMID: 8945508.
ROS1 wild-type	Telford BJ, Chen A, Beetham H, Frick J, Brew TP, Gould CM, Single A, Godwin T, Simpson KJ, Guilford P. Synthetic Lethal Screens Identify Vulnerabilities in GPCR Signaling and Cytoskeletal Organization in E-Cadherin-Deficient Cells. Mol Cancer Ther. 2015 May;14(5):1213-23. doi: 10.1158/1535-7163.MCT-14-1092. Epub 2015 Mar 16. PubMed PMID: 25777964. Li D, Lo W, Rudloff U. Merging perspectives: genotype-directed molecular therapy for hereditary diffuse gastric cancer (HDGC) and E-cadherin-EGFR crosstalk. Clin Transl Med. 2018 Feb 22;7(1):7. doi: 10.1186/s40169-018-0184-7. PubMed PMID: 29468433; PubMed Central PMCID: PMC5821620. Bajrami I, Marlow R, van de Ven M, Brough R, Pemberton HN, Frankum J, Song F, Rafiq R, Konde A, Krastev DB, Menon M, Campbell J, Gulati A, Kumar R, Pettitt SJ, Gurden MD, Cardenosa ML, Chong I, Gazinska P, Wallberg F, Sawyer EJ, Martin LA, Dowsett M, Linardopoulos S, Natrajan R, Ryan CJ, Derksen PWB, Jonkers J, Tutt ANJ, Ashworth A, Lord CJ. E-Cadherin/ROS1 Inhibitor Synthetic Lethality in Breast Cancer. Cancer Discov. 2018 Apr;8(4): 498-515. doi: 10.1158/2159-8290.CD-17-0603. PubMed PMID: 29610289.
PIK3CB wild-type	Telford BJ, Chen A, Beetham H, Frick J, Brew TP, Gould CM, Single A, Godwin T, Simpson KJ, Guilford P. Synthetic Lethal Screens Identify Vulnerabilities in GPCR Signaling and Cytoskeletal Organization in E-Cadherin-Deficient Cells. Mol Cancer Ther. 2015 May;14(5):1213-23. doi: 10.1158/1535-7163.MCT-14-1092. Epub 2015 Mar 16. PubMed PMID: 25777964. Li D, Lo W, Rudloff U. Merging perspectives: genotype-directed molecular therapy for hereditary diffuse gastric cancer (HDGC) and E-cadherin-EGFR crosstalk. Clin Transl Med. 2018 Feb 22;7(1):7. doi: 10.1186/s40169-018-0184-7. PubMed PMID: 29468433; PubMed Central PMCID: PMC5821620.

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TARGET GENES	REFERENCES
ALK wild-type	Telford BJ, Chen A, Beetham H, Frick J, Brew TP, Gould CM, Single A, Godwin T, Simpson KJ, Guilford P. Synthetic Lethal Screens Identify Vulnerabilities in GPCR Signaling and Cytoskeletal Organization in E-Cadherin-Deficient Cells. Mol Cancer Ther. 2015 May;14(5):1213-23. doi: 10.1158/1535-7163.MCT-14-1092. Epub 2015 Mar 16. PubMed PMID: 25777964. Li D, Lo W, Rudloff U. Merging perspectives: genotype-directed molecular therapy for hereditary diffuse gastric cancer (HDGC) and E-cadherin-EGFR crosstalk. Clin Transl Med. 2018 Feb 22;7(1):7. doi: 10.1186/s40169-018-0184-7. PubMed PMID: 29468433; PubMed Central PMCID: PMC5821620.
PIK3CD wild-type	Telford BJ, Chen A, Beetham H, Frick J, Brew TP, Gould CM, Single A, Godwin T, Simpson KJ, Guilford P. Synthetic Lethal Screens Identify Vulnerabilities in GPCR Signaling and Cytoskeletal Organization in E-Cadherin-Deficient Cells. Mol Cancer Ther. 2015 May;14(5):1213-23. doi: 10.1158/1535-7163.MCT-14-1092. Epub 2015 Mar 16. PubMed PMID: 25777964. Li D, Lo W, Rudloff U. Merging perspectives: genotype-directed molecular therapy for hereditary diffuse gastric cancer (HDGC) and E-cadherin-EGFR crosstalk. Clin Transl Med. 2018 Feb 22;7(1):7. doi: 10.1186/s40169-018-0184-7. PubMed PMID: 29468433; PubMed Central PMCID: PMC5821620.
AURKA wild-type	Telford BJ, Chen A, Beetham H, Frick J, Brew TP, Gould CM, Single A, Godwin T, Simpson KJ, Guilford P. Synthetic Lethal Screens Identify Vulnerabilities in GPCR Signaling and Cytoskeletal Organization in E-Cadherin-Deficient Cells. Mol Cancer Ther. 2015 May;14(5):1213-23. doi: 10.1158/1535-7163.MCT-14-1092. Epub 2015 Mar 16. PubMed PMID: 25777964. Li D, Lo W, Rudloff U. Merging perspectives: genotype-directed molecular therapy for hereditary diffuse gastric cancer (HDGC) and E-cadherin-EGFR crosstalk. Clin Transl Med. 2018 Feb 22;7(1):7. doi: 10.1186/s40169-018-0184-7. PubMed PMID: 29468433; PubMed Central PMCID: PMC5821620.
PIK3CG wild-type	Telford BJ, Chen A, Beetham H, Frick J, Brew TP, Gould CM, Single A, Godwin T, Simpson KJ, Guilford P. Synthetic Lethal Screens Identify Vulnerabilities in GPCR Signaling and Cytoskeletal Organization in E-Cadherin-Deficient Cells. Mol Cancer Ther. 2015 May;14(5):1213-23. doi: 10.1158/1535-7163.MCT-14-1092. Epub 2015 Mar 16. PubMed PMID: 25777964. Li D, Lo W, Rudloff U. Merging perspectives: genotype-directed molecular therapy for hereditary diffuse gastric cancer (HDGC) and E-cadherin-EGFR crosstalk. Clin Transl Med. 2018 Feb 22;7(1):7. doi: 10.1186/s40169-018-0184-7. PubMed PMID: 29468433; PubMed Central PMCID: PMC5821620.
AURKC wild-type	Telford BJ, Chen A, Beetham H, Frick J, Brew TP, Gould CM, Single A, Godwin T, Simpson KJ, Guilford P. Synthetic Lethal Screens Identify Vulnerabilities in GPCR Signaling and Cytoskeletal Organization in E-Cadherin-Deficient Cells. Mol Cancer Ther. 2015 May;14(5):1213-23. doi: 10.1158/1535-7163.MCT-14-1092. Epub 2015 Mar 16. PubMed PMID: 25777964. Li D, Lo W, Rudloff U. Merging perspectives: genotype-directed molecular therapy for hereditary diffuse gastric cancer (HDGC) and E-cadherin-EGFR crosstalk. Clin Transl Med. 2018 Feb 22;7(1):7. doi: 10.1186/s40169-018-0184-7. PubMed PMID: 29468433; PubMed Central PMCID: PMC5821620.
FGFR1 wild-type	Telford BJ, Chen A, Beetham H, Frick J, Brew TP, Gould CM, Single A, Godwin T, Simpson KJ, Guilford P. Synthetic Lethal Screens Identify Vulnerabilities in GPCR Signaling and Cytoskeletal Organization in E-Cadherin-Deficient Cells. Mol Cancer Ther. 2015 May;14(5):1213-23. doi: 10.1158/1535-7163.MCT-14-1092. Epub 2015 Mar 16. PubMed PMID: 25777964.
SRC wild-type	Telford BJ, Chen A, Beetham H, Frick J, Brew TP, Gould CM, Single A, Godwin T, Simpson KJ, Guilford P. Synthetic Lethal Screens Identify Vulnerabilities in GPCR Signaling and Cytoskeletal Organization in E-Cadherin-Deficient Cells. Mol Cancer Ther. 2015 May;14(5):1213-23. doi: 10.1158/1535-7163.MCT-14-1092. Epub 2015 Mar 16. PubMed PMID: 25777964.
JAK3 wild-type	Telford BJ, Chen A, Beetham H, Frick J, Brew TP, Gould CM, Single A, Godwin T, Simpson KJ, Guilford P. Synthetic Lethal Screens Identify Vulnerabilities in GPCR Signaling and Cytoskeletal Organization in E-Cadherin-Deficient Cells. Mol Cancer Ther. 2015 May;14(5):1213-23. doi: 10.1158/1535-7163.MCT-14-1092. Epub 2015 Mar 16. PubMed PMID: 25777964.
NPY5R wild-type	Telford BJ, Chen A, Beetham H, Frick J, Brew TP, Gould CM, Single A, Godwin T, Simpson KJ, Guilford P. Synthetic Lethal Screens Identify Vulnerabilities in GPCR Signaling and Cytoskeletal Organization in E-Cadherin-Deficient Cells. Mol Cancer Ther. 2015 May;14(5):1213-23. doi: 10.1158/1535-7163.MCT-14-1092. Epub 2015 Mar 16. PubMed PMID: 25777964.
RET wild-type	Telford BJ, Chen A, Beetham H, Frick J, Brew TP, Gould CM, Single A, Godwin T, Simpson KJ, Guilford P. Synthetic Lethal Screens Identify Vulnerabilities in GPCR Signaling and Cytoskeletal Organization in E-Cadherin-Deficient Cells. Mol Cancer Ther. 2015 May;14(5):1213-23. doi: 10.1158/1535-7163.MCT-14-1092. Epub 2015 Mar 16. PubMed PMID: 25777964.
JAK2 wild-type	Telford BJ, Chen A, Beetham H, Frick J, Brew TP, Gould CM, Single A, Godwin T, Simpson KJ, Guilford P. Synthetic Lethal Screens Identify Vulnerabilities in GPCR Signaling and Cytoskeletal Organization in E-Cadherin-Deficient Cells. Mol Cancer Ther. 2015 May;14(5):1213-23. doi: 10.1158/1535-7163.MCT-14-1092. Epub 2015 Mar 16. PubMed PMID: 25777964.
NTRK1 wild-type	Telford BJ, Chen A, Beetham H, Frick J, Brew TP, Gould CM, Single A, Godwin T, Simpson KJ, Guilford P. Synthetic Lethal Screens Identify Vulnerabilities in GPCR Signaling and Cytoskeletal Organization in E-Cadherin-Deficient Cells. Mol Cancer Ther. 2015 May;14(5):1213-23. doi: 10.1158/1535-7163.MCT-14-1092. Epub 2015 Mar 16. PubMed PMID: 25777964.
BCL2 wild-type	Telford BJ, Chen A, Beetham H, Frick J, Brew TP, Gould CM, Single A, Godwin T, Simpson KJ, Guilford P. Synthetic Lethal Screens Identify Vulnerabilities in GPCR Signaling and Cytoskeletal Organization in E-Cadherin-Deficient Cells. Mol Cancer Ther. 2015 May;14(5):1213-23. doi: 10.1158/1535-7163.MCT-14-1092. Epub 2015 Mar 16. PubMed PMID: 25777964.

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TARGET GENES	REFERENCES
PDGFRA wild-type	Telford BJ, Chen A, Beetham H, Frick J, Brew TP, Gould CM, Single A, Godwin T, Simpson KJ, Guilford P. Synthetic Lethal Screens Identify Vulnerabilities in GPCR Signaling and Cytoskeletal Organization in E-Cadherin-Deficient Cells. Mol Cancer Ther. 2015 May;14(5):1213-23. doi: 10.1158/1535-7163.MCT-14-1092. Epub 2015 Mar 16. PubMed PMID: 25777964.
PDGFRB wild-type	Telford BJ, Chen A, Beetham H, Frick J, Brew TP, Gould CM, Single A, Godwin T, Simpson KJ, Guilford P. Synthetic Lethal Screens Identify Vulnerabilities in GPCR Signaling and Cytoskeletal Organization in E-Cadherin-Deficient Cells. Mol Cancer Ther. 2015 May;14(5):1213-23. doi: 10.1158/1535-7163.MCT-14-1092. Epub 2015 Mar 16. PubMed PMID: 25777964.
JAK1 wild-type	Telford BJ, Chen A, Beetham H, Frick J, Brew TP, Gould CM, Single A, Godwin T, Simpson KJ, Guilford P. Synthetic Lethal Screens Identify Vulnerabilities in GPCR Signaling and Cytoskeletal Organization in E-Cadherin-Deficient Cells. Mol Cancer Ther. 2015 May;14(5):1213-23. doi: 10.1158/1535-7163.MCT-14-1092. Epub 2015 Mar 16. PubMed PMID: 25777964.
ABL1 wild-type	Telford BJ, Chen A, Beetham H, Frick J, Brew TP, Gould CM, Single A, Godwin T, Simpson KJ, Guilford P. Synthetic Lethal Screens Identify Vulnerabilities in GPCR Signaling and Cytoskeletal Organization in E-Cadherin-Deficient Cells. Mol Cancer Ther. 2015 May;14(5):1213-23. doi: 10.1158/1535-7163.MCT-14-1092. Epub 2015 Mar 16. PubMed PMID: 25777964.
GBF1 wild-type	Telford BJ, Chen A, Beetham H, Frick J, Brew TP, Gould CM, Single A, Godwin T, Simpson KJ, Guilford P. Synthetic Lethal Screens Identify Vulnerabilities in GPCR Signaling and Cytoskeletal Organization in E-Cadherin-Deficient Cells. Mol Cancer Ther. 2015 May;14(5):1213-23. doi: 10.1158/1535-7163.MCT-14-1092. Epub 2015 Mar 16. PubMed PMID: 25777964.
HMGCR wild-type	Single, Andrew, Augustine Chen, Bryony Telford, Henry Beetham, and Parry Guilford. "Abstract B41: Statins show synthetic lethality in E-cadherin-deficient cells and are synergistic with SRC and HDAC inhibitors." (2017): B41-B41.

DETAILED DESCRIPTION OF DRIVER AND TARGET GENES

DRIVER GENES

Name	Description
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.
CDH1	Cadherins are calcium-dependent cell adhesion proteins. They preferentially interact with themselves in a homophilic manner in connecting cells; cadherins may thus contribute to the sorting of heterogeneous cell types. CDH1 is involved in mechanisms regulating cell-cell adhesions, mobility and proliferation of epithelial cells. Has a potent invasive suppressor role. It is a ligand for integrin alpha-E/beta-7. E-Cad/CTF2 promotes non-amyloidogenic degradation of Abeta precursors. Has a strong inhibitory effect on APP C99 and C83 production.
CDKN1A	May be the important intermediate by which p53/TP53 mediates its role as an inhibitor of cellular proliferation in response to DNA damage. Binds to and inhibits cyclin-dependent kinase activity, preventing phosphorylation of critical cyclin-dependent kinase substrates and blocking cell cycle progression. Functions in the nuclear localization and assembly of cyclin D-CDK4 complex and promotes its kinase activity towards RB1. At higher stoichiometric ratios, inhibits the kinase activity of the cyclin D-CDK4 complex.
DAXX	Transcription corepressor known to repress transcriptional potential of several sumoylated transcription factors. Down-regulates basal and activated transcription. Its transcription repressor activity is modulated by recruiting it to subnuclear compartments like the nucleolus or PML/POD/ND10 nuclear bodies through interactions with MCSR1 and PML, respectively. Seems to regulate transcription in PML/POD/ND10 nuclear bodies together with PML and may influence TNFRSF6-dependent apoptosis thereby. Inhibits transcriptional activatiopn of PAX3 and ETS1 through direct protein-protein interactions. Modulates PAX5 activity; the function seems to involve CREBBP. Acts as an adapter protein in a MDM2-DAXX-USP7 complex by regulating the RING-finger E3 ligase MDM2 ubiquitination activity. Under non-stress condition, in association with the deubiquitinating USP7, prevents MDM2 self-ubiquitination and enhances the intrinsic E3 ligase activity of MDM2 towards TP53, thereby promoting TP53 ubiquitination and subsequent proteasomal degradation. Upon DNA damage, its association with MDM2 and USP7 is disrupted, resulting in increased MDM2 autoubiquitination and consequently, MDM2 degradation, which leads to TP53 stabilization. Acts as histone chaperone that facilitates deposition of histone H3.3. Acts as targeting component of the chromatin remodeling complex ATRX:DAXX which has ATP-dependent DNA translocase activity and catalyzes the replication-independent deposition of histone H3.3 in pericentric DNA repeats outside S-phase and telomeres, and the in vitro remodeling of H3.3-containing nucleosomes. Does not affect the ATPase activity of ATRX but alleviates its transcription repression activity. Upopn neuronal activation asociates with regulatory elements of selected immediate early genes where it promotes deposition of histone H3.3 which may be linked to transcriptional induction of these genes. Required for the recruitment of histone H3.3:H4 dimers to PML-nuclear bodies (PML-NBs); the process is independent of ATRX and facilitated by ASF1A; PML-NBs are suggested to function as regulatory sites for the incorporation of newly synthesized histone H3.3 into chromatin. In case of overexpression of centromeric histone variant CENPA (as found in various tumors) is involved in its mislocalization to chromosomes; the ectopic localization involves a heterotypic tetramer containing CENPA, and histones H3.3 and H4 and decreases binding of CTCF to chromatin. Proposed to mediate activation of the JNK pathway and apoptosis via MAP3K5 in response to signaling from TNFRSF6 and TGFBR2. Interaction with HSPB1/HSP27 may prevent interaction with TNFRSF6 and MAP3K5 and block DAXX-mediated apoptosis. In contrast, in lymphoid cells JNC activation and TNFRSF6-mediated apoptosis may not involve DAXX. Shows restriction activity towards human cytomegalovirus (HCMV).

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DETAILED DESCRIPTION OF DRIVER AND TARGET GENES

DRIVER GENES

Name	Description
DDR1	Tyrosine kinase that functions as cell surface receptor for fibrillar collagen and regulates cell attachment to the extracellular matrix, remodeling of the extracellular matrix, cell migration, differentiation, survival and cell proliferation. Collagen binding triggers a signaling pathway that involves SRC and leads to the activation of MAP kinases. Regulates remodeling of the extracellular matrix by up-regulation of the matrix metalloproteinases MMP2, MMP7 and MMP9, and thereby facilitates cell migration and wound healing. Required for normal blastocyst implantation during pregnancy, for normal mammary gland differentiation and normal lactation. Required for normal ear morphology and normal hearing (By similarity). Promotes smooth muscle cell migration, and thereby contributes to arterial wound healing. Also plays a role in tumor cell invasion. Phosphorylates PTPN11.
INPP4B	Catalyzes the hydrolysis of the 4-position phosphate of phosphatidylinositol 3,4-bisphosphate, inositol 1,3,4-trisphosphate and inositol 1,4-bisphosphate
KDR	Tyrosine-protein kinase that acts as a cell-surface receptor for VEGFA, VEGFC and VEGFD. Plays an essential role in the regulation of angiogenesis, vascular development, vascular permeability, and embryonic hematopoiesis. Promotes proliferation, survival, migration and differentiation of endothelial cells. Promotes reorganization of the actin cytoskeleton. Isoforms lacking a transmembrane domain, such as isoform 2 and isoform 3, may function as decoy receptors for VEGFA, VEGFC and/or VEGFD. Isoform 2 plays an important role as negative regulator of VEGFA- and VEGFC-mediated lymphangiogenesis by limiting the amount of free VEGFA and/or VEGFC and preventing their binding to FLT4. Modulates FLT1 and FLT4 signaling by forming heterodimers. Binding of vascular growth factors to isoform 1 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 and the activation of protein kinase C. Mediates activation of MAPK1/ERK2, MAPK3/ERK1 and the MAP kinase signaling pathway, as well as of the AKT1 signaling pathway. Mediates phosphorylation of PIK3R1, the regulatory subunit of phosphatidylinositol 3-kinase, reorganization of the actin cytoskeleton and activation of PTK2/FAK1. Required for VEGFA-mediated induction of NOS2 and NOS3, leading to the production of the signaling molecule nitric oxide (NO) by endothelial cells. Phosphorylates PLCG1. Promotes phosphorylation of FYN, NCK1, NOS3, PIK3R1, PTK2 /FAK1 and SRC.
KLHL6	Involved in B-lymphocyte antigen receptor signaling and germinal center formation.
MYC	Transcription factor that binds DNA in a non-specific manner, yet also specifically recognizes the core sequence 5-CAC[GA]TG-3. Activates the transcription of growth-related genes
NF1	Stimulates the GTPase activity of Ras. NF1 shows greater affinity for Ras GAP, but lower specific activity. May be a regulator of Ras activity.
NOTCH2	Functions as a receptor for membrane-bound ligands Jagged1, Jagged2 and Delta1 to regulate cell-fate determination. Upon ligand activation through the released notch intracellular domain (NICD) it forms a transcriptional activator complex with RBPJ/RBPSUH and activates genes of the enhancer of split locus. Affects the implementation of differentiation, proliferation and apoptotic programs (By similarity). Involved in bone remodeling and homeostasis. In collaboration with RELA/p65 enhances NFATc1 promoter activity and positively regulates RANKL-induced osteoclast differentiation.
PIM1	Proto-oncogene with serine/threonine kinase activity involved in cell survival and cell proliferation and thus providing a selective advantage in tumorigenesis. Exerts its oncogenic activity through: the regulation of MYC transcriptional activity, the regulation of cell cycle progression and by phosphorylation and inhibition of proapoptotic proteins (BAD, MAP3K5, FOXO3). Phosphorylation of MYC leads to an increase of MYC protein stability and thereby an increase of transcriptional activity. The stabilization of MYC exerted by PIM1 might explain partly the strong synergism between these two oncogenes in tumorigenesis. Mediates survival signaling through phosphorylation of BAD, which induces release of the anti-apoptotic protein Bcl-X(L)/BCL2L1. Phosphorylation of MAP3K5, an other proapoptotic protein, by PIM1, significantly decreases MAP3K5 kinase activity and inhibits MAP3K5-mediated phosphorylation of JNK and JNK/p38MAPK subsequently reducing caspase-3 activation and cell apoptosis. Stimulates cell cycle progression at the G1-S and G2-M transitions by phosphorylation of CDC25A and CDC25C. Phosphorylation of CDKN1A, a regulator of cell cycle progression at G1, results in the relocation of CDKN1A to the cytoplasm and enhanced CDKN1A protein stability. Promote cell cycle progression and tumorigenesis by down-regulating expression of a regulator of cell cycle progression, CDKN1B, at both transcriptional and post-translational levels. Phosphorylation of CDKN1B,induces 14-3-3-proteins binding, nuclear export and proteasome-dependent degradation. May affect the structure or silencing of chromatin by phosphorylating HP1 gamma/CBX3. Acts also as a regulator of homing and migration of bone marrow cells involving functional interaction with the CXCL12-CXCR4 signaling axis.
TNFRSF14	Receptor for BTLA. Receptor for TNFSF14/LIGHT and homotrimeric TNFSF1/lymphotoxin-alpha. Involved in lymphocyte activation. Plays an important role in HSV pathogenesis because it enhanced the entry of several wild-type HSV strains of both serotypes into CHO cells, and mediated HSV entry into activated human T-cells.
TP53	Acts as a tumor suppressor in many tumor types; induces growth arrest or apoptosis depending on the physiological circumstances and cell type. Involved in cell cycle regulation as a trans-activator that acts to negatively regulate cell division by controlling a set of genes required for this process. One of the activated genes is an inhibitor of cyclin-dependent kinases. Apoptosis induction seems to be mediated either by stimulation of BAX and FAS antigen expression, or by repression of Bcl-2 expression. In cooperation with mitochondrial PPIF is involved in activating oxidative stress-induced necrosis; the function is largely independent of transcription. Induces the transcription of long intergenic non-coding RNA p21 (lincRNA-p21) and lincRNA-Mkln1. LincRNA-p21 participates in TP53-dependent transcriptional repression leading to apoptosis and seem to have to effect on cell-cycle regulation. Implicated in Notch signaling cross-over. Prevents CDK7 kinase activity when associated to CAK complex in response to DNA damage, thus stopping cell cycle progression. Isoform 2 enhances the transactivation activity of isoform 1 from some but not all TP53-inducible promoters. Isoform 4 suppresses transactivation activity and impairs growth suppression mediated by isoform 1. Isoform 7 inhibits isoform 1-mediated apoptosis. Regulates the circadian clock by repressing CLOCK-ARNTL/BMAL1-mediated transcriptional activation of PER2 (PubMed: 24051492).

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DETAILED DESCRIPTION OF DRIVER AND TARGET GENES

TARGET GENES

Name	Description
ABL1	Non-receptor tyrosine-protein kinase that plays a role in many key processes linked to cell growth and survival such as cytoskeleton remodeling in response to extracellular stimuli, cell motility and adhesion, receptor endocytosis, autophagy, DNA damage response and apoptosis. Coordinates actin remodeling through tyrosine phosphorylation of proteins controlling cytoskeleton dynamics like WASF3 (involved in branch formation); ANXA1 (involved in membrane anchoring); DBN1, DBNL, CTTN, RAPH1 and ENAH (involved in signaling); or MAPT and PXN (microtubule-binding proteins). Phosphorylation of WASF3 is critical for the stimulation of lamellipodia formation and cell migration. Involved in the regulation of cell adhesion and motility through phosphorylation of key regulators of these processes such as BCAR1, CRK, CRKL, DOK1, EFS or NEDD9. Phosphorylates multiple receptor tyrosine kinases and more particularly promotes endocytosis of EGFR, facilitates the formation of neuromuscular synapses through MUSK, inhibits PDGFRB-mediated chemotaxis and modulates the endocytosis of activated B-cell receptor complexes. Other substrates which are involved in endocytosis regulation are the caveolin (CAV1) and RIN1. Moreover, ABL1 regulates the CBL family of ubiquitin ligases that drive receptor down-regulation and actin remodeling. Phosphorylation of CBL leads to increased EGFR stability. Involved in late-stage autophagy by regulating positively the trafficking and function of lysosomal components. ABL1 targets to mitochondria in response to oxidative stress and thereby mediates mitochondrial dysfunction and cell death. ABL1 is also translocated in the nucleus where it has DNA-binding activity and is involved in DNA-damage response and apoptosis. Many substrates are known mediators of DNA repair: DDB1, DDB2, ERCC3, ERCC6, RAD9A, RAD51, RAD52 or WRN. Activates the proapoptotic pathway when the DNA damage is too severe to be repaired. Phosphorylates TP73, a primary regulator for this type of damage-induced apoptosis. Phosphorylates the caspase CASP9 on Tyr-153 and regulates its processing in the apoptotic response to DNA damage. Phosphorylates PSMA7 that leads to an inhibition of proteasomal activity and cell cycle transition blocks. ABL1 acts also as a regulator of multiple pathological signaling cascades during infection. Several known tyrosine-phosphorylated microbial proteins have been identified as ABL1 substrates. This is the case of A36R of Vaccinia virus, Tir (translocated intimin receptor) of pathogenic E.coli and possibly Citrobacter, CagA (cytotoxin-associated gene A) of H.pylori, or AnkA (ankyrin repeat-containing protein A) of A.phagocytophilum. Pathogens can highjack ABL1 kinase signaling to reorganize the host actin cytoskeleton for multiple purposes, like facilitating intracellular movement and host cell exit. Finally, functions as its own regulator through autocatalytic activity as well as through phosphorylation of its inhibitor, ABI1.
ALK	Neuronal orphan receptor tyrosine kinase that is essentially and transiently expressed in specific regions of the central and peripheral nervous systems and plays an important role in the genesis and differentiation of the nervous system. Transduces signals from ligands at the cell surface, through specific activation of the mitogen-activated protein kinase (MAPK) pathway. Phosphorylates almost exclusively at the first tyrosine of the Y-x-x-x-Y-Y motif. Following activation by ligand, ALK induces tyrosine phosphorylation of CBL, FRS2, IRS1 and SHC1, as well as of the MAP kinases MAPK1/ERK2 and MAPK3/ERK1. Acts as a receptor for ligands pleiotrophin (PTN), a secreted growth factor, and midkine (MDK), a PTN-related factor, thus participating in PTN and MDK signal transduction. PTN-binding induces MAPK pathway activation, which is important for the anti-apoptotic signaling of PTN and regulation of cell proliferation. MDK-binding induces phosphorylation of the ALK target insulin receptor substrate (IRS1), activates mitogen-activated protein kinases (MAPKs) and PI3-kinase, resulting also in cell proliferation induction. Drives NF-kappa-B activation, probably through IRS1 and the activation of the AKT serine/threonine kinase. Recruitment of IRS1 to activated ALK and the activation of NF-kappa-B are essential for the autocrine growth and survival signaling of MDK.
ATR	Serine/threonine protein kinase which activates checkpoint signaling upon genotoxic stresses such as ionizing radiation (IR), ultraviolet light (UV), or DNA replication stalling, thereby acting as a DNA damage sensor. Recognizes the substrate consensus sequence [ST]-Q. Phosphorylates BRCA1, CHEK1, MCM2, RAD17, RPA2, SMC1 and p53 /TP53, which collectively inhibit DNA replication and mitosis and promote DNA repair, recombination and apoptosis. Phosphorylates Ser-139 of histone variant H2AX/H2AFX at sites of DNA damage, thereby regulating DNA damage response mechanism. Required for FANCD2 ubiquitination. Critical for maintenance of fragile site stability and efficient regulation of centrosome duplication.
AURKA	Mitotic serine/threonine kinases that contributes to the regulation of cell cycle progression. Associates with the centrosome and the spindle microtubules during mitosis and plays a critical role in various mitotic events including the establishment of mitotic spindle, centrosome duplication, centrosome separation as well as maturation, chromosomal alignment, spindle assembly checkpoint, and cytokinesis. Required for initial activation of CDK1 at centrosomes. Phosphorylates numerous target proteins, including ARHGEF2, BORA, BRCA1, CDC25B, DLGP5, HDAC6, KIF2A, LATS2, NDEL1, PARD3, PPP1R2, PLK1, RASSF1, TACC3, p53/TP53 and TPX2. Regulates KIF2A tubulin depolymerase activity. Required for normal axon formation. Plays a role in microtubule remodeling during neurite extension. Important for microtubule formation and/or stabilization. Also acts as a key regulatory component of the p53/TP53 pathway, and particularly the checkpoint-response pathways critical for oncogenic transformation of cells, by phosphorylating and stabilizing p53/TP53. Phosphorylates its own inhibitors, the protein phosphatase type 1 (PP1) isoforms, to inhibit their activity. Necessary for proper cilia disassembly prior to mitosis.
AURKB	Serine/threonine-protein kinase component of the chromosomal passenger complex (CPC), a complex that acts as a key regulator of mitosis. The CPC complex has essential functions at the centromere in ensuring correct chromosome alignment and segregation and is required for chromatin-induced microtubule stabilization and spindle assembly. Involved in the bipolar attachment of spindle microtubules to kinetochores and is a key regulator for the onset of cytokinesis during mitosis. Required for central/midzone spindle assembly and cleavage furrow formation. Key component of the cytokinesis checkpoint, a process required to delay abscission to prevent both premature resolution of intercellular chromosome bridges and accumulation of DNA damage: phosphorylates CHMP4C, leading to retain abscission-competent VPS4 (VPS4A and/or VPS4B) at the midbody ring until abscission checkpoint signaling is terminated at late cytokinesis (PubMed:22422861, PubMed:24814515). AURKB phosphorylates the CPC complex subunits BIRC5/survivin, CDCA8/borealin and INCENP. Phosphorylation of INCENP leads to increased AURKB activity. Other known AURKB substrates involved in centromeric functions and mitosis are CENPA, DES/desmin, GPAF, KIF2C, NSUN2, RACGAP1, SEPT1, VIM/vimentin, GSG2/Haspin, and histone H3. A positive feedback loop involving GSG2 and AURKB contributes to localization of CPC to centromeres. Phosphorylation of VIM controls vimentin filament segregation in cytokinetic process, whereas histone H3 is phosphorylated at Ser-10 and Ser-28 during mitosis (H3S10ph and H3S28ph, respectively). A positive feedback between GSG2 and AURKB contributes to CPC localization. AURKB is also required for kinetochore localization of

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Name	Description
	BUB1 and SGOL1. Phosphorylation of p53/TP53 negatively regulates its transcriptional activity. Key regulator of active promoters in resting B- and T-lymphocytes: acts by mediating phosphorylation of H3S28ph at active promoters in resting B-cells, inhibiting RNF2/RING1B-mediated ubiquitination of histone H2A and enhancing binding and activity of the USP16 deubiquitinase at transcribed genes.
BCL2	Suppresses apoptosis in a variety of cell systems including factor-dependent lymphohematopoietic and neural cells. Regulates cell death by controlling the mitochondrial membrane permeability. Appears to function in a feedback loop system with caspases. Inhibits caspase activity either by preventing the release of cytochrome c from the mitochondria and/or by binding to the apoptosis-activating factor (APAF-1).
BRD4	Chromatin reader protein that recognizes and binds acetylated histones and plays a key role in transmission of epigenetic memory across cell divisions and transcription regulation. Remains associated with acetylated chromatin throughout the entire cell cycle and provides epigenetic memory for postmitotic G1 gene transcription by preserving acetylated chromatin status and maintaining high-order chromatin structure. During interphase, plays a key role in regulating the transcription of signal-inducible genes by associating with the P-TEFb complex and recruiting it to promoters: BRD4 is required to form the transcriptionally active P-TEFb complex by displacing negative regulators such as HEXIM1 and 7SKsnRNA complex from P-TEFb, thereby transforming it into an active form that can then phosphorylate the C-terminal domain (CTD) of RNA polymerase II. Promotes phosphorylation of Ser-2 of the C-terminal domain (CTD) of RNA polymerase II. According to a report, directly acts as an atypical protein kinase and mediates phosphorylation of Ser-2 of the C-terminal domain (CTD) of RNA polymerase II; these data however need additional evidences in vivo (PubMed:22509028). In addition to acetylated histones, also recognizes and binds acetylated RELA, leading to further recruitment of the P-TEFb complex and subsequent activation of NF-kappa-B. Also acts as a regulator of p53/TP53-mediated transcription: following phosphorylation by CK2, recruited to p53/TP53 specific target promoters. Isoform B: Acts as a chromatin insulator in the DNA damage response pathway. Inhibits DNA damage response signaling by recruiting the condensin-2 complex to acetylated histones, leading to chromatin structure remodeling, insulating the region from DNA damage response by limiting spreading of histone H2AFX/H2A.x phosphorylation
CDK1	Plays a key role in the control of the eukaryotic cell cycle by modulating the centrosome cycle as well as mitotic onset; promotes G2-M transition, and regulates G1 progress and G1-S transition via association with multiple interphase cyclins. Required in higher cells for entry into S-phase and mitosis. Phosphorylates PARVA/actopaxin, APC, AMPH, APC, BARD1, Bcl-xL/BCL2L1, BRCA2, CALD1, CASP8, CDC7, CDC20, CDC25A, CDC25C, CC2D1A, CSNK2 proteins/CKII, FZR1/CDH1, CDK7, CEBPB, CHAMP1, DMD/dystrophin, EEF1 proteins/EF-1, EZH2, KIF11/EG5, EGFR, FANCG, FOS, GFAP, GOLGA2/GM130, GRASP1, UBE2A/hHR6A, HIST1H1 proteins/histone H1, HMGA1, HIVEP3/KRC, LMNA, LMNB, LMNC, LBR, LATS1, MAP1B, MAP4, MARCKS, MCM2, MCM4, MKLP1, MYB, NEFH, NFIC, NPC/nuclear pore complex, PITPNM1/NIR2, NPM1, NCL, NUCKS1, NPM1/numatrin, ORC1, PRKAR2A, EEF1E1/p18, EIF3F/p47, p53/TP53, NONO/p54NRB, PAPOLA, PLEC/plectin, RB1, UL40/R2, RAB4A, RAP1GAP, RCC1, RPS6KB1 /S6K1, KHDRBS1/SAM68, ESPL1, SKI, BIRC5/survivin, STIP1, TEX14, beta-tubulins, MAPT/TAU, NEDD1, VIM/vimentin, TK1, FOXO1, RUNX1/AML1, SIRT2 and RUNX2. CDK1/CDC2-cyclin-B controls pronuclear union in interphase fertilized eggs. Essential for early stages of embryonic development. During G2 and early mitosis, CDC25A/B/C-mediated dephosphorylation activates CDK1/cyclin complexes which phosphorylate several substrates that trigger at least centrosome separation, Golgi dynamics, nuclear envelope breakdown and chromosome condensation. Once chromosomes are condensed and aligned at the metaphase plate, CDK1 activity is switched off by WEE1- and PKMYT1-mediated phosphorylation to allow sister chromatid separation, chromosome decondensation, reformation of the nuclear envelope and cytokinesis. Inactivated by PKR/EIF2AK2- and WEE1-mediated phosphorylation upon DNA damage to stop cell cycle and genome replication at the G2 checkpoint thus facilitating DNA repair. Reactivated after successful DNA repair through WIP1-dependent signaling leading to CDC25A/B/C-mediated dephosphorylation and restoring cell cycle progression. In proliferating cells, CDK1-mediated FOXO1 phosphorylation at the G2-M phase represses FOXO1 interaction with 14-3-3 proteins and thereby promotes FOXO1 nuclear accumulation and transcription factor activity, leading to cell death of postmitotic neurons. The phosphorylation of beta-tubulins regulates microtubule dynamics during mitosis. NEDD1 phosphorylation promotes PLK1-mediated NEDD1 phosphorylation and subsequent targeting of the gamma-tubulin ring complex (gTuRC) to the centrosome, an important step for spindle formation. In addition, CC2D1A phosphorylation regulates CC2D1A spindle pole localization and association with SCC1/RAD21 and centriole cohesion during mitosis. The phosphorylation of Bcl-xL/BCL2L1 after prolongated G2 arrest upon DNA damage triggers apoptosis. In contrast, CASP8 phosphorylation during mitosis prevents its activation by proteolysis and subsequent apoptosis. This phosphorylation occurs in cancer cell lines, as well as in primary breast tissues and lymphocytes. EZH2 phosphorylation promotes H3K27me3 maintenance and epigenetic gene silencing. CALD1 phosphorylation promotes Schwann cell migration during peripheral nerve regeneration.
CDK12	Cyclin-dependent kinase that phosphorylates the C-terminal domain (CTD) of the large subunit of RNA polymerase II (POLR2A), thereby acting as a key regulator of transcription elongation. Regulates the expression of genes involved in DNA repair and is required for the maintenance of genomic stability. Preferentially phosphorylates Ser-5 in CTD repeats that are already phosphorylated at Ser-7, but can also phosphorylate Ser-2. Required for RNA splicing, possibly by phosphorylating SRSF1/SF2. Involved in regulation of MAP kinase activity, possibly leading to affect the response to estrogen inhibitors.
CDK2	Serine/threonine-protein kinase involved in the control of the cell cycle; essential for meiosis, but dispensable for mitosis. Phosphorylates CTNNB1, USP37, p53/TP53, NPM1, CDK7, RB1, BRCA2, MYC, NPAT, EZH2. Interacts with cyclins A, B1, B3, D, or E. Triggers duplication of centrosomes and DNA. Acts at the G1-S transition to promote the E2F transcriptional program and the initiation of DNA synthesis, and modulates G2 progression; controls the timing of entry into mitosis/meiosis by controlling the subsequent activation of cyclin B/CDK1 by phosphorylation, and coordinates the activation of cyclin B/CDK1 at the centrosome and in the nucleus. Crucial role in orchestrating a fine balance between cellular proliferation, cell death, and DNA repair in human embryonic stem cells (hESCs). Activity of CDK2 is maximal during S phase and G2; activated by interaction with cyclin E during the early stages of DNA synthesis to permit G1-S transition, and subsequently activated by cyclin A2 (cyclin A1 in germ cells) during the late stages of DNA replication to drive the transition from S phase to mitosis, the G2 phase. EZH2 phosphorylation promotes H3K27me3 maintenance and epigenetic gene silencing. Phosphorylates CABLES1 (By similarity). Cyclin E /CDK2 prevents oxidative stress-mediated Ras-induced senescence by phosphorylating MYC. Involved in G1-S phase DNA damage checkpoint that prevents cells with damaged DNA from initiating mitosis; regulates

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	homologous recombination-dependent repair by phosphorylating BRCA2, this phosphorylation is low in S phase when recombination is active, but increases as cells progress towards mitosis. In response to DNA damage, double-strand break repair by homologous recombination a reduction of CDK2-mediated BRCA2 phosphorylation. Phosphorylation of RB1 disturbs its interaction with E2F1. NPM1 phosphorylation by cyclin E/CDK2 promotes its dissociates from unduplicated centrosomes, thus initiating centrosome duplication. Cyclin E/CDK2-mediated phosphorylation of NPAT at G1-S transition and until prophase stimulates the NPAT-mediated activation of histone gene transcription during S phase. Required for vitamin D-mediated growth inhibition by being itself inactivated. Involved in the nitric oxide- (NO) mediated signaling in a nitrosylation/activation-dependent manner. USP37 is activated by phosphorylation and thus triggers G1-S transition. CTNNB1 phosphorylation regulates insulin internalization. Phosphorylates FOXP3 and negatively regulates its transcriptional activity and protein stability (By similarity).
CDK4	Ser/Thr-kinase component of cyclin D-CDK4 (DC) complexes that phosphorylate and inhibit members of the retinoblastoma (RB) protein family including RB1 and regulate the cell-cycle during G(1)/S transition. Phosphorylation of RB1 allows dissociation of the transcription factor E2F from the RB/E2F complexes and the subsequent transcription of E2F target genes which are responsible for the progression through the G(1) phase. Hypophosphorylates RB1 in early G(1) phase. Cyclin D-CDK4 complexes are major integrators of various mitogenenic and antimitogenic signals. Also phosphorylates SMAD3 in a cell-cycle-dependent manner and represses its transcriptional activity. Component of the ternary complex, cyclin D/CDK4/CDKN1B, required for nuclear translocation and activity of the cyclin D-CDK4 complex.
CDK9	Protein kinase involved in the regulation of transcription. Member of the cyclin-dependent kinase pair (CDK9/cyclin-T) complex, also called positive transcription elongation factor b (P-TEFb), which facilitates the transition from abortive to productive elongation by phosphorylating the CTD (C-terminal domain) of the large subunit of RNA polymerase II (RNAP II) POLR2A, SUPT5H and RDBP. This complex is inactive when in the 7SK snRNP complex form. Phosphorylates EP300, MYOD1, RPB1/POLR2A and AR, and the negative elongation factors DSIF and NELF. Regulates cytokine inducible transcription networks by facilitating promoter recognition of target transcription factors (e.g. TNF-inducible RELA/p65 activation and IL-6-inducible STAT3 signaling). Promotes RNA synthesis in genetic programs for cell growth, differentiation and viral pathogenesis. P-TEFb is also involved in cotranscriptional histone modification, mRNA processing and mRNA export. Modulates a complex network of chromatin modifications including histone H2B monoubiquitination (H2Bub1), H3 lysine 4 trimethylation (H3K4me3) and H3K36me3; integrates phosphorylation during transcription with chromatin modifications to control co-transcriptional histone mRNA processing. The CDK9/cyclin-K complex has also a kinase activity towards CTD of RNAP II and can substitute for CDK9/cyclin-T P-TEFb in vitro. Replication stress response protein; the CDK9/cyclin-K complex is required for genome integrity maintenance, by promoting cell cycle recovery from replication arrest and limiting single-stranded DNA amount in response to replication stress, thus reducing the breakdown of stalled replication forks and avoiding DNA damage. In addition, probable function in DNA repair of isoform 2 via interaction with KU70/XRCC6. Promotes cardiac myocyte enlargement. RPB1/POLR2A phosphorylation on Ser-2 in CTD activates transcription. AR phosphorylation modulates AR transcription factor promoter selectivity and cell growth. DSIF and NELF phosphorylation promotes transcription by inhibiting their negative effect. The phosphorylation of MYOD1 enhances its transcriptional activity and thus promotes muscle differentiation.
CHEK1	Serine/threonine-protein kinase which is required for checkpoint-mediated cell cycle arrest and activation of DNA repair in response to the presence of DNA damage or unreplicated DNA. May also negatively regulate cell cycle progression during unperturbed cell cycles. This regulation is achieved by a number of mechanisms that together help to preserve the integrity of the genome. Recognizes the substrate consensus sequence [R-X-X-S/T]. Binds to and phosphorylates CDC25A, CDC25B and CDC25C. Phosphorylation of CDC25A at Ser-178 and Thr-507 and phosphorylation of CDC25C at Ser-216 creates binding sites for 14-3-3 proteins which inhibit CDC25A and CDC25C. Phosphorylation of CDC25A at Ser-76, Ser-124, Ser-178, Ser-279 and Ser-293 promotes proteolysis of CDC25A. Phosphorylation of CDC25A at Ser-76 primes the protein for subsequent phosphorylation at Ser-79, Ser-82 and Ser-88 by NEK11, which is required for polyubiquitination and degradation of CDCD25A. Inhibition of CDC25 leads to increased inhibitory tyrosine phosphorylation of CDK-cyclin complexes and blocks cell cycle progression. Also phosphorylates NEK6. Binds to and phosphorylates RAD51 at Thr-309, which promotes the release of RAD51 from BRCA2 and enhances the association of RAD51 with chromatin, thereby promoting DNA repair by homologous recombination. Phosphorylates multiple sites within the C-terminus of TP53, which promotes activation of TP53 by acetylation and promotes cell cycle arrest and suppression of cellular proliferation. Also promotes repair of DNA cross-links through phosphorylation of FANCE. Binds to and phosphorylates TLK1 at Ser-743, which prevents the TLK1-dependent phosphorylation of the chromatin assembly factor ASF1A. This may enhance chromatin assembly both in the presence or absence of DNA damage. May also play a role in replication fork maintenance through regulation of PCNA. May regulate the transcription of genes that regulate cell-cycle progression through the phosphorylation of histones. Phosphorylates histone H3.1 (to form H3T11ph), which leads to epigenetic inhibition of a subset of genes. May also phosphorylate RB1 to promote its interaction with the E2F family of transcription factors and subsequent cell cycle arrest Isoform 2: Endogenous repressor of isoform 1, interacts with, and antagonizes CHK1 to promote the S to G2/M phase transition
FGFR1	Tyrosine-protein kinase that acts as cell-surface receptor for fibroblast growth factors and plays an essential role in the regulation of embryonic development, cell proliferation, differentiation and migration. Required for normal mesoderm patterning and correct axial organization during embryonic development, normal skeletogenesis and normal development of the gonadotropin-releasing hormone (GnRH) neuronal system. Phosphorylates PLCG1, FRS2, GAB1 and SHB. Ligand binding leads to the activation of several signaling cascades. Activation of PLCG1 leads to the production of the cellular signaling molecules diacylglycerol and inositol 1,4,5-trisphosphate. Phosphorylation of FRS2 triggers recruitment of GRB2, GAB1, PIK3R1 and SOS1, and mediates activation of RAS, MAPK1/ERK2, MAPK3/ERK1 and the MAP kinase signaling pathway, as well as of the AKT1 signaling pathway. Promotes phosphorylation of SHC1, STAT1 and PTPN11/SHP2. In the nucleus, enhances RPS6KA1 and CREB1 activity and contributes to the regulation of transcription. FGFR1 signaling is down-regulated by IL17RD/SEF, and by FGFR1 ubiquitination, internalization and degradation.
GBF1	This gene encodes a member of the Sec7 domain family. The encoded protein is a guanine nucleotide exchange factor that regulates the recruitment of proteins to membranes by mediating GDP to GTP exchange. The encoded protein is localized to the Golgi apparatus and plays a role in vesicular trafficking by activating ADP ribosylation

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	factor 1. The encoded protein has also been identified as an important host factor for viral replication. Multiple transcript variants have been observed for this gene.
HMGCR	HMG-CoA reductase is the rate-limiting enzyme for cholesterol synthesis and is regulated via a negative feedback mechanism mediated by sterols and non-sterol metabolites derived from mevalonate, the product of the reaction catalyzed by reductase. Normally in mammalian cells this enzyme is suppressed by cholesterol derived from the internalization and degradation of low density lipoprotein (LDL) via the LDL receptor. Competitive inhibitors of the reductase induce the expression of LDL receptors in the liver, which in turn increases the catabolism of plasma LDL and lowers the plasma concentration of cholesterol, an important determinant of atherosclerosis. Alternatively spliced transcript variants encoding different isoforms have been found for this gene.
JAK1	Tyrosine kinase of the non-receptor type, involved in the IFN-alpha/beta/gamma signal pathway. Kinase partner for the interleukin (IL)-2 receptor.
JAK2	Non-receptor tyrosine kinase involved in various processes such as cell growth, development, differentiation or histone modifications. Mediates essential signaling events in both innate and adaptive immunity. In the cytoplasm, plays a pivotal role in signal transduction via its association with type I receptors such as growth hormone (GHR), prolactin (PRLR), leptin (LEPR), erythropoietin (EPOR), thrombopoietin (THPO); or type II receptors including IFN-alpha, IFN-beta, IFN-gamma and multiple interleukins. Following ligand-binding to cell surface receptors, phosphorylates specific tyrosine residues on the cytoplasmic tails of the receptor, creating docking sites for STATs proteins. Subsequently, phosphorylates the STATs proteins once they are recruited to the receptor. Phosphorylated STATs then form homodimer or heterodimers and translocate to the nucleus to activate gene transcription. For example, cell stimulation with erythropoietin (EPO) during erythropoiesis leads to JAK2 autophosphorylation, activation, and its association with erythropoietin receptor (EPOR) that becomes phosphorylated in its cytoplasmic domain. Then, STAT5 (STAT5A or STAT5B) is recruited, phosphorylated and activated by JAK2. Once activated, dimerized STAT5 translocates into the nucleus and promotes the transcription of several essential genes involved in the modulation of erythropoiesis. In addition, JAK2 mediates angiotensin-2-induced ARHGEF1 phosphorylation. Plays a role in cell cycle by phosphorylating CDKN1B. Cooperates with TEC through reciprocal phosphorylation to mediate cytokine-driven activation of FOS transcription. In the nucleus, plays a key role in chromatin by specifically mediating phosphorylation of Tyr-41 of histone H3 (H3Y41ph), a specific tag that promotes exclusion of CBX5 (HP1 alpha) from chromatin.
JAK3	Non-receptor tyrosine kinase involved in various processes such as cell growth, development, or differentiation. Mediates essential signaling events in both innate and adaptive immunity and plays a crucial role in hematopoiesis during T-cells development. In the cytoplasm, plays a pivotal role in signal transduction via its association with type I receptors sharing the common subunit gamma such as IL2R, IL4R, IL7R, IL9R, IL15R and IL21R. Following ligand binding to cell surface receptors, phosphorylates specific tyrosine residues on the cytoplasmic tails of the receptor, creating docking sites for STATs proteins. Subsequently, phosphorylates the STATs proteins once they are recruited to the receptor. Phosphorylated STATs then form homodimer or heterodimers and translocate to the nucleus to activate gene transcription. For example, upon IL2R activation by IL2, JAK1 and JAK3 molecules bind to IL2R beta (IL2RB) and gamma chain (IL2RG) subunits inducing the tyrosine phosphorylation of both receptor subunits on their cytoplasmic domain. Then, STAT5A AND STAT5B are recruited, phosphorylated and activated by JAK1 and JAK3. Once activated, dimerized STAT5 translocates to the nucleus and promotes the transcription of specific target genes in a cytokine-specific fashion.
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 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.
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

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	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.
NPY5R	The protein encoded by this gene is a receptor for neuropeptide Y and peptide YY. The encoded protein appears to be involved in regulating food intake, with defects in this gene being associated with eating disorders. Also, the encoded protein is involved in a pathway that protects neuroblastoma cells from chemotherapy-induced cell death, providing a possible therapeutic target against neuroblastoma. Three transcript variants encoding the same protein have been found for this gene.
NTRK1	Receptor tyrosine kinase involved in the development and the maturation of the central and peripheral nervous systems through regulation of proliferation, differentiation and survival of sympathetic and nervous neurons. High affinity receptor for NGF which is its primary ligand, it can also bind and be activated by NTF3/neurotrophin-3. However, NTF3 only supports axonal extension through NTRK1 but has no effect on neuron survival. Upon dimeric NGF ligand-binding, undergoes homodimerization, autophosphorylation and activation. Recruits, phosphorylates and/or activates several downstream effectors including SHC1, FRS2, SH2B1, SH2B2 and PLCG1 that regulate distinct overlapping signaling cascades driving cell survival and differentiation. Through SHC1 and FRS2 activates a GRB2-Ras-MAPK cascade that regulates cell differentiation and survival. Through PLCG1 controls NF-Kappa-B activation and the transcription of genes involved in cell survival. Through SHC1 and SH2B1 controls a Ras-PI3 kinase-AKT1 signaling cascade that is also regulating survival. In absence of ligand and activation, may promote cell death, making the survival of neurons dependent on trophic factors Isoform TrkA-III is resistant to NGF, constitutively activates AKT1 and NF-kappa-B and is unable to activate the Ras-MAPK signaling cascade. Antagonizes the anti-proliferative NGF-NTRK1 signaling that promotes neuronal precursors differentiation. Isoform TrkA-III promotes angiogenesis and has oncogenic activity when overexpressed
PDGFRA	Tyrosine-protein kinase that acts as a cell-surface receptor for PDGFA, PDGFB and PDGFC and plays an essential role in the regulation of embryonic development, cell proliferation, survival and chemotaxis. Depending on the context, promotes or inhibits cell proliferation and cell migration. Plays an important role in the differentiation of bone marrow-derived mesenchymal stem cells. Required for normal skeleton development and cephalic closure during embryonic development. Required for normal development of the mucosa lining the gastrointestinal tract, and for recruitment of mesenchymal cells and normal development of intestinal villi. Plays a role in cell migration and chemotaxis in wound healing. Plays a role in platelet activation, secretion of agonists from platelet granules, and in thrombin-induced platelet aggregation. Binding of its cognate ligands - homodimeric PDGFA, homodimeric PDGFB, heterodimers formed by PDGFA and PDGFB or homodimeric PDGFC -leads to the activation of several signaling cascades; the response depends on the nature of the bound ligand and is modulated by the formation of heterodimers between PDGFRA and PDGFRB. Phosphorylates PIK3R1, PLCG1, and PTPN11. Activation of PLCG1 leads to the production of the cellular signaling molecules diacylglycerol and inositol 1,4,5-trisphosphate, mobilization of cytosolic Ca(2+) and the activation of protein kinase C. Phosphorylates PIK3R1, the regulatory subunit of phosphatidylinositol 3-kinase, and thereby mediates activation of the AKT1 signaling pathway. Mediates activation of HRAS and of the MAP kinases MAPK1/ERK2 and/or MAPK3/ERK1. Promotes activation of STAT family members STAT1, STAT3 and STAT5A and/or STAT5B. Receptor signaling is down-regulated by protein phosphatases that dephosphorylate the receptor and its down-stream effectors, and by rapid internalization of the activated receptor.
PDGFRB	Tyrosine-protein kinase that acts as cell-surface receptor for homodimeric PDGFB and PDGFD and for heterodimers formed by PDGFA and PDGFB, and plays an essential role in the regulation of embryonic development, cell proliferation, survival, differentiation, chemotaxis and migration. Plays an essential role in blood vessel development by promoting proliferation, migration and recruitment of pericytes and smooth muscle cells to endothelial cells. Plays a role in the migration of vascular smooth muscle cells and the formation of neointima at vascular injury sites. Required for normal development of the cardiovascular system. Required for normal recruitment of pericytes (mesangial cells) in the kidney glomerulus, and for normal formation of a branched network of capillaries in kidney glomeruli. Promotes rearrangement of the actin cytoskeleton and the formation of membrane ruffles. Binding of its cognate ligands - homodimeric PDGFB, heterodimers formed by PDGFA and PDGFB or homodimeric PDGFD -leads to the activation of several signaling cascades; the response depends on the nature of the bound ligand and is modulated by the formation of heterodimers between PDGFRA and PDGFRB. Phosphorylates PLCG1, PIK3R1, PTPN11, RASA1/GAP, CBL, SHC1 and NCK1. Activation of PLCG1 leads to the production of the cellular signaling molecules diacylglycerol and inositol 1,4,5-trisphosphate, mobilization of cytosolic Ca(2+) and the activation of protein kinase C. Phosphorylation of PIK3R1, the regulatory subunit of phosphatidylinositol 3-kinase, leads to the activation of the AKT1 signaling pathway. Phosphorylation of SHC1, or of the C-terminus of PTPN11, creates a binding site for GRB2, resulting in the activation of HRAS, RAF1 and down-stream MAP kinases, including MAPK1/ERK2 and/or MAPK3/ERK1. Promotes phosphorylation and activation of SRC family kinases. Promotes phosphorylation of PDCD6IP/ALIX and STAM. Receptor signaling is down-regulated by protein phosphatases that dephosphorylate the receptor and its down-stream effectors, and by rapid internalization of the activated receptor.
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

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	intracellular level of PtdIns3P (Phosphatidylinositol 3-phosphate) and activates PIK3C3 kinase activity. May act as a scaffold, independently of its lipid kinase activity to positively regulate autophagy. May have a role in insulin signaling as scaffolding protein in which the lipid kinase activity is not required. May have a kinase-independent function in regulating cell proliferation and in clathrin-mediated endocytosis. Mediator of oncogenic signal in cell lines lacking PTEN. The lipid kinase activity is necessary for its role in oncogenic transformation. Required for the growth of ERBB2 and RAS driven tumors
PIK3CG	Phosphoinositide-3-kinase (PI3K) that phosphorylates PtdIns(4,5)P2 (Phosphatidylinositol 4,5-bisphosphate) to generate phosphatidylinositol 3,4,5-trisphosphate (PIP3). PIP3 plays a key role by recruiting PH domain-containing proteins to the membrane, including AKT1 and PDPK1, activating signaling cascades involved in cell growth, survival, proliferation, motility and morphology. Links G-protein coupled receptor activation to PIP3 production. Involved in immune, inflammatory and allergic responses. Modulates leukocyte chemotaxis to inflammatory sites and in response to chemoattractant agents. May control leukocyte polarization and migration by regulating the spatial accumulation of PIP3 and by regulating the organization of F-actin formation and integrin-based adhesion at the leading edge. Controls motility of dendritic cells. Together with PIK3CD is involved in natural killer (NK) cell development and migration towards the sites of inflammation. Participates in T-lymphocyte migration. Regulates T-lymphocyte proliferation and cytokine production. Together with PIK3CD participates in T-lymphocyte development. Required for B-lymphocyte development and signaling. Together with PIK3CD participates in neutrophil respiratory burst. Together with PIK3CD is involved in neutrophil chemotaxis and extravasation. Together with PIK3CB promotes platelet aggregation and thrombosis. Regulates alpha-IIb/beta-3 integrins (ITGA2B/ITGB3) adhesive function in platelets downstream of P2Y12 through a lipid kinase activity-independent mechanism. May have also a lipid kinase activity-dependent function in platelet aggregation. Involved in endothelial progenitor cell migration. Negative regulator of cardiac contractility. Modulates cardiac contractility by anchoring protein kinase A (PKA) and PDE3B activation, reducing cAMP levels. Regulates cardiac contractility also by promoting beta-adrenergic receptor internalization by binding to ADRBK1 and by non-muscle tropomyosin phosphorylation. Also has serine/threonine protein kinase activity: both lipid and protein kinase activities are required for beta-adrenergic receptor endocytosis. May also have a scaffolding role in modulating cardiac contractility. Contributes to cardiac hypertrophy under pathological stress. Through simultaneous binding of PDE3B to RAPGEF3 and PIK3R6 is assembled in a signaling complex in which the PI3K gamma complex is activated by RAPGEF3 and which is involved in angiogenesis.
PIM1	Proto-oncogene with serine/threonine kinase activity involved in cell survival and cell proliferation and thus providing a selective advantage in tumorigenesis. Exerts its oncogenic activity through: the regulation of MYC transcriptional activity, the regulation of cell cycle progression and by phosphorylation and inhibition of proapoptotic proteins (BAD, MAP3K5, FOXO3). Phosphorylation of MYC leads to an increase of MYC protein stability and thereby an increase of transcriptional activity. The stabilization of MYC exerted by PIM1 might explain partly the strong synergism between these two oncogenes in tumorigenesis. Mediates survival signaling through phosphorylation of BAD, which induces release of the anti-apoptotic protein Bcl-X(L)/BCL2L1. Phosphorylation of MAP3K5, an other proapoptotic protein, by PIM1, significantly decreases MAP3K5 kinase activity and inhibits MAP3K5-mediated phosphorylation of JNK and JNK/p38MAPK subsequently reducing caspase-3 activation and cell apoptosis. Stimulates cell cycle progression at the G1-S and G2-M transitions by phosphorylation of CDC25A and CDC25C. Phosphorylation of CDKN1A, a regulator of cell cycle progression at G1, results in the relocation of CDKN1A to the cytoplasm and enhanced CDKN1A protein stability. Promote cell cycle progression and tumorigenesis by down-regulating expression of a regulator of cell cycle progression, CDKN1B, at both transcriptional and post-translational levels. Phosphorylation of CDKN1B,induces 14-3-3-proteins binding, nuclear export and proteasome-dependent degradation. May affect the structure or silencing of chromatin by phosphorylating HP1 gamma/CBX3. Acts also as a regulator of homing and migration of bone marrow cells involving functional interaction with the CXCL12-CXCR4 signaling axis.
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

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	transcription factor p73/TP73, leading to inhibit p73/TP73-mediated transcriptional activation and pro-apoptotic functions. Phosphorylates BORA, and thereby promotes the degradation of BORA. Contributes to the regulation of AURKA function. Also required for recovery after DNA damage checkpoint and entry into mitosis. Phosphorylates MISP, leading to stabilization of cortical and astral microtubule attachments required for proper spindle positioning (PubMed:8991084, PubMed:11202906, PubMed:12207013, PubMed:12447691, PubMed:12524548, PubMed:12738781, PubMed:12852856, PubMed:12939256, PubMed:14532005, PubMed:14734534, PubMed:15070733, PubMed:15148369, PubMed:15469984, PubMed:16198290, PubMed:16247472, PubMed:16980960, PubMed:17081991, PubMed:17351640, PubMed:17376779, PubMed:17617734, PubMed:18174154, PubMed:18331714, PubMed:18418051, PubMed:18477460, PubMed:18521620, PubMed:1
PRKDC	Serine/threonine-protein kinase that acts as a molecular sensor for DNA damage. Involved in DNA non-homologous end joining (NHEJ) required for double-strand break (DSB) repair and V(D)J recombination. Must be bound to DNA to express its catalytic properties. Promotes processing of hairpin DNA structures in V(D)J recombination by activation of the hairpin endonuclease artemis (DCLRE1C). The assembly of the DNA-PK complex at DNA ends is also required for the NHEJ ligation step. Required to protect and align broken ends of DNA. May also act as a scaffold protein to aid the localization of DNA repair proteins to the site of damage. Found at the ends of chromosomes, suggesting a further role in the maintenance of telomeric stability and the prevention of chromosomal end fusion. Also involved in modulation of transcription. Recognizes the substrate consensus sequence [ST]-Q. Phosphorylates Ser-139 of histone variant H2AX/H2AFX, thereby regulating DNA damage response mechanism. Phosphorylates DCLRE1C, c-Abl/ABL1, histone H1, HSPCA, c-jun/JUN, p53/TP53, PARP1, POU2F1, DHX9, SRF, XRCC1, XRCC1, XRCC4, XRCC5, XRCC6, WRN, MYC and RFA2. Can phosphorylate C1D not only in the presence of linear DNA but also in the presence of supercoiled DNA. Ability to phosphorylate p53/TP53 in the presence of supercoiled DNA is dependent on C1D. Contributes to the determination of the circadian period length by antagonizing phosphorylation of CRY1 Ser-588 and increasing CRY1 protein stability, most likely through an indirect machanism. Interacts with CRY1 and CRY2; negatively regulates CRY1 phosphorylation.
RARG	Receptor for retinoic acid. Retinoic acid receptors bind as heterodimers to their target response elements in response to their ligands, all-trans or 9-cis retinoic acid, and regulate gene expression in various biological processes. The RAR/RXR heterodimers bind to the retinoic acid response elements (RARE) composed of tandem 5'-AGGTCA-3' sites known as DR1-DR5. In the absence of ligand, acts mainly as an activator of gene expression due to weak binding to corepressors. Required for limb bud development. In concert with RARA or RARB, required for skeletal growth, matrix homeostasis and growth plate function (By similarity).
RET	Receptor tyrosine-protein kinase involved in numerous cellular mechanisms including cell proliferation, neuronal navigation, cell migration, and cell differentiation upon binding with glial cell derived neurotrophic factor family ligands. Phosphorylates PTK2/FAK1. Regulates both cell death/survival balance and positional information. Required for the molecular mechanisms orchestration during intestine organogenesis; involved in the development of enteric nervous system and renal organogenesis during embryonic life, and promotes the formation of Peyers patch-like structures, a major component of the gut-associated lymphoid tissue. Modulates cell adhesion via its cleavage by caspase in sympathetic neurons and mediates cell migration in an integrin (e.g. ITGB1 and ITGB3)-dependent manner. Involved in the development of the neural crest. Active in the absence of ligand, triggering apoptosis through a mechanism that requires receptor intracellular caspase cleavage. Acts as a dependence receptor; in the presence of the ligand GDNF in somatotrophs (within pituitary), promotes survival and down regulates growth hormone (GH) production, but triggers apoptosis in absence of GDNF. Regulates nociceptor survival and size. Triggers the differentiation of rapidly adapting (RA) mechanoreceptors. Mediator of several diseases such as neuroendocrine cancers; these diseases are characterized by aberrant integrins-regulated cell migration.
ROS1	Orphan receptor tyrosine kinase (RTK) that plays a role in epithelial cell differentiation and regionalization of the proximal epididymal epithelium. May activate several downstream signaling pathways related to cell differentiation, proliferation, growth and survival including the PI3 kinase-mTOR signaling pathway. Mediates the phosphorylation of PTPN11, an activator of this pathway. May also phosphorylate and activate the transcription factor STAT3 to control anchorage-independent cell growth. Mediates the phosphorylation and the activation of VAV3, a guanine nucleotide exchange factor regulating cell morphology. May activate other downstream signaling proteins including AKT1, MAPK1, MAPK3, IRS1 and PLCG2.
SRC	Non-receptor protein tyrosine kinase which is activated following engagement of many different classes of cellular receptors including immune response receptors, integrins and other adhesion receptors, receptor protein tyrosine kinases, G protein-coupled receptors as well as cytokine receptors. Participates in signaling pathways that control a diverse spectrum of biological activities including gene transcription, immune response, cell adhesion, cell cycle progression, apoptosis, migration, and transformation. Due to functional redundancy between members of the SRC kinase family, identification of the specific role of each SRC kinase is very difficult. SRC appears to be one of the primary kinases activated following engagement of receptors and plays a role in the activation of other protein tyrosine kinase (PTK) families. Receptor clustering or dimerization leads to recruitment of SRC to the receptor complexes where it phosphorylates the tyrosine residues within the receptor cytoplasmic domains. Plays an important role in the regulation of cytoskeletal organization through phosphorylation of specific substrates such as AFAP1. Phosphorylation of AFAP1 allows the SRC SH2 domain to bind AFAP1 and to localize to actin filaments. Cytoskeletal reorganization is also controlled through the phosphorylation of cortactin (CTTN). When cells adhere via focal adhesions to the extracellular matrix, signals are transmitted by integrins into the cell resulting in tyrosine phosphorylation of a number of focal adhesion proteins, including PTK2/FAK1 and paxillin (PXN). In addition to phosphorylating focal adhesion proteins, SRC is also active at the sites of cell-cell contact adherens junctions and phosphorylates substrates such as beta-catenin (CTNNB1), delta-catenin (CTNND1), and plakoglobin (JUP). Another type of cell-cell junction, the gap junction, is also a target for SRC, which phosphorylates connexin-43 (GJA1). SRC is implicated in regulation of pre-mRNA-processing and phosphorylates RNA-binding proteins such as KHDRBS1. Also plays a role in PDGF-mediated tyrosine phosphorylation of both STAT1 and STAT3, leading to increased DNA binding activity of these transcription factors. Involved in the RAS pathway through phosphorylation of RASA1 and RASGRF1. Plays a role in EGF-mediated calcium-activated chloride channel activation. Required for epidermal growth factor receptor (EGFR) internalization through phosphorylation of clathrin heavy chain (CLTC and CLTCL1) at Tyr-1477. Involved in beta-arrestin (ARRB1 and ARRB2) desensitization through phosphorylation and activation of ADRBK1, leading to beta-arrestin phosphorylation and internalization. Has a critical role in the stimulation of the

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	CDK20/MAPK3 mitogen-activated protein kinase cascade by epidermal growth factor. Might be involved not only in mediating the transduction of mitogenic signals at the level of the plasma membrane but also in controlling progression through the cell cycle via interaction with regulatory proteins in the nucleus. Plays an important role in osteoclastic bone resorption in conjunction with PTK2B/PYK2. Both the formation of a SRC-PTK2B/PYK2 complex and SRC kinase activity are necessary for this function. Recruited to activated integrins by PTK2B/PYK2, thereby phosphorylating CBL, which in turn induces the activation and recruitment of phosphatidylinositol 3-kinase to the cell membrane in a signaling pathway that is critical for osteoclast function. Promotes energy production in osteoclasts by activating mitochondrial cytochrome C oxidase. Phosphorylates DDR2 on tyrosine residues, thereby promoting its subsequent autophosphorylation. Phosphorylates RUNX3 and COX2 on tyrosine residues, TNK2 on Tyr-284 and CBL on Tyr-731. Enhances DDX58/RIG-I-elicited antiviral signaling. Phosphorylates PDPK1 at Tyr-9, Tyr-373 and Tyr-376. Phosphorylates BCAR1 at Tyr-128. Phosphorylates CBLC at multiple tyrosine residues, phosphorylation at Tyr-341 activates CBLC E3 activity.
WEE1	Acts as a negative regulator of entry into mitosis (G2 to M transition) by protecting the nucleus from cytoplasmically activated cyclin B1-complexed CDK1 before the onset of mitosis by mediating phosphorylation of CDK1 on Tyr-15. Specifically phosphorylates and inactivates cyclin B1-complexed CDK1 reaching a maximum during G2 phase and a minimum as cells enter M phase. Phosphorylation of cyclin B1-CDK1 occurs exclusively on Tyr-15 and phosphorylation of monomeric CDK1 does not occur. Its activity increases during S and G2 phases and decreases at M phase when it is hyperphosphorylated. A correlated decrease in protein level occurs at M/G1 phase, probably due to its degradation

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

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

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