ONCOMPASS™ REPORT

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Oncompass Report

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ID	201007
NAME	Anonymous
RELEASE DATE	2018-10-19 09:41

PATIENT INFORMATION

Oncompass™ ID: 123152
Name: Anonymous
Year of birth: 1953

Primary Tumor Site: soft tissue
Histology Type: giant cell tumor
Metastatic sites: lung, bone

MEDICAL TEAM

Molecular Pharmacologist: István Peták MD PhD
Molecular Biologist: Edit Várkondi PhD
Genetic Counselor: Júlia Déri MSc
Consulting Physician: Csongor Lengyel MD
Case Coordinator: Lilian Hári

PATHOLOGICAL AND MOLECULAR DIAGNOSTIC TESTS

Oncompass tumor molecular profiling was performed on a sample from the pleura of the patient.
Tumor cell ratio selected for molecular testing: 50%

Tests performed:
NGS - 595 genes

SUMMARY

The mutation in the PIK3CA gene (PIK3CA-E542K) is a well-known Class 1 activating hot spot mutation in the catalytic subunit of the PIK3CA gene (PIK3CA-E542K). The driver mutation in the PIK3CA oncogene, may be associated with sensitivity to PAM-pathway (PI3K/AKT/mTOR) inhibitors. Based on preclinical evidence activating PIK3CA mutations increase the sensitivity to PIK3CA inhibitors. COPANLISIB is an FDA approved PIK3CA inhibitor for follicular lymphoma patients. EVEROLIMUS, TEMSIROLIMUS, METFORMIN and SIROLIMUS are mTOR inhibitors in clinical use.

The mutation in the CHEK2 gene (CHEK2-D438Y) was interpreted as a driver mutation as well since it may cause partial loss-of-function of the CHEK2 protein. PARP- and SOD1 inhibitors are in positive association with loss-of-function CHEK2 mutations. PARP inhibitors in clinical use are OLAPARIB, RUCAPARIB and NIRAPARIB. Niraparib is approved by the FDA only. The ATN-224 SOD1 inhibitor is currently being tested in several trials (Phase 2 in CRC, in oesophageal cancer, in HCC, in melanoma, in breast and prostate cancer, Phase 1-2 in NSCLC and Multiple Myeloma).

The following alterations were classified as drivers by the Precision Oncology Calculator: LTK-D535N, ESR1-G90D, WRN-Y1034F. This classification provided by the Precision Oncology Calculator is based on its actual evidence database, because the scientific literature associated other mutations of the affected genes in tumorigenesis. It is important to emphasize that - according to our present knowledge- by manual interpretation none of these alterations were described to be clinically relevant nor actionable. The following alterations were classified as non-confirmed drivers: ROS1-T734M. The following alterations were classified as VUS (Variant of Unknown Significance): MST1R-H1184R. The following alterations were classified as polymorphisms: CYP2B6-M46V, CYP2D6-R278L, SMO-R168H. Hereby I attach the Report with the open clinical trials (33 trials are listed), the patient has no trial option in Turkey. In the US the NCT02834013 trial titled Nivolumab and Ipilimumab in Treating Patients With Rare Tumors may be an option.

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MOLECULAR TARGET ANALYSIS

MOLECULAR ALTERATIONS

PIK3CA-E542K driver (AEL: 195.58, AF/TR: 17.73%/50%),
CHEK2-D438Y driver (AEL: 37.35, AF/TR: 60.27%/50%),
ESR1-G90D driver (AEL: 20.76, AF/TR: 51.52%/50%),
LTK-D535N driver (AEL: 2.35, AF/TR: 60.14%/50%),
WRN-Y1034F driver (AEL: 0.35, AF/TR: 48.72%/50%),
TP53 wild-type biomarker (AEL: 0.00),
NF2-S205* non-confirmed driver (AEL: 0.00, AF/TR: 2%/50%),
SPTA1-H126Y non-confirmed driver (AEL: 0.00, AF/TR: 52.39%/50%),
ROS1-T734M non-confirmed driver (AEL: 0.00, AF/TR: 52.72%/50%),
CYP2B6-M46V variant of unknown significance (AEL: 0.00, AF/TR: 44.96%/50%),
BCL9-M1211I variant of unknown significance (AEL: 0.00, AF/TR: 47.85%/50%),
MUC16-S11201F variant of unknown significance (AEL: 0.00, AF/TR: 45.65%/50%),
CYP2D6-R278L variant of unknown significance (AEL: 0.00, AF/TR: 14.42%/50%),
PRDM1-S220N variant of unknown significance (AEL: 0.00, AF/TR: 64.69%/50%),
CHD1-V238I variant of unknown significance (AEL: 0.00, AF/TR: 59.83%/50%),
TMEM127-Q160DEL variant of unknown significance (AEL: 0.00, AF/TR: 1%/50%),
KMT2A-G909D variant of unknown significance (AEL: 0.00, AF/TR: 49.58%/50%),
ARID2-A838P variant of unknown significance (AEL: 0.00, AF/TR: 47.71%/50%),
BCL6-E164D variant of unknown significance (AEL: 0.00, AF/TR: 46%/50%),
MST1R-H1184R variant of unknown significance (AEL: 0.00, AF/TR: 49.78%/50%),
HSPH1-Q465R variant of unknown significance (AEL: 0.00, AF/TR: 37.72%/50%),
RANBP2-T2500I non-driver (AEL: -0.14, AF/TR: 42.23%/50%),
SMO-R168H non-driver (AEL: -3.95, AF/TR: 53.61%/50%)

TARGET GENES

PIK3CA wild-type (AEL: 228.53),
- PIK3CA-E542K driver (AEL: 195.58)

mTOR wild-type (AEL: 200.31),
- PIK3CA-E542K driver (AEL: 195.58)

PIK3CA ngs mutant (AEL: 199.01),
- PIK3CA-E542K driver (AEL: 195.58)

AKT1 wild-type (AEL: 196.69),
- PIK3CA-E542K driver (AEL: 195.58)

AKT2 wild-type (AEL: 196.69),
- PIK3CA-E542K driver (AEL: 195.58)

AKT3 wild-type (AEL: 195.94),
- PIK3CA-E542K driver (AEL: 195.58)

SOD1 wild-type (AEL: 147.81),
- CHEK2-D371Y driver (AEL: 27.33) ;
- CHEK2-D481Y driver (AEL: 27.33) ;
- CHEK2-D217Y driver (AEL: 27.33) ;
- CHEK2-D438Y driver (AEL: 37.35) ;
- CHEK2-D409Y driver (AEL: 27.33)

PARP1 wild-type (AEL: 147.63),
- CHEK2-D481Y driver (AEL: 27.33) ;
- CHEK2-D217Y driver (AEL: 27.33) ;
- CHEK2-D371Y driver (AEL: 27.33) ;
- CHEK2-D438Y driver (AEL: 37.35) ;
- CHEK2-D409Y driver (AEL: 27.33)

MDM2 wild-type (AEL: 0.46)

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DRUGS POSITIVELY ASSOCIATED

DRUGS IN CLINICAL USE
10 selected from 13

METFORMIN (AEL: 428.84)
- PIK3CA wild-type target (AEL: 228.53) ;
- mTOR wild-type target (AEL: 200.31)

EVEROLIMUS (rectum - neuroendocrine carcinoma [FDA+EMEA]; all - neuroendocrine carcinoma [FDA]; kidney - renal cell carcinoma [FDA+EMEA]; pancreas - all [FDA]; pancreas - neuroendocrine carcinoma [FDA+EMEA]; breast - all [FDA+EMEA]; colon - neuroendocrine carcinoma [FDA+EMEA]; lung - neuroendocrine carcinoma [FDA+EMEA]) (AEL: 402.84)
- mTOR wild-type target (AEL: 200.31) ;
- PIK3CA-E542K driver (AEL: 195.58)

SIROLIMUS (AEL: 396.94)
- PIK3CA-E542K driver (AEL: 195.58) ;
- mTOR wild-type target (AEL: 200.31)

OLAPARIB (fallopian tube - all [FDA]; ovary - all [FDA]; peritoneum - all [FDA]) (AEL: 335.08)
- CHEK2-D217Y driver (AEL: 27.33) ;
- CHEK2-D438Y driver (AEL: 37.35) ;
- CHEK2-D409Y driver (AEL: 27.33) ;
- PARP1 wild-type target (AEL: 147.63) ;
- CHEK2-D371Y driver (AEL: 27.33) ;
- CHEK2-D481Y driver (AEL: 27.33)

aspirin (AEL: 308.26)
- PIK3CA-E542K driver (AEL: 195.58)

PALBOCICLIB (breast - all [FDA]) (AEL: 229.82)
- PIK3CA-E542K driver (AEL: 195.58)

Copanlisib (lymph node - follicular non-hodgkin lymphoma [FDA]) (AEL: 228.53)
- PIK3CA wild-type target (AEL: 228.53)

TEMSIROLIMUS (kidney - renal cell carcinoma [FDA]) (AEL: 200.38)
- mTOR wild-type target (AEL: 200.31)

NIRAPARIB (ovary - epithelial carcinoma [FDA]; peritoneum - all [FDA]; fallopian tube - all [FDA]) (AEL: 147.63)
- PARP1 wild-type target (AEL: 147.63)

RUCAPARIB (ovary - all [FDA]) (AEL: 147.63)
- PARP1 wild-type target (AEL: 147.63)

DRUGS NEGATIVELY ASSOCIATED

DRUGS IN CLINICAL USE
11 selected from 17

PANITUMUMAB (rectum - all [FDA]; colon - all [FDA]) (AEL: -448.22)
- PIK3CA-E542K driver (AEL: -195.58) ;
- EGFR wild-type target (AEL: -216.68)

CETUXIMAB (head-neck - squamous cell carcinoma [FDA+EMEA]; colon - all [FDA+EMEA]; rectum - all [FDA+EMEA]) (AEL: -446.97)
- PIK3CA-E542K driver (AEL: -195.58) ;
- EGFR wild-type target (AEL: -216.68)

DACOMITINIB (lung - non-small cell carcinoma [FDA]) (AEL: -414.99)
- EGFR wild-type target (AEL: -216.68) ;
- ERBB2 wild-type target (AEL: -198.49)

NERATINIB (breast - all [FDA]) (AEL: -414.89)
- ERBB2 wild-type target (AEL: -198.49) ;
- EGFR wild-type target (AEL: -216.68)

AFATINIB (lung - non-small cell carcinoma [FDA+EMEA]) (AEL: -414.84)
- EGFR wild-type target (AEL: -216.68) ;
- ERBB2 wild-type target (AEL: -198.49)

TRASTUZUMAB (gastroesophageal junction - adenocarcinoma [FDA]; stomach - adenocarcinoma [FDA]; breast - all [FDA]; gastric - adenocarcinoma [FDA]) (AEL: -400.21)
- PIK3CA-E542K driver (AEL: -195.58) ;
- ERBB2 wild-type target (AEL: -198.49)

BRIGATINIB (lung - non-small cell carcinoma [FDA]) (AEL: -216.68)
- EGFR wild-type target (AEL: -216.68)

VANDETANIB (thyroid - medullary carcinoma [FDA]) (AEL: -216.68)
- EGFR wild-type target (AEL: -216.68)

OSIMERTINIB (lung - non-small cell carcinoma [FDA]) (AEL: -216.68)
- EGFR wild-type target (AEL: -216.68)

NECITUMUMAB (lung - squamous [FDA]) (AEL: -216.53)
- EGFR wild-type target (AEL: -216.68)

GEFITINIB (lung - non-small cell carcinoma [FDA+EMEA]) (AEL: -216.29)
- EGFR wild-type target (AEL: -216.68)

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DRUGS POSITIVELY ASSOCIATED

DRUGS IN CLINICAL DEVELOPMENT
10 selected from 76

Dactolisib (AEL: 625.44)
- mTOR wild-type target (AEL: 200.31) ;
- PIK3CA wild-type target (AEL: 228.53) ;
- PIK3CA-E542K driver (AEL: 195.58)

TASELISIB (AEL: 624.49)
- PIK3CA ngs mutant target (AEL: 199.01) ;
- PIK3CA wild-type target (AEL: 228.53) ;
- PIK3CA-E542K driver (AEL: 195.58)

IPATASERTIB (AEL: 589.32)
- AKT3 wild-type target (AEL: 195.94) ;
- AKT2 wild-type target (AEL: 196.69) ;
- AKT1 wild-type target (AEL: 196.69)

VOXTALISIB (AEL: 429.03)
- mTOR wild-type target (AEL: 200.31) ;
- PIK3CA wild-type target (AEL: 228.53)

PI-103 (AEL: 428.84)
- PIK3CA wild-type target (AEL: 228.53) ;
- mTOR wild-type target (AEL: 200.31)

VS-5584 (AEL: 428.84)
- PIK3CA wild-type target (AEL: 228.53) ;
- mTOR wild-type target (AEL: 200.31)

PKI179 (AEL: 428.84)
- PIK3CA wild-type target (AEL: 228.53) ;
- mTOR wild-type target (AEL: 200.31)

LY3023414 (AEL: 428.84)
- PIK3CA wild-type target (AEL: 228.53) ;
- mTOR wild-type target (AEL: 200.31)

GSK2126458 (AEL: 428.84)
- mTOR wild-type target (AEL: 200.31) ;
- PIK3CA wild-type target (AEL: 228.53)

GEDATOLISIB (AEL: 428.84)
- mTOR wild-type target (AEL: 200.31) ;
- PIK3CA wild-type target (AEL: 228.53)

DRUGS NEGATIVELY ASSOCIATED

DRUGS IN CLINICAL DEVELOPMENT
9 selected from 35

Allitinib (AEL: -415.16)
- ERBB2 wild-type target (AEL: -198.49) ;
- EGFR wild-type target (AEL: -216.68)

AV-412 (AEL: -415.16)
- EGFR wild-type target (AEL: -216.68) ;
- ERBB2 wild-type target (AEL: -198.49)

CUDC-101 (AEL: -415.16)
- ERBB2 wild-type target (AEL: -198.49) ;
- EGFR wild-type target (AEL: -216.68)

PELITINIB (AEL: -415.16)
- EGFR wild-type target (AEL: -216.68) ;
- ERBB2 wild-type target (AEL: -198.49)

TAK-285 (AEL: -415.16)
- ERBB2 wild-type target (AEL: -198.49) ;
- EGFR wild-type target (AEL: -216.68)

S-222611 (AEL: -415.16)
- ERBB2 wild-type target (AEL: -198.49) ;
- EGFR wild-type target (AEL: -216.68)

BMS-690514 (AEL: -415.16)
- EGFR wild-type target (AEL: -216.68) ;
- ERBB2 wild-type target (AEL: -198.49)

AEE788 (AEL: -216.68)
- EGFR wild-type target (AEL: -216.68)

SAPITINIB (AEL: -216.68)
- EGFR wild-type target (AEL: -216.68)

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)

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AVAILABLE CLINICAL TRIALS

Search Criteria

IDENTIFIER	DESCRIPTION
NCT01226316	Safety, Tolerability & Potential Anti-cancer Activity of Increasing Doses of AZD5363 in Different Treatment Schedules

Active recruiting

Line	Phase	Compounds
Neoadjuvant-10	1a-1b	AZD5363

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

Inclusive Biomarkers

AKT1 ngs mutant, PIK3CA ngs mutant, PTEN ngs mutant

Active recruiting

Line	Phase	Compounds
Neoadjuvant-10	1a-1b	AZD5363

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

NCT02458638 — A Study of Atezolizumab in Advanced Solid Tumors

Active (not recruiting)

Line	Phase	Compounds
1-4	2	MPDL3280A

Countries	Allocation	Masking
Brazil, Germany, Russian Federation, Austria, Switzerland, Italy, United Kingdom, France, Ireland, Poland, Spain, Netherlands	N/A	Single Group Assignment

Active (not recruiting)

Line	Phase	Compounds
1-4	2	MPDL3280A

Countries	Allocation	Masking
Norway, Finland, Denmark, Turkey, Canada, United States	N/A	Single Group Assignment

Exclusive Biomarkers

PDL1 wild-type

NCT02410512 — A Dose-Escalation Study of the Safety and Pharmacokinetics of MOXR0916 and MPDL3280A in Patients With Locally Advanced or Metastatic Solid Tumors

Active (not recruiting)

Line	Phase	Compounds
Neoadjuvant-4	1a-1b	BEVACIZUMAB, MOXR0916, MOXR0916, MOXR0916, MPDL3280A, MPDL3280A

Countries	Allocation	Masking
	Non Randomized	Single Group Assignment

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AVAILABLE CLINICAL TRIALS

NCT02598960 A Phase 1/2a Dose Escalation and Cohort Expansion Study for Safety, Tolerability, and Efficacy of BMS-986156 Administered Alone and in Combination With Nivolumab (BMS-936558, Anti PD-1 Monoclonal Antibody) in Advanced Solid Tumors

Active (not recruiting)

Line	Phase	Compounds
2-10	1-2	BMS-986156, BMS-986156, NIVOLUMAB

Countries	Allocation	Masking
Germany, Belgium, Switzerland, Italy, France, Spain, Netherlands, United States, Canada	Non Randomized	Single Group Assignment

NCT02784795 A Study of LY3039478 in Participants With Advanced or Metastatic Solid Tumors

Active (not recruiting)

Line	Phase	Compounds
Neoadjuvant-10	1b	ABEMACICLIB, LY 3039478

Countries	Allocation	Masking
United States	N/A	Single Group Assignment

Active (not recruiting)

Line	Phase	Compounds
Neoadjuvant-10	1b	LY 2940680, LY 3039478

Countries	Allocation	Masking
United States	N/A	Single Group Assignment

Active (not recruiting)

Line	Phase	Compounds
Neoadjuvant-10	1b	LY3023414, LY3039478

Countries	Allocation	Masking
United States	N/A	Single Group Assignment

Active (not recruiting)

Line	Phase	Compounds
Neoadjuvant-10	1b	ABEMACICLIB, CARBOPLATIN, CISPLATIN, GEMCITABINE, LY 2940680, LY 3039478, LY3023414, LY3039478, LY3039478, LY3039478, LY3039478, LY3039478

Countries	Allocation	Masking
United States	Non Randomized	Single Group Assignment

Active (not recruiting)

Line	Phase	Compounds
Neoadjuvant-2	1b	CISPLATIN, GEMCITABINE, LY 3039478

Countries	Allocation	Masking
United States	N/A	Single Group Assignment

Active (not recruiting)

Line	Phase	Compounds
Neoadjuvant-3	1b	CARBOPLATIN, GEMCITABINE, LY 3039478

Countries	Allocation	Masking
United States	N/A	Single Group Assignment

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AVAILABLE CLINICAL TRIALS

NCT01714739 — A Phase 1/2 Study of the Combination of Lirilumab (Anti-KIR) Plus Nivolumab (Anti-PD-1) or Lirilumab Plus Nivolumab and Ipilimumab in Advanced Refractory Solid Tumors

Active (not recruiting)

Line	Phase	Compounds
2-6	1-2	IPILIMUMAB, LIRILUMAB, LIRILUMAB, NIVOLUMAB, NIVOLUMAB

Countries	Allocation	Masking
Germany, Singapore	Randomized	Double Blind

Active (not recruiting)

Line	Phase	Compounds
2-6	1-2	IPILIMUMAB, LIRILUMAB, LIRILUMAB, NIVOLUMAB, NIVOLUMAB

Countries	Allocation	Masking
Switzerland, Italy, France, United States, Spain, Canada	Randomized	Double Blind

NCT02130466 — A Study of the Safety and Efficacy of Pembrolizumab (MK-3475) in Combination With Trametinib and Dabrafenib in Participants With Advanced Melanoma (MK-3475-022/KEYNOTE-022)

Active recruiting

Line	Phase	Compounds
Neoadjuvant-10	1-2	PEMBROLIZUMAB, TRAMETINIB

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

Inclusive Biomarkers

BRAF wild-type

Active recruiting

Line	Phase	Compounds
Neoadjuvant-10	1-2	DABRAFENIB, DABRAFENIB, DABRAFENIB, PEMBROLIZUMAB, PEMBROLIZUMAB, PEMBROLIZUMAB, PLACEBO, TRAMETINIB, TRAMETINIB, TRAMETINIB

Countries	Allocation	Masking
Australia, Italy, Canada, United States	Randomized	Double Blind

Inclusive Biomarkers

BRAF-V600E, BRAF-V600K

NCT02588105 — Study to Assess the Safety and Preliminary Efficacy of AZD0156 at Increasing Doses Alone or in Combination With Other Anti-cancer Treatment in Patients With Advanced Cancer (AToM)

Active recruiting

Line	Phase	Compounds
2-10	1a-1b	AZD0156, OLAPARIB

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

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AVAILABLE CLINICAL TRIALS

NCT03127215 Study of Olaparib/Trabectedin vs. Doctor's Choice in Solid Tumors (NCT-PMO-1603)

Not yet recruiting

Line	Phase	Compounds
2-10	2	OLAPARIB, TRABECTEDIN

Countries	Allocation	Masking
Germany	N/A	Single Group Assignment

NCT02684318 Study to Evaluate PM01183 in Combination With Olaparib in Advanced Solid Tumors

Active recruiting

Line	Phase	Compounds
2-10	1a-1b	OLAPARIB, PM01183

Countries	Allocation	Masking
Spain	N/A	Single Group Assignment

Active recruiting

Line	Phase	Compounds
2-10	2	OLAPARIB, PM01183

Countries	Allocation	Masking
Spain	N/A	Single Group Assignment

Active recruiting

Line	Phase	Compounds
2-10	2	OLAPARIB, PM01183

Countries	Allocation	Masking
Spain	N/A	Single Group Assignment

Inclusive Biomarkers

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

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AVAILABLE CLINICAL TRIALS

NCT02758587 Study of FAK (Defactinib) and PD-1 (Pembrolizumab) Inhibition in Advanced Solid Malignancies (FAK-PD1)

Active recruiting

Line	Phase	Compounds
Neoadjuvant-10	2	DEFACTINIB, PEMBROLIZUMAB

Countries	Allocation	Masking
United Kingdom	N/A	Single Group Assignment

Active recruiting

Line	Phase	Compounds
Neoadjuvant-10	2	DEFACTINIB, PEMBROLIZUMAB

Countries	Allocation	Masking
United Kingdom	N/A	Single Group Assignment

Active recruiting

Line	Phase	Compounds
Neoadjuvant-10	1a-1b	DEFACTINIB, PEMBROLIZUMAB

Countries	Allocation	Masking
United Kingdom	N/A	Single Group Assignment

Active recruiting

Line	Phase	Compounds
Neoadjuvant-10	2	DEFACTINIB, PEMBROLIZUMAB

Countries	Allocation	Masking
United Kingdom	N/A	Single Group Assignment

AVAILABLE CLINICAL TRIALS

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

Active recruiting

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

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

Active recruiting

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

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

Active recruiting

Line	Phase	Compounds
2	1-2	AZD6738, CARBOPLATIN

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

Inclusive Biomarkers

ATM loss presence, ATM protein lack of expression

Active recruiting

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

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

Inclusive Biomarkers

BRCA1 ngs mutant, BRCA2 ngs mutant

Exclusive Biomarkers

ERBB2 amplification presence, ERBB2 protein overexpression

Active recruiting

Line	Phase	Compounds
2	1-2	AZD6738, OLAPARIB

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

Active recruiting

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

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

Inclusive Biomarkers

ESR1 protein lack of expression, PGR protein lack of expression

Exclusive Biomarkers

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

Oncompass Report

powered by Realtime Oncology Molecular Treatment Calculator

ID	201007
NAME	Anonymous
RELEASE DATE	2018-10-19 09:41

AVAILABLE CLINICAL TRIALS

NCT03006172

A Phase I, Open-Label, Dose-Escalation Study Evaluating the Safety, Tolerability, and Pharmacokinetics of GDC-0077 as a Single Agent in Patients With Locally Advanced or Metastatic PIK3CA-Mutant Solid Tumors and in Combination With Endocrine and Targeted Therapies in Patients With Locally Advanced or Metastatic PIK3CA-Mutant Hormone-Receptor Positive Breast Cancer

Active recruiting

Line	Phase	Compounds
1-10	1a-1b	GDC-0077

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

Inclusive Biomarkers

PIK3CA ngs mutant

Active recruiting

Line	Phase	Compounds
1-10	1a-1b	FULVESTRANT, GDC-0077, LETROZOLE, PALBOCICLIB

Countries	Allocation	Masking
Spain, United States, Canada	Non Randomized	Single Group Assignment

Inclusive Biomarkers

ERBB2 protein lack of expression, ERBB2 amplification absence, ERBB2 protein normal expression, ESR1 protein overexpression, PGR protein overexpression, PIK3CA ngs mutant

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Not yet recruiting

Line	Phase	Compounds
1-10	1a-1b	GDC-0077

Countries	Allocation	Masking
United Kingdom, France	N/A	Single Group Assignment

Inclusive Biomarkers

PIK3CA ngs mutant

Not yet recruiting

Line	Phase	Compounds
1-10	1a-1b	FULVESTRANT, GDC-0077, LETROZOLE, PALBOCICLIB

Countries	Allocation	Masking
United Kingdom, France	Non Randomized	Single Group Assignment

Inclusive Biomarkers

ERBB2 amplification absence, ERBB2 protein normal expression, ERBB2 protein lack of expression, ESR1 protein overexpression, PGR protein overexpression, PIK3CA ngs mutant

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

DETAILED MOLECULAR PROFILE

MUTANT GENES

ARID2-A838P, BCL6-E164D, BCL9-M1211I, CHD1-V238I, CHEK2-D217Y, CHEK2-D371Y, CHEK2-D409Y, CHEK2-D438Y, CHEK2-D481Y, CYP2B6-M46V, CYP2D6-R278L, CYP2D6-R329L, ESR1-G90D, HSPH1-Q389R, HSPH1-Q465R, HSPH1-Q467R, KMT2A-G909D, LTK-D474N, LTK-D535N, MST1R-H1184R, MST1R-H1241R, MST1R-H1290R, MUC16-S11201F, NF2-S205*, NF2-S246*, NF2-S247*, NF2-S288*, PIK3CA-E542K, PRDM1-S220N, PRDM1-S354N, RANBP2-T2500I, ROS1-T734M, SMO-R168H, SPTA1-H126Y, TMEM127-Q160DEL, WRN-Y1034F

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DETAILED MOLECULAR PROFILE

WILD TYPE GENES

ABCB1, ABCC2, ABL1, ABL2, ACVR1B, ACVRL1, AGTRAP, AIP, AKAP9, AKT1, AKT2, AKT3, ALK, AMER1, AMPH, APC, APEX1, AR, ARAF, ARFRP1, ARID1A, ARID1B, ASXL1, ATM, ATP11B, ATP4A, ATP6V0D2, ATR, ATRX, AURKA, AURKB, AXIN1, AXIN2, AXL, B2M, BAI3, BAP1, BARD1, BAX, BAZ2B, BCL2, BCL2L1, BCL2L2, BCOR, BCORL1, BCR, BIM, BIRC2, BIRC3, BLM, BMPR1A, BRAF, BRCA1, BRCA2, BRD4, BRIP1, BTG1, BTK, BUB1B, CARD11, CASP8, CASR, CBFB, CBL, CBLB, CBLC, CCDC178, CCDC6, CCND1, CCND2, CCND3, CCNE1, CD74, CD79A, CD79B, CDA, CDC27, CDC73, CDH1, CDK12, CDK4, CDK6, CDK8, CDKN1A, CDKN1B, CDKN1C, CDKN2A, CDKN2B, CDKN2C, CEBPA, CEP57, CHD2, CHD4, CHD7, CHEK1, CHIC2, CIC, CIT, CREBBP, CRKL, CRLF2, CSF1R, CSMD3, CSNK2A1, CTCF, CTNNA1, CTNNB1, CUBN, CUL3, CYLD, CYP19A1, CYP2A6, CYP2C19, CYP2C9, DAXX, DCC, DCUN1D1, DDB2, DDR1, DDR2, DDX3X, DICER1, DIS3L2, DMD, DNMT3A, DOT1L, DPYD, DSE, ECT2L, EED, EGFR, ELMO1, EML4, EMSY, ENO1, EP300, EPB41, EPCAM, EPHA2, EPHA3, EPHA5, EPHA7, EPHB1, ERBB2, ERBB3, ERBB4, ERCC1, ERCC2, ERCC3, ERCC4, ERCC5, ERG, ERRFI1, ESR2, ESRP1, ETV6, EXOC2, EXT1, EXT2, EZH2, EZR, FAM175A, FAM46C, FANCA, FANCB, FANCC, FANCD2, FANCE, FANCF, FANCG, FANCI, FANCL, FANCM, FAS, FAT1, FAT3, FBXO11, FBXO32, FBXW7, FGF1, FGF10, FGF14, FGF19, FGF2, FGF23, FGF3, FGF4, FGF5, FGF6, FGF7, FGF8, FGF9, FGFR1, FGFR2, FGFR3, FGFR4, FH, FLCN, FLT1, FLT3, FLT4, FN1, FOXA1, FOXL2, FOXO1, FOXP1, FRS2, FSTL5, FUBP1, FZD3, G6PD, GABRA6, GAS6, GATA1, GATA2, GATA3, GATA4, GATA6, GEN1, GID4, GLI1, GNA11, GNA13, GNAI2, GNAQ, GNAS, GNAT2, GOPC, GPC3, GPR124, GPR78, GREM1, GRIN2A, GRM3, GRM8, GSK3B, GSTP1, GXYLT1, H3F3A, HGF, HIST1H3B, HNF1A, HOXB13, HRAS, HSD3B1, HSP90AA1, IDH1, IDH2, IFITM1, IFITM3, IGF1R, IGF2, IGF2R, IGSF10, IKBKE, IKZF1, IKZF4, IL2RA, IL2RB, IL2RG, IL6, IL6ST, IL7R, INHBA, INPP4B, IRAK4, IRF2, IRF4, IRS2, ITCH, JAK1, JAK2, JAK3, JUN, KAT6A, KDM4B, KDM5A, KDM5C, KDM6A, KDR, KEAP1, KEL, KIAA1549, KIF5B, KIT, KLC1, KLF6, KLHL6, KMT2C, KMT2D, KNSTRN, KRAS, KREMEN1, LAMA2, LCK, LMO1, LPAR2, LRP1B, LRRK2, LYN, LZTR1, MAGI2, MAGI3, MAGOH, MAP2K1, MAP2K2, MAP2K4, MAP3K1, MAP3K4, MAP4K3, MAP7, MAPK1, MAPK3, MAS1L, MAX, MCL1, MDM2, MDM4, MED12, MED13, MEF2B, MEN1, MET, MIER3, MITF, MLH1, MLLT3, MPL, MRE11, MSH2, MSH3, MSH6, MTOR, MUTYH, MYC, MYCL1, MYCN, MYD88, MYO18A, MYO1B, NBN, NCOA2, NCOR1, NEK2, NELL2, NF1, NFE2L2, NFKBIA, NIPA2, NKX2-1, NKX2-8, NKX3-1, NOTCH1, NOTCH2, NOTCH3, NPM1, NRAS, NRCAM, NRG1, NSD1, NT5C2, NTRK1, NTRK2, NTRK3, NUP93, OR5L1, OTOP1, PAK3, PALB2, PARK2, PAX3, PAX5, PAX7, PBRM1, PCBP1, PCGF2, PDGFRA, PDGFRB, PDK1, PDL1, PDL2, PDZRN3, PHF6, PHOX2B, PIK3C2B, PIK3CB, PIK3CD, PIK3CG, PIK3R1, PIK3R2, PLCG2, PMS1, PMS2, PNP, POLD1, POLE, POT1, PPARG, PPM1L, PPP2R1A, PPP2R2A, PREX2, PRF1, PRKAR1A, PRKCI, PRKDC, PRPF40B, PRSS8, PSMB1, PSMB2, PSMB5, PSMD1, PSMD2, PTCH1, PTEN, PTGFR, PTPN11, PTPN12, PTPRD, QKI, RAC1, RAC2, RAD21, RAD50, RAD51, RAD51B, RAD51C, RAD51D, RAD54L, RAF1, RARA, RARB, RARG, RB1, RBM10, RECQL4, RET, RHBDF2, RHEB, RHOA, RICTOR, RIT1, RNF43, RPS6KB1, RPTOR, RUNX1, RUNX1T1, RXRA, RXRB, RXRG, S1PR2, SAMD9L, SBDS, SCN11A, SDC4, SDHA, SDHAF2, SDHB, SDHC, SDHD, SEC16A, SEPT9, SETBP1, SETD2, SF1, SF3A1, SF3B1, SH2B3, SHH, SHOC2, SLC22A1, SLC22A2, SLC31A1, SLC34A2, SLC45A3, SLC7A8, SLC9A9, SLCO1B1, SLIT2, SLX4, SMAD2, SMAD3, SMAD4, SMARCA4, SMARCB1, SMARCE1, SMC1A, SMC3, SNCAIP, SOCS1, SOS1, SOX10, SOX2, SOX9, SPEG, SPEN, SPOP, SPRED1, SRC, SRSF2, SSTR1, STAG2, STAT3, STAT4, STK11, SUFU, SUZ12, SYK, SYNE3, TACC3, TAF1, TAS2R38, TBX20, TBX3, TCERG1, TCF7L2, TERT, TET2, TFG, TGFBR2, THSD7B, TIAF1, TMPRSS2, TNFAIP3, TNFRSF14, TOP1, TOP2A, TP53, TP53BP1, TP63, TPM3, TPM4, TPMT, TRAF5, TRIO, TRRAP, TSC1, TSC2, TSHR, TYK2, U2AF1, U2AF2, UBR3, UGT1A1, USP16, USP25, VCL, VEGFA, VHL, WBSCR17, WDCP, WEE1, WISP3, WNK2, WT1, WWP1, XPA, XPC, XPO1, XRCC2, YAP1, YES1, ZBED4, ZBTB2, ZFHX3, ZIC3, ZMYM3, ZNF2, ZNF217, ZNF226, ZNF473, ZNF595, ZNF703, ZRSR2

FISH/CNA/IHC POSITIVE GENES

FISH/CNA/IHC NEGATIVE GENES

ABL1 TRANSLOCATION ABSENCE, ALK TRANSLOCATION ABSENCE, BCR TRANSLOCATION ABSENCE, BRAF TRANSLOCATION ABSENCE, BRD4 TRANSLOCATION ABSENCE, CD74 TRANSLOCATION ABSENCE, EGFR TRANSLOCATION ABSENCE, FGFR1 TRANSLOCATION ABSENCE, FGFR2 TRANSLOCATION ABSENCE, FGFR3 TRANSLOCATION ABSENCE, KIF5B TRANSLOCATION ABSENCE, MET TRANSLOCATION ABSENCE, NRG1 TRANSLOCATION ABSENCE, NTRK1 TRANSLOCATION ABSENCE, RAF1 TRANSLOCATION ABSENCE, RARA TRANSLOCATION ABSENCE, RET TRANSLOCATION ABSENCE, ROS1 TRANSLOCATION ABSENCE, TACC1 TRANSLOCATION ABSENCE, TACC3 TRANSLOCATION ABSENCE

BIOINFORMATICAL AND FUNCTIONAL ANALYSIS

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DETAILED MOLECULAR PROFILE

MOLECULAR ALTERATIONS

PIK3CA-E542K driver (AEL: 195.58, AF/TR: 17.73%/50%),
CHEK2-D438Y driver (AEL: 37.35, AF/TR: 60.27%/50%),
ESR1-G90D driver (AEL: 20.76, AF/TR: 51.52%/50%),
LTK-D535N driver (AEL: 2.35, AF/TR: 60.14%/50%),
WRN-Y1034F driver (AEL: 0.35, AF/TR: 48.72%/50%),
TP53 wild-type biomarker (AEL: 0.00),
NF2-S205* non-confirmed driver (AEL: 0.00, AF/TR: 2%/50%),
SPTA1-H126Y non-confirmed driver (AEL: 0.00, AF/TR: 52.39%/50%),
ROS1-T734M non-confirmed driver (AEL: 0.00, AF/TR: 52.72%/50%),
CYP2B6-M46V variant of unknown significance (AEL: 0.00, AF/TR: 44.96%/50%),
BCL9-M1211I variant of unknown significance (AEL: 0.00, AF/TR: 47.85%/50%),
MUC16-S11201F variant of unknown significance (AEL: 0.00, AF/TR: 45.65%/50%),
CYP2D6-R278L variant of unknown significance (AEL: 0.00, AF/TR: 14.42%/50%),
PRDM1-S220N variant of unknown significance (AEL: 0.00, AF/TR: 64.69%/50%),
CHD1-V238I variant of unknown significance (AEL: 0.00, AF/TR: 59.83%/50%),
TMEM127-Q160DEL variant of unknown significance (AEL: 0.00, AF/TR: 1%/50%),
KMT2A-G909D variant of unknown significance (AEL: 0.00, AF/TR: 49.58%/50%),
ARID2-A838P variant of unknown significance (AEL: 0.00, AF/TR: 47.71%/50%),
BCL6-E164D variant of unknown significance (AEL: 0.00, AF/TR: 46%/50%),
MST1R-H1184R variant of unknown significance (AEL: 0.00, AF/TR: 49.78%/50%),
HSPH1-Q465R variant of unknown significance (AEL: 0.00, AF/TR: 37.72%/50%),
RANBP2-T2500I non-driver (AEL: -0.14, AF/TR: 42.23%/50%),
SMO-R168H non-driver (AEL: -3.95, AF/TR: 53.61%/50%)

TARGET GENES

PIK3CA wild-type (AEL: 228.53),
- PIK3CA-E542K driver (AEL: 195.58)

mTOR wild-type (AEL: 200.31),
- PIK3CA-E542K driver (AEL: 195.58)

PIK3CA ngs mutant (AEL: 199.01),
- PIK3CA-E542K driver (AEL: 195.58)

AKT1 wild-type (AEL: 196.69),
- PIK3CA-E542K driver (AEL: 195.58)

AKT2 wild-type (AEL: 196.69),
- PIK3CA-E542K driver (AEL: 195.58)

AKT3 wild-type (AEL: 195.94),
- PIK3CA-E542K driver (AEL: 195.58)

SOD1 wild-type (AEL: 147.81),
- CHEK2-D371Y driver (AEL: 27.33) ;
- CHEK2-D481Y driver (AEL: 27.33) ;
- CHEK2-D217Y driver (AEL: 27.33) ;
- CHEK2-D438Y driver (AEL: 37.35) ;
- CHEK2-D409Y driver (AEL: 27.33)

PARP1 wild-type (AEL: 147.63),
- CHEK2-D481Y driver (AEL: 27.33) ;
- CHEK2-D217Y driver (AEL: 27.33) ;
- CHEK2-D371Y driver (AEL: 27.33) ;
- CHEK2-D438Y driver (AEL: 37.35) ;
- CHEK2-D409Y driver (AEL: 27.33)

MDM2 wild-type (AEL: 0.46)

BIOINFORMATICAL AND FUNCTIONAL ANALYSIS

Oncompass tumor molecular profiling was performed on a sample from the pleura of the patient.
Sample ID: 2017B1754 - 1B, 1C, 1D, 1E, 1F, 1I, 1J, 1G, 1H, 2A, 2B, 3A, 3B, 3C, 4, 5, 6A, 6B, 7A, 7C, FBI, FBS, FPL
Tumor cell ratio selected for molecular testing: 50%

The NGS sequencing of 596 genes resulted in 4895 genetic alterations. The 22 variants listed in the molecular profile were selected via bioinformatic and functional filtering.
These variants have been uploaded into the Precision Medicine Calculator for further biomedical functional interpretation and medical decision support.

The following filters of the Ingenuity Variant Analysis software were used:

- CONFIDENCE: Filtering is based on variant call quality (QUAL), read depth (DP), allele fraction (computed from AD), upstream filter (PASS) and genotype quality (GQ). If the presence of a variant was uncertain based on the sequencing quality scores, the alteration was filtered out.
- COMMON VARIANTS: The filter is used to exclude variants that are commonly observed in the healthy population. If the frequency of a certain variant is at least 10% in the population according to the 1000 Genomes Project, the ExAC or the NHLBI ESP exomes database, it was excluded from further analysis.
- PREDICTED DELETERIOUS: The filter was used to identify variants in a dataset that have either predicted or observed evidence suggesting they could disrupt gene function or expression. The alterations, which are "benign" or "likely benign" according to the ACMG guideline were filtered out.
- CANCER DRIVER VARIANTS: The filter can be used to identify variants within a dataset that have predicted or established association with driving tumorigenesis or metastasis. Variants, which are related to cancer pathways, cell cycle regulation or cellular processes according to the scientific literature were selected. Alterations, which have been mentioned in the scientific literature related to cancer indication were also selected.

Other filtering methods were used besides the Variant Analysis:
- Non-exonic alterations were excluded
- Further bioinformatic filtering was used considering other sequencing quality scores

The filtered variants are listed in the molecular profile of the patient.

The evidence database related to variants of the following genes were also manually updated during the interpretation from publications identified in PUBMED:

BIOINFORMATICAL AND FUNCTIONAL ANALYSIS

ABCB1, ABCC2, ABL1, ABL2, AKT1, AKT2, AKT3, ALK, APC, ASXL1, ATM, ATRX, BRAF, BRCA1, BRCA2, CBL, CDA, CDH1, CDKN2A, CDKN2B, CEBPA, CHD7, CHEK2, CHIC2, CREBBP, CRLF2, CTNNB1, CYP19A1, CYP2A6, CYP2B6, CYP2C19, CYP2C9, CYP2D6, CSF1R, DDR1, DDR2, DDX3X, DNMT3A, DPYD, EGFR, ERBB2, ERBB3, ERBB4, ERG, ESR1, ESR2, EZH2, FBXW7, FGFR1, FGFR2, FGFR3, FGFR4, FLT1, FLT3, FLT4, FSTL5, GNA11, GNAQ, GNAS, GSTP1, H3F3A, HNF1A, HRAS, IDH1, IDH2, IGF1R, IKZF1, IL2RA, IL2RB, IL2RG, INPP4B, JAK1, JAK2, JAK3, KDM6A, KDR, KIT, KRAS, LAMA2, LCK, LTK, MAP2K1, MAP2K2, MAP2K4, MAP3K1, MAPK1, MED13, MET, MLH1, MLL, MPL, MSH2, MSH6, MST1R, MTOR, MYC, MYD88, NELL2, NF1, NOTCH1, NPM1, NRAS, NTRK1, NTRK2, NTRK3, PALB2, PDGFRA, PDGFRB, PHF6, PIK3CA, PIK3R1, PMS2, POLE, PSMB1, PSMB2, PSMB5, PSMD1, PSMD2, PTCH1, PTEN, PTPN11, PTPN12, PTPN13, RAF1, RARA, RARB, RARG, RB1, RET, ROS1, RPS6KB1, RUNX1, RXRA, RXRB, RXRG, SHH, SHOC2, SLC22A1, SLC22A2, SLC31A1, SLC34A2, SLC45A3, SLCO1B1, SMAD4, SMARCA4, SMARCB1, SMO, SNCAIP, SOS1, SPRED1, SRC, STAG2, STK11, SUFU, TAS2R38, TET2, TGFBR2, TP53, TRRAP, TSC1, TSC2, TYK2, UGT1A1, VHL, WT1, YES1, ZMYM3

A protein may have several isoforms depending on alternative transcription, splicing and different modifications during translation. Histology, developmental status and other circumstances define which transcript and which protein isoform is expressed (1, 2). With the NGS analysis the genomic sequence variants can be identified. The alterations identified in the genome can result in different protein changes in different transcripts. If a certain alteration has effect on multiple different protein isoforms, we marked the different transcript IDs according to NCBI Reference Sequence (RefSeq).

Databases used during the interpretation of the detected alterations:

COSMIC (Catalogue Of Somatic Mutations In Cancer): This database is designed to store and display somatic mutations detected in various neoplasms.
NCBI dbSNP (National Center for Biotechnology Information, Single Nucleotide Polymorphism database): Database dbSNP serves as a central repository for both single base nucleotide substitutions and short deletion and insertion polymorphisms detected as germline variants in either healthy population or in patients with various diseases (including, but not only cancer patients).
NCBI ClinVar: It is a publicly available archive of relations between human variations and phenotypes (clinical significance), with supporting evidence. It is not restricted to cancer diseases.

PIK3CA-E542K (in 17.73% of the DNA analyzed):
This alteration is listed in the COSMIC database. It has been detected in more than 1400 samples. In the scientific literature it is described as a driver mutation (3-5). The mutant protein has increased kinase activity and it is oncogenic (6).
Because of the driver mutation detected in the PIK3CA oncogene, the tumor is associated with response to PI3K/AKT/mTOR signaling pathway inhibitors (7-10). Based on preclinical evidence activating PIK3CA mutations increase the sensitivity to PIK3CA inhibitors (11).
COPANLISIB is an FDA approved PIK3CA inhibitor for follicular lymphoma patients. EVEROLIMUS, TEMSIROLIMUS, METFORMIN and SIROLIMUS are mTOR inhibitors in clinical use.

CHEK2-D438Y (CHEK2-D217Y, CHEK2-D481Y, CHEK2-D409Y, CHEK2-D371Y; in 60.27% of the DNA analyzed):
This alteration has uncertain significance according to the ClinVar database. It has been detected among diffuse large B-cell lymphoma patients (12). In a study this alteration was identified in a breast cancer patient with a family history of breast cancer, while it was absent in the control group. The authors concluded that this variant might increase the risk of breast cancer (13). In a large study no association was found between the presence of the variant and breast cancer risk, but it was associated with prostate cancer risk (14). According to in vitro analysis CHEK2 D438Y cause partial loss-of-function of the CHEK2 protein (15). It is considered as a driver mutation.
PARP (16, 17) and SOD1 (18) inhibitors are in positive association with loss-of-function CHEK2 mutations. PARP inhibitors in clinical use are OLAPARIB, RUCAPARIB and NIRAPARIB. Niraparib is approved by the FDA only.

LTK-D535N (LTK-D474N; in 60.14% of the DNA analyzed):
This alteration is listed in the dbSNP database (rs35932273). It has been detected in multiple myeloma (19). No experimental data is available about the functional significance of the variant.
The variant is classified as a driver by the algorithm of the Molecular Treatment Calculator using its actual evidence database.

ESR1-G90D (in 51.52% of the DNA analyzed):
No data is available in the scientific literature about the function of this variant.
The variant is classified as a driver by the algorithm of the Molecular Treatment Calculator using its actual evidence database. The classification is based on evidence describing the mutant gene or other specific mutations of the same gene as driver alterations.

ROS1-T734M (in 52.72% of the DNA analyzed)
No data is available in the scientific literature about the function of this variant.
The variant is classified as a non-confirmed driver by the algorithm of the Molecular Treatment Calculator based on its actual evidence database, because another mutation in the same gene has been described in the COSMIC database with low locus frequency.

WRN-Y1034F (in 48.72% of the DNA analyzed):
This alteration is listed in the COSMIC database. It has been detected in one sample. In the scientific literature no data is available about the function of this variant.
The variant is classified as a driver by the algorithm of the Molecular Treatment Calculator using its actual evidence database. The classification is based on evidence describing the mutant gene or other specific mutations of the same gene as driver alterations.

MST1R-H1184R (MST1R-H1290R, MST1R-H1241R; in 49.78% of the DNA analyzed):
No data is available in the scientific literature about the function of this variant. It is classified as a VUS (Variant of Unknown Significance).

CYP2B6-M46V (in 44.96% of the DNA analyzed):
CYP2B6 is a drug metabolizing enzyme. CYP2B6-M46V is a polymorphism (rs35303484), CYP2B6*11. It is assotiated with efavirenz (anti-viral agent) plasma concentration (20), but no assotiation is known with anti-cancer compounds.

CYP2D6-R278L (CYP2D6-R329L; in 14.42% of the DNA analyzed):
This alteration is a polymorphism (rs3915951) (21). Its significance is unknown (22).

SMO-R168H (in 53.61% of the DNA analyzed):
This alteration is described as a polymorphism in the scientific literature (23). In in vitro experiments it has been shown to have similar activity as the wild type variant (24).

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COMPOUND NAME	REFERENCES
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CHEK2-D438Y	Wellcome Trust Sanger Institute
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AKT3 wild-type	Li J, Davies BR, Han S, Zhou M, Bai Y, Zhang J, Xu Y, Tang L, Wang H, Liu YJ, Yin X, Ji Q, Yu DH. The AKT inhibitor AZD5363 is selectively active in PI3KCA mutant gastric cancer, and sensitizes a patient-derived gastric cancer xenograft model with PTEN loss to Taxotere. J Transl Med. 2013 Oct 2;11:241. doi: 10.1186/1479-5876-11-241. PubMed PMID: 24088382; PubMed Central PMCID: PMC3850695.
SOD1 wild-type	Sajesh BV, McManus KJ. Targeting SOD1 induces synthetic lethal killing in BLM- and CHEK2-deficient colorectal cancer cells. Oncotarget. 2015 Sep 29;6(29):27907-22. doi: 10.18632/oncotarget.4875. PubMed PMID: 26318585; PubMed Central PMCID: PMC4695034.
PARP1 wild-type	Ledermann JA, Drew Y, Kristeleit RS. Homologous recombination deficiency and ovarian cancer. Eur J Cancer. 2016 Jun;60:49-58. doi: 10.1016/j.ejca.2016.03.005. Epub 2016 Apr 9. Review. PubMed PMID: 27065456.
MDM2 wild-type	Mir R, Tortosa A, Martinez-Soler F, Vidal A, Condom E, Pérez-Perarnau A, Ruiz-Larroya T, Gil J, Giménez-Bonafé P. Mdm2 antagonists induce apoptosis and synergize with cisplatin overcoming chemoresistance in TP53 wild-type ovarian cancer cells. Int J Cancer. 2013 Apr 1;132(7):1525-36. doi: 10.1002/ijc.27832. Epub 2012 Oct 11. PubMed PMID: 22961628.

DETAILED DESCRIPTION OF DRIVER AND TARGET GENES

DRIVER GENES

Name	Description

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DETAILED DESCRIPTION OF DRIVER AND TARGET GENES

DRIVER GENES

Name	Description
ARID2	Involved in transcriptional activation and repression of select genes by chromatin remodeling (alteration of DNA-nucleosome topology). Required for the stability of the SWI/SNF chromatin remodeling complex SWI/SNF-B (PBAF). May be involved in targeting the complex to different genes. May be involved in regulating transcriptional activation of cardiac genes.
BCL6	Transcriptional repressor mainly required for germinal center (GC) formation and antibody affinity maturation which has different mechanisms of action specific to the lineage and biological functions. Forms complexes with different corepressors and histone deacetylases to repress the transcriptional expression of different subsets of target genes. Represses its target genes by binding directly to the DNA sequence 5-TTCCTAGAA-3 (BCL6-binding site) or indirectly by repressing the transcriptional activity of transcription factors. In GC B-cells, represses genes that function in differentiation, inflammation, apoptosis and cell cycle control, also autoregulates its transcriptional expression and up-regulates, indirectly, the expression of some genes important for GC reactions, such as AICDA, through the repression of microRNAs expression, like miR155. An important function is to allow GC B-cells to proliferate very rapidly in response to T-cell dependent antigens and tolerate the physiological DNA breaks required for immunglobulin class switch recombination and somatic hypermutation without inducing a p53/TP53-dependent apoptotic response. In follicular helper CD4(+) T-cells (T(FH) cells), promotes the expression of T(FH)-related genes but inhibits the differentiation of T(H)1, T(H)2 and T(H)17 cells. Also required for the establishment and maintenance of immunological memory for both T- and B-cells. Suppresses macrophage proliferation through competition with STAT5 for STAT-binding motifs binding on certain target genes, such as CCL2 and CCND2. In response to genotoxic stress, controls cell cycle arrest in GC B-cells in both p53/TP53-dependedent and -independent manners. Besides, also controls neurogenesis through the alteration of the composition of NOTCH-dependent transcriptional complexes at selective NOTCH targets, such as HES5, including the recruitment of the deacetylase SIRT1 and resulting in an epigenetic silencing leading to neuronal differentiation.
CHD1	ATP-dependent chromatin-remodeling factor which functions as substrate recognition component of the transcription regulatory histone acetylation (HAT) complex SAGA. Regulates polymerase II transcription. Also required for efficient transcription by RNA polymerase I, and more specifically the polymerase I transcription termination step. Regulates negatively DNA replication. Not only involved in transcription-related chromatin-remodeling, but also required to maintain a specific chromatin configuration across the genome. Is also associated with histone deacetylase (HDAC) activity (By similarity). Required for the bridging of SNF2, the FACT complex, the PAF complex as well as the U2 snRNP complex to H3K4me3. Functions to modulate the efficiency of pre-mRNA splicing in part through physical bridging of spliceosomal components to H3K4me3. Required for maintaining open chromatin and pluripotency in embryonic stem cells.
CHEK2	Serine/threonine-protein kinase which is required for checkpoint-mediated cell cycle arrest, activation of DNA repair and apoptosis in response to the presence of DNA double-strand breaks. May also negatively regulate cell cycle progression during unperturbed cell cycles. Following activation, phosphorylates numerous effectors preferentially at the consensus sequence [L-X-R-X-X-S/T]. Regulates cell cycle checkpoint arrest through phosphorylation of CDC25A, CDC25B and CDC25C, inhibiting their activity. Inhibition of CDC25 phosphatase activity leads to increased inhibitory tyrosine phosphorylation of CDK-cyclin complexes and blocks cell cycle progression. May also phosphorylate NEK6 which is involved in G2/M cell cycle arrest. Regulates DNA repair through phosphorylation of BRCA2, enhancing the association of RAD51 with chromatin which promotes DNA repair by homologous recombination. Also stimulates the transcription of genes involved in DNA repair (including BRCA2) through the phosphorylation and activation of the transcription factor FOXM1. Regulates apoptosis through the phosphorylation of p53/TP53, MDM4 and PML. Phosphorylation of p53/TP53 at Ser-20 by CHEK2 may alleviate inhibition by MDM2, leading to accumulation of active p53/TP53. Phosphorylation of MDM4 may also reduce degradation of p53/TP53. Also controls the transcription of pro-apoptotic genes through phosphorylation of the transcription factor E2F1. Tumor suppressor, it may also have a DNA damage-independent function in mitotic spindle assembly by phosphorylating BRCA1. Its absence may be a cause of the chromosomal instability observed in some cancer cells.
CYP2B6	Cytochromes P450 are a group of heme-thiolate monooxygenases. In liver microsomes, this enzyme is involved in an NADPH-dependent electron transport pathway. It oxidizes a variety of structurally unrelated compounds, including steroids, fatty acids, and xenobiotics. Acts as a 1,4-cineole 2-exo-monooxygenase.
CYP2D6	Responsible for the metabolism of many drugs and environmental chemicals that it oxidizes. It is involved in the metabolism of drugs such as antiarrhythmics, adrenoceptor antagonists, and tricyclic antidepressants.
ESR1	Nuclear hormone receptor. The steroid hormones and their receptors are involved in the regulation of eukaryotic gene expression and affect cellular proliferation and differentiation in target tissues. Ligand-dependent nuclear transactivation involves either direct homodimer binding to a palindromic estrogen response element (ERE) sequence or association with other DNA-binding transcription factors, such as AP-1/c-Jun, c-Fos, ATF-2, Sp1 and Sp3, to mediate ERE-independent signaling. Ligand binding induces a conformational change allowing subsequent or combinatorial association with multiprotein coactivator complexes through LXXLL motifs of their respective components. Mutual transrepression occurs between the estrogen receptor (ER) and NF-kappa-B in a cell-type specific manner. Decreases NF-kappa-B DNA-binding activity and inhibits NF-kappa-B-mediated transcription from the IL6 promoter and displace RELA/p65 and associated coregulators from the promoter. Recruited to the NF-kappa-B response element of the CCL2 and IL8 promoters and can displace CREBBP. Present with NF-kappa-B components RELA/p65 and NFKB1/p50 on ERE sequences. Can also act synergistically with NF-kappa-B to activate transcription involving respective recruitment adjacent response elements; the function involves CREBBP. Can activate the transcriptional activity of TFF1. Also mediates membrane-initiated estrogen signaling involving various kinase cascades. Isoform 3 is involved in activation of NOS3 and endothelial nitric oxide production. Isoforms lacking one or several functional domains are thought to modulate transcriptional activity by competitive ligand or DNA binding and/or heterodimerization with the full length receptor. Essential for MTA1-mediated transcriptional regulation of BRCA1 and BCAS3. Isoform 3 can bind to ERE and inhibit isoform 1.
HSPH1	Acts as a nucleotide-exchange factor (NEF) for chaperone proteins HSPA1A and HSPA1B, promoting the release of ADP from HSPA1A/B thereby triggering client/substrate protein release (PubMed:24318877). Prevents the aggregation of denatured proteins in cells under severe stress, on which the ATP levels decrease markedly. Inhibits HSPA8/HSC70 ATPase and chaperone activities (By similarity).

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DETAILED DESCRIPTION OF DRIVER AND TARGET GENES

DRIVER GENES

Name	Description
KMT2A	Histone methyltransferase that plays an essential role in early development and hematopoiesis. Catalytic subunit of the MLL1/MLL complex, a multiprotein complex that mediates both methylation of Lys-4 of histone H3 (H3K4me) complex and acetylation of Lys-16 of histone H4 (H4K16ac). In the MLL1/MLL complex, it specifically mediates H3K4me, a specific tag for epigenetic transcriptional activation. Has weak methyltransferase activity by itself, and requires other component of the MLL1/MLL complex to obtain full methyltransferase activity. Has no activity toward histone H3 phosphorylated on Thr-3, less activity toward H3 dimethylated on Arg-8 or Lys-9, while it has higher activity toward H3 acetylated on Lys-9. Required for transcriptional activation of HOXA9. Promotes PPP1R15A-induced apoptosis. Plays a critical role in the control of circadian gene expression and is essential for the transcriptional activation mediated by the CLOCK-ARNTL/BMAL1 heterodimer. Establishes a permissive chromatin state for circadian transcription by mediating a rhythmic methylation of Lys-4 of histone H3 (H3K4me) and this histone modification directs the circadian acetylation at H3K9 and H3K14 allowing the recruitment of CLOCK-ARNTL /BMAL1 to chromatin (By similarity).
MST1R	Receptor tyrosine kinase that transduces signals from the extracellular matrix into the cytoplasm by binding to MST1 ligand. Regulates many physiological processes including cell survival, migration and differentiation. Ligand binding at the cell surface induces autophosphorylation of RON on its intracellular domain that provides docking sites for downstream signaling molecules. Following activation by ligand, interacts with the PI3-kinase subunit PIK3R1, PLCG1 or the adapter GAB1. Recruitment of these downstream effectors by RON leads to the activation of several signaling cascades including the RAS-ERK, PI3 kinase-AKT, or PLCgamma-PKC. RON signaling activates the wound healing response by promoting epithelial cell migration, proliferation as well as survival at the wound site. Plays also a role in the innate immune response by regulating the migration and phagocytic activity of macrophages. Alternatively, RON can also promote signals such as cell migration and proliferation in response to growth factors other than MST1 ligand.
MUC16	Thought to provide a protective, lubricating barrier against particles and infectious agents at mucosal surfaces.
NF2	Probable regulator of the Hippo/SWH (Sav/Wts/Hpo) signaling pathway, a signaling pathway that plays a pivotal role in tumor suppression by restricting proliferation and promoting apoptosis. Along with WWC1 can synergistically induce the phosphorylation of LATS1 and LATS2 and can probably function in the regulation of the Hippo/SWH (Sav /Wts/Hpo) signaling pathway. May act as a membrane stabilizing protein. May inhibit PI3 kinase by binding to AGAP2 and impairing its stimulating activity. Suppresses cell proliferation and tumorigenesis by inhibiting the CUL4A-RBX1-DDB1-VprBP/DCAF1 E3 ubiquitin-protein ligase complex.
PIK3CA	Phosphoinositide-3-kinase (PI3K) that phosphorylates PtdIns (Phosphatidylinositol), PtdIns4P (Phosphatidylinositol 4-phosphate) and PtdIns(4,5)P2 (Phosphatidylinositol 4,5-bisphosphate) to generate phosphatidylinositol 3,4,5-trisphosphate (PIP3). PIP3 plays a key role by recruiting PH domain-containing proteins to the membrane, including AKT1 and PDPK1, activating signaling cascades involved in cell growth, survival, proliferation, motility and morphology. Participates in cellular signaling in response to various growth factors. Involved in the activation of AKT1 upon stimulation by receptor tyrosine kinases ligands such as EGF, insulin, IGF1, VEGFA and PDGF. Involved in signaling via insulin-receptor substrate (IRS) proteins. Essential in endothelial cell migration during vascular development through VEGFA signaling, possibly by regulating RhoA activity. Required for lymphatic vasculature development, possibly by binding to RAS and by activation by EGF and FGF2, but not by PDGF. Regulates invadopodia formation in breast cancer cells through the PDPK1-AKT1 pathway. Participates in cardiomyogenesis in embryonic stem cells through a AKT1 pathway. Participates in vasculogenesis in embryonic stem cells through PDK1 and protein kinase C pathway. Has also serine-protein kinase activity: phosphorylates PIK3R1 (p85alpha regulatory subunit), EIF4EBP1 and HRAS.
PRDM1	Transcriptional repressor that binds specifically to the PRDI element in the promoter of the beta-interferon gene (PubMed:1851123). Drives the maturation of B-lymphocytes into Ig secreting cells (PubMed:12626569).
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.
SMO	G protein-coupled receptor that probably associates with the patched protein (PTCH) to transduce the hedgehogs proteins signal. Binding of sonic hedgehog (SHH) to its receptor patched is thought to prevent normal inhibition by patched of smoothened (SMO). Required for the accumulation of KIF7 and GLI3 in the cilia.
TMEM127	Controls cell proliferation acting as a negative regulator of TOR signaling pathway mediated by mTORC1. May act as a tumor suppressor.
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

DRIVER GENES

Name	Description
WRN	Multifunctional enzyme that has both magnesium and ATP-dependent DNA-helicase activity and 3->5 exonuclease activity towards double-stranded DNA with a 5-overhang. Has no nuclease activity towards single-stranded DNA or blunt-ended double-stranded DNA. Binds preferentially to DNA substrates containing alternate secondary structures, such as replication forks and Holliday junctions. May play an important role in the dissociation of joint DNA molecules that can arise as products of homologous recombination, at stalled replication forks or during DNA repair. Alleviates stalling of DNA polymerases at the site of DNA lesions. Important for genomic integrity. Plays a role in the formation of DNA replication focal centers; stably associates with foci elements generating binding sites for RP-A (By similarity). Plays a role in double-strand break repair after gamma-irradiation.

DETAILED DESCRIPTION OF DRIVER AND TARGET GENES

TARGET GENES

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

DETAILED DESCRIPTION OF DRIVER AND TARGET GENES

TARGET GENES

Name	Description
AKT2	AKT2 is one of 3 closely related serine/threonine-protein kinases (AKT1, AKT2 and AKT3) called the AKT kinase, and which regulate many processes including metabolism, proliferation, cell survival, growth and angiogenesis. This is mediated through serine and/or threonine phosphorylation of a range of downstream substrates. Over 100 substrate candidates have been reported so far, but for most of them, no isoform specificity has been reported. AKT is responsible of the regulation of glucose uptake by mediating insulin-induced translocation of the SLC2A4 /GLUT4 glucose transporter to the cell surface. Phosphorylation of PTPN1 at Ser-50 negatively modulates its phosphatase activity preventing dephosphorylation of the insulin receptor and the attenuation of insulin signaling. Phosphorylation of TBC1D4 triggers the binding of this effector to inhibitory 14-3-3 proteins, which is required for insulin-stimulated glucose transport. AKT regulates also the storage of glucose in the form of glycogen by phosphorylating GSK3A at Ser-21 and GSK3B at Ser-9, resulting in inhibition of its kinase activity. Phosphorylation of GSK3 isoforms by AKT is also thought to be one mechanism by which cell proliferation is driven. AKT regulates also cell survival via the phosphorylation of MAP3K5 (apoptosis signal-related kinase). Phosphorylation of Ser-83 decreases MAP3K5 kinase activity stimulated by oxidative stress and thereby prevents apoptosis. AKT mediates insulin-stimulated protein synthesis by phosphorylating TSC2 at Ser-939 and Thr-1462, thereby activating mTORC1 signaling and leading to both phosphorylation of 4E-BP1 and in activation of RPS6KB1. AKT is involved in the phosphorylation of members of the FOXO factors (Forkhead family of transcription factors), leading to binding of 14-3-3 proteins and cytoplasmic localization. In particular, FOXO1 is phosphorylated at Thr-24, Ser-256 and Ser-319. FOXO3 and FOXO4 are phosphorylated on equivalent sites. AKT has an important role in the regulation of NF-kappa-B-dependent gene transcription and positively regulates the activity of CREB1 (cyclic AMP (cAMP)-response element binding protein). The phosphorylation of CREB1 induces the binding of accessory proteins that are necessary for the transcription of pro-survival genes such as BCL2 and MCL1. AKT phosphorylates Ser-454 on ATP citrate lyase (ACLY), thereby potentially regulating ACLY activity and fatty acid synthesis. Activates the 3B isoform of cyclic nucleotide phosphodiesterase (PDE3B) via phosphorylation of Ser-273, resulting in reduced cyclic AMP levels and inhibition of lipolysis. Phosphorylates PIKFYVE on Ser-318, which results in increased PI(3)P-5 activity. The Rho GTPase-activating protein DLC1 is another substrate and its phosphorylation is implicated in the regulation cell proliferation and cell growth. AKT plays a role as key modulator of the AKT-mTOR signaling pathway controlling the tempo of the process of newborn neurons integration during adult neurogenesis, including correct neuron positioning, dendritic development and synapse formation. Signals downstream of phosphatidylinositol 3-kinase (PI (3)K) to mediate the effects of various growth factors such as platelet-derived growth factor (PDGF), epidermal growth factor (EGF), insulin and insulin-like growth factor I (IGF-I). AKT mediates the antiapoptotic effects of IGF-I. Essential for the SPATA13-mediated regulation of cell migration and adhesion assembly and disassembly. May be involved in the regulation of the placental development One of the few specific substrates of AKT2 identified recently is PITX2. Phosphorylation of PITX2 impairs its association with the CCND1 mRNA-stabilizing complex thus shortening the half-life of CCND1. AKT2 seems also to be the principal isoform responsible of the regulation of glucose uptake. Phosphorylates C2CD5 on Ser-197 during insulin-stimulated adipocytes. AKT2 is also specifically involved in skeletal muscle differentiation, one of its substrates in this process being ANKRD2. Down-regulation by RNA interference reduces the expression of the pho
AKT3	AKT3 is one of 3 closely related serine/threonine-protein kinases (AKT1, AKT2 and AKT3) called the AKT kinase, and which regulate many processes including metabolism, proliferation, cell survival, growth and angiogenesis. This is mediated through serine and/or threonine phosphorylation of a range of downstream substrates. Over 100 substrate candidates have been reported so far, but for most of them, no isoform specificity has been reported. AKT3 is the least studied AKT isoform. It plays an important role in brain development and is crucial for the viability of malignant glioma cells. AKT3 isoform may also be the key molecule in up-regulation and down-regulation of MMP13 via IL13. Required for the coordination of mitochondrial biogenesis with growth factor-induced increases in cellular energy demands. Down-regulation by RNA interference reduces the expression of the phosphorylated form of BAD, resulting in the induction of caspase-dependent apoptosis.
MDM2	E3 ubiquitin-protein ligase that mediates ubiquitination of p53/TP53, leading to its degradation by the proteasome. Inhibits p53/TP53- and p73/TP73-mediated cell cycle arrest and apoptosis by binding its transcriptional activation domain. Also acts as a ubiquitin ligase E3 toward itself and ARRB1. Permits the nuclear export of p53/TP53. Promotes proteasome-dependent ubiquitin-independent degradation of retinoblastoma RB1 protein. Inhibits DAXX-mediated apoptosis by inducing its ubiquitination and degradation. Component of the TRIM28/KAP1-MDM2-p53 /TP53 complex involved in stabilizing p53/TP53. Also component of the TRIM28/KAP1-ERBB4-MDM2 complex which links growth factor and DNA damage response pathways. Mediates ubiquitination and subsequent proteasome degradation of DYRK2 in nucleus. Ubiquitinates IGF1R and SNAI1 and promotes them to proteasomal degradation.

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DETAILED DESCRIPTION OF DRIVER AND TARGET GENES

TARGET GENES

Name	Description
mTOR	Serine/threonine protein kinase which is a central regulator of cellular metabolism, growth and survival in response to hormones, growth factors, nutrients, energy and stress signals. MTOR directly or indirectly regulates the phosphorylation of at least 800 proteins. Functions as part of 2 structurally and functionally distinct signaling complexes mTORC1 and mTORC2 (mTOR complex 1 and 2). Activated mTORC1 up-regulates protein synthesis by phosphorylating key regulators of mRNA translation and ribosome synthesis. This includes phosphorylation of EIF4EBP1 and release of its inhibition toward the elongation initiation factor 4E (eiF4E). Moreover, phosphorylates and activates RPS6KB1 and RPS6KB2 that promote protein synthesis by modulating the activity of their downstream targets including ribosomal protein S6, eukaryotic translation initiation factor EIF4B, and the inhibitor of translation initiation PDCD4. Stimulates the pyrimidine biosynthesis pathway, both by acute regulation through RPS6KB1-mediated phosphorylation of the biosynthetic enzyme CAD, and delayed regulation, through transcriptional enhancement of the pentose phosphate pathway which produces 5-phosphoribosyl-1-pyrophosphate (PRPP), an allosteric activator of CAD at a later step in synthesis, this function is dependent on the mTORC1 complex. Regulates ribosome synthesis by activating RNA polymerase III-dependent transcription through phosphorylation and inhibition of MAF1 an RNA polymerase III-repressor. In parallel to protein synthesis, also regulates lipid synthesis through SREBF1/SREBP1 and LPIN1. To maintain energy homeostasis mTORC1 may also regulate mitochondrial biogenesis through regulation of PPARGC1A. mTORC1 also negatively regulates autophagy through phosphorylation of ULK1. Under nutrient sufficiency, phosphorylates ULK1 at Ser-758, disrupting the interaction with AMPK and preventing activation of ULK1. Also prevents autophagy through phosphorylation of the autophagy inhibitor DAP. mTORC1 exerts a feedback control on upstream growth factor signaling that includes phosphorylation and activation of GRB10 a INSR-dependent signaling suppressor. Among other potential targets mTORC1 may phosphorylate CLIP1 and regulate microtubules. As part of the mTORC2 complex MTOR may regulate other cellular processes including survival and organization of the cytoskeleton. Plays a critical role in the phosphorylation at Ser-473 of AKT1, a pro-survival effector of phosphoinositide 3-kinase, facilitating its activation by PDK1. mTORC2 may regulate the actin cytoskeleton, through phosphorylation of PRKCA, PXN and activation of the Rho-type guanine nucleotide exchange factors RHOA and RAC1A or RAC1B. mTORC2 also regulates the phosphorylation of SGK1 at Ser-422.
PARP1	Involved in the base excision repair (BER) pathway, by catalyzing the poly(ADP-ribosyl)ation of a limited number of acceptor proteins involved in chromatin architecture and in DNA metabolism. This modification follows DNA damages and appears as an obligatory step in a detection/signaling pathway leading to the reparation of DNA strand breaks. Mediates the poly(ADP-ribosyl)ation of APLF and CHFR. Positively regulates the transcription of MTUS1 and negatively regulates the transcription of MTUS2/TIP150. With EEF1A1 and TXK, forms a complex that acts as a T-helper 1 (Th1) cell-specific transcription factor and binds the promoter of IFN-gamma to directly regulate its transcription, and is thus involved importantly in Th1 cytokine production. Required for PARP9 and DTX3L recruitment to DNA damage sites. PARP1-dependent PARP9-DTX3L-mediated ubiquitination promotes the rapid and specific recruitment of 53BP1/TP53BP1, UIMC1/RAP80, and BRCA1 to DNA damage sites.
PIK3CA	Phosphoinositide-3-kinase (PI3K) that phosphorylates PtdIns (Phosphatidylinositol), PtdIns4P (Phosphatidylinositol 4-phosphate) and PtdIns(4,5)P2 (Phosphatidylinositol 4,5-bisphosphate) to generate phosphatidylinositol 3,4,5-trisphosphate (PIP3). PIP3 plays a key role by recruiting PH domain-containing proteins to the membrane, including AKT1 and PDPK1, activating signaling cascades involved in cell growth, survival, proliferation, motility and morphology. Participates in cellular signaling in response to various growth factors. Involved in the activation of AKT1 upon stimulation by receptor tyrosine kinases ligands such as EGF, insulin, IGF1, VEGFA and PDGF. Involved in signaling via insulin-receptor substrate (IRS) proteins. Essential in endothelial cell migration during vascular development through VEGFA signaling, possibly by regulating RhoA activity. Required for lymphatic vasculature development, possibly by binding to RAS and by activation by EGF and FGF2, but not by PDGF. Regulates invadopodia formation in breast cancer cells through the PDPK1-AKT1 pathway. Participates in cardiomyogenesis in embryonic stem cells through a AKT1 pathway. Participates in vasculogenesis in embryonic stem cells through PDK1 and protein kinase C pathway. Has also serine-protein kinase activity: phosphorylates PIK3R1 (p85alpha regulatory subunit), EIF4EBP1 and HRAS.
SOD1	Destroys radicals which are normally produced within the cells and which are toxic to biological systems.

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NAME	Anonymous
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APPENDIX

TARGETED COMPOUNDS

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

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

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

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