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: 1973

Primary Tumor Site: lung
Histology Type: adenocarcinoma
Metastatic sites: brain, bone

MEDICAL TEAM

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

PATHOLOGICAL AND MOLECULAR DIAGNOSTIC TESTS

Sample ID: 4519B8895 2 (histology sample)
Sample source: primary tumor
Sampling type: biopsy
Tumor type: lung adenocarcinoma

Results of previous molecular diagnostic tests:
NGS - FoundationOne (324 genes) - (4519B8895 2)
IHC - PDL1 - Tumor Proportion Score (TPS): 0%

PREVIOUS THERAPIES

1. line - TRASTUZUMAB + ZOLEDRONIC ACID + docetaxel - 9 cycle - (2020-01-28 - 2020-08-04)
2. line - AFATINIB + DENOSUMAB - (2020-08-26 - 2020-12-17)
3. line - TRASTUZUMAB EMTANSINE - 4 cycle - (2020-12-17 - 2021-02-24)
4. line - NIVOLUMAB - 6 cycle - (2021-03-17 - 2021-05-20)

SUMMARY

Oncompass Report of your patient, DH, diagnosed with lung adenocarcinoma, has been completed for digital drug assignment and therapy planning purposes using Realtime Oncology Treatment Calculator. Our reinterpretation was carried out from an FMI-based molecular profile using a primary tumor tissue sample (ID: 4519B8895 2).

Tumor-agnostic biomarkers/immunotherapy biomarkers:
MSI and TMB status is unknown (could not be determined).
NTRK fusions were not detected.

Tumor-specific on-label biomarkers:
The tumor is PD-L1-IHC negative (normal expression).
No activating mutations/fusions were detected in the following genes: EGFR, KRAS, NRAS, BRAF, ALK, ROS1
EGFR inhibitors, such as Erlotinib, an on-label option, are contraindicated due to the detected ERBB2-A775_G776insYVMA driver mutation, which is thought to cause resistance to EGFR inhibition.
Immunotherapeutic agents in NSCLC independent of PD-L1 status:

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SUMMARY

NIVOLUMAB (PD-1 inhibitor) is approved for NSCLC patients after systematic treatment. NIVOLUMAB is also approved in combination with IPILUMUMAB (CTLA-4 monoclonal antibody) and platinum-based chemotherapy as a first-line treatment for metastatic or recurrent NSCLC patients with no EGFR or ALK mutations. ATEZOLIZUMAB (PD-L1 inhibitor) is approved for the treatment of patients with locally advanced or metastatic NSCLC after they have been previously treated with chemotherapy or as a first-line treatment combined with bevacizumab and chemotherapy. PEMBROLIZUMAB (PD-1 inhibitor) in combination with first-line chemotherapy (carboplatin + pemetrexed) is approved for the treatment of non-squamous NSCLC patients.

HER2 mutant NSCLC patients had 7% response rate on checkpoint inhibitors according to a retrospective study, which is lower compared to the general population. The authors recommend considering immunotherapies only after receiving targeted therapies, and chemotherapies to patients with actionable driver alterations.

Histology based on-label therapies:

Docetaxel-Nintedanib 2ndL

Ramucirumab-Docetaxel 2ndL

Bevacizumab-Platinum-based chemotherapy 1stL

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

ERBB2-A775_G776insYVMA driver (AEL: 976.79, AF/TR: NA/NA), TP53-R267W driver (AEL: 56.54, AF/TR: NA/NA)

ERBB2-A775_G776insYVMA is a HER2 exon 20 insertion listed in the COSMIC database (n> 50), according to the ClinVar database, it is a likely pathogenic alteration. ERBB2-Y772_A775dup is the most common HER2 exon 20 insertion and also occurs in the literature under the following names: ERBB2- Y772_A775dup, M774_A775insAYVM, E770delinsEAYVM. According to preclinical data, it is sensitive to neratinib and poziotinib (currently under development), but it was shown to be less sensitive to lapatinib, dacomitinib, and afatinib compared to wild-type EGFR.

Response to afatinib with specific ERBB2 ex 20 insertions varies from 0% to 100% DCR, results are controversial.

In one study, 11 NSCLC patients, carrying the Y772_A775dup mutation, were treated with afatinib. A partial response was achieved in two patients and stable disease in one. Additional case studies also report the efficacy of afatinib therapy in patients carrying the Y772_A775dup mutation. The efficacy of erlotinib, trastuzumab, afatinib and/or sirolimus in mutant xenografts was investigated in a preclinical trial. The most effective inhibitory effect was elicited by afatinib + sirolimus therapy. In another study, the efficacy of afatinib was investigated. Patients with this mutation (n=10) had a median TTF of 9.6 months compared to 2.9 in the whole group (n=28). In patients with response data available (6 in patients with this mutation, and 16 carrying other HER2 mutations) disease control rate (DCR) was 100%, and 69% respectively. Contradictory, a study also looking at the efficacy of afatinib found that the objective response rates with afatinib were 0% (n=14) in patients with the ERBB2-Y772_A775dup mutation. TP53 co-mutations conferred additional resistance to afatinib.

In one patient with HER2 + and Y772_A775dup mutants, T-DM1 therapy resulted in an immediate partial response. Tumor response to trastuzumab deruxtecan was found in 6 of 8 HER2 exon 20 insertion mutant NSCLC patients, although specific mutations are not detailed in the article. Adding neratinib to T-DM1 or trastuzumab deruxtecan has been shown to be synergetic in ERBB2-Y772_A775dup mutant breast cancer models, as neratinib increases the endocytosis of these drugs.

HER2-mutant non-small cell lung cancer (NSCLC) patients were treated with **trastuzumab deruxtecan** in a phase I study. The response rate was 72.7% (8/11), and median progression-free survival (PFS) was 11.3 months. In a phase II clinical trial HER2-mutant NSCLC patients (HER2 mutations were predominantly in the kinase domain) were treated with trastuzumab deruxtecan. The objective response rate was 61.9%, the disease control rate was 90.5% and the estimated median PFS was 14.0 months. **TDM-1** therapy reached 44% response rate in HER2 mutant NSCLC patients. The median PFS was 5 months. Afatinib therapy resulted in 19% response rate and 69% disease control rate in heavily pretreated HER2 mutant NSCLC patients. In a prospective trial, afatinib resulted in 53,8% disease control rate at 12 weeks in HER2 mutant NSCLC patients. Neratinib + temsirolimus therapy reached 19% response rate in a phase II trial in HER2 mutant lung cancer patients. The median PFS was 4.1 months and the median overall survival was 15.8 months.

TP53-R267W is a non-functional, deleterious variant. According to preclinical studies, the mutation results in partial loss of function of the TP53 gene. In the presence of loss of function TP53 alterations CHEK1, ATR, PLK1, WEE1 and CDK inhibitors can be mentioned in positive association with the molecular profile. The CDK inhibitors PALBOCICLIB, RIBOCICLIB, and ABEMACICLIB are approved in breast cancer indication.

Based on the histology, previous molecular profile and therapies, the patient would likely benefit from the following treatments if this HER2 ex 20 insertion is still present:

Trastuzumab deruxtecan or pyrotinib or poziotinib in clinical trial. Adding neratinib to trastuzumab deruxtecan, or T-DM1 (if TDx is unavailable) could be synergistic.

Immunotherapy could be supported after HER2 inhibitions, which the patient is currently receiving.

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MOLECULAR TARGET ANALYSIS

MOLECULAR ALTERATIONS

ERBB2-A775_G776insYVMA driver (AEL: 1042.51, AF/TR: NA/NA),
TP53-R267W driver (AEL: 56.56, AF/TR: NA/NA),
STAG2-E403D VUS in a driver gene (AEL: 4.32, AF/TR: NA/NA),
STAG2-H1191Y VUS in a driver gene (AEL: 4.32, AF/TR: NA/NA),
MYD88-P11R VUS in a driver gene (AEL: 1.62, AF/TR: NA/NA),
ASXL1-G653R VUS in a driver gene (AEL: 1.21, AF/TR: NA/NA),
SETD2-D699G VUS in a driver gene (AEL: 0.24, AF/TR: NA/NA),
FANCL-T23I driver (AEL: 0.15, AF/TR: NA/NA),
SPEN-N2957D VUS in a driver gene (AEL: 0.12, AF/TR: NA/NA),
KRAS wild-type biomarker (AEL: 0.00),
BCL6-R459C conflicting driver (AEL: 0.00, AF/TR: NA/NA),
TYRO3-P266R variant of unknown significance (AEL: 0.00, AF/TR: NA /NA)

TARGET GENES

ERBB2 wild-type (AEL: 1628.06),
- ERBB2-A775_G776insYVMA driver (AEL: 1042.51)

TP53 mutant gene (AEL: 125.68),
- TP53-R267W driver (AEL: 56.56)

ATR wild-type (AEL: 67.52),
- TP53-R267W driver (AEL: 56.56) ;
- STAG2-H1191Y VUS in a driver (AEL: 4.32) ;
- STAG2-E403D VUS in a driver (AEL: 4.32)

PRKDC wild-type (AEL: 66.58),
- STAG2-E403D VUS in a driver (AEL: 4.32) ;
- STAG2-H1191Y VUS in a driver (AEL: 4.32) ;
- TP53-R267W driver (AEL: 56.56)

WEE1 wild-type (AEL: 60.36),
- TP53-R267W driver (AEL: 56.56)

CHEK1 wild-type (AEL: 58.34),
- TP53-R267W driver (AEL: 56.56)

CDK4 wild-type (AEL: 57.54),
- TP53-R267W driver (AEL: 56.56)

RARG wild-type (AEL: 57.45),
- TP53-R267W driver (AEL: 56.56)

PLK1 wild-type (AEL: 57.04),
- TP53-R267W driver (AEL: 56.56)

CDK9 wild-type (AEL: 56.89),
- TP53-R267W driver (AEL: 56.56)

CDK1 wild-type (AEL: 56.89),
- TP53-R267W driver (AEL: 56.56)

CDK2 wild-type (AEL: 56.89),
- TP53-R267W driver (AEL: 56.56)

AURKB wild-type (AEL: 56.85),
- TP53-R267W driver (AEL: 56.56)

BTK wild-type (AEL: 18.29),
- MYD88-P11R VUS in a driver (AEL: 1.62)

PARP1 wild-type (AEL: 13.74),
- STAG2-E403D VUS in a driver (AEL: 4.32) ;
- FANCL-T23I driver (AEL: 0.15) ;
- STAG2-H1191Y VUS in a driver (AEL: 4.32)

STAG1 wild-type (AEL: 12.07),
- STAG2-H1191Y VUS in a driver (AEL: 4.32) ;
- STAG2-E403D VUS in a driver (AEL: 4.32)

XRCC5 wild-type (AEL: 9.62),
- STAG2-E403D VUS in a driver (AEL: 4.32) ;
- STAG2-H1191Y VUS in a driver (AEL: 4.32)

BRCA1 wild-type (AEL: 9.62),
- STAG2-H1191Y VUS in a driver (AEL: 4.32) ;
- STAG2-E403D VUS in a driver (AEL: 4.32)

RAD51 wild-type (AEL: 9.62),
- STAG2-H1191Y VUS in a driver (AEL: 4.32) ;
- STAG2-E403D VUS in a driver (AEL: 4.32)

HCK wild-type (AEL: 3.52),
- MYD88-P11R VUS in a driver (AEL: 1.62)

BRD4 wild-type (AEL: 2.16),
- ASXL1-G653R VUS in a driver (AEL: 1.21)

PIK3CB wild-type (AEL: 1.29)
- SETD2-D699G VUS in a driver (AEL: 0.24)

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DRUGS POSITIVELY ASSOCIATED

DRUGS IN CLINICAL USE

10 selected from 95

TRASTUZUMAB EMTANSINE (breast - all [FDA+EMA]) (AEL: 2938.57)
- ERBB2-A775_G776insYVMA driver (AEL: 1042.51) ;
- ERBB2 wild-type target (AEL: 1628.06)

TRASTUZUMAB DERUXTECAN (gastric - adenocarcinoma [FDA]; breast - all [FDA+EMA]; gastroesophageal junction - adenocarcinoma [FDA]) (AEL: 2699.21)
- ERBB2-A775_G776insYVMA driver (AEL: 1042.51) ;
- ERBB2 wild-type target (AEL: 1628.06)

TRASTUZUMAB (gastroesophageal junction - adenocarcinoma [FDA+EMA]; gastric - adenocarcinoma [FDA+EMA]; breast - all [FDA+EMA]) (AEL: 2691.97)
- ERBB2 wild-type target (AEL: 1628.06) ;
- ERBB2-A775_G776insYVMA driver (AEL: 1042.51)

BEVACIZUMAB (ovary - epithelial carcinoma [FDA+EMA]; breast - all [FDA+EMA]; lung - non-small cell carcinoma [FDA+EMA]; kidney - renal cell carcinoma [FDA+EMA]; colon - all [FDA+EMA]; cervix - all [FDA+EMA]; fallopian tube - all [FDA+EMA]; liver - hepatocellular carcinoma [FDA]; rectum - all [FDA+EMA]; peritoneum - all [FDA+EMA]; brain - glioblastoma multiforme [FDA]) (AEL: 78.94)
- TP53-R267W driver (AEL: 56.56)

PAZOPANIB (kidney - renal cell carcinoma [FDA+EMA]; soft tissue - sarcoma [FDA+EMA]) (AEL: 66.27)
- TP53-R267W driver (AEL: 56.56)

ABEMACICLIB (breast - all [FDA+EMA]) (AEL: 58.22)
- CDK4 wild-type target (AEL: 57.54)

RIBOCICLIB (breast - all [FDA+EMA]) (AEL: 57.80)
- CDK4 wild-type target (AEL: 57.54)

IBRUTINIB (all - mantle cell lymphoma [FDA+EMA]; all - chronic lymphocytic leukemia (CLL) [FDA+EMA]; all - marginal zone lymphoma [FDA]; all - small lymphocytic lymphoma [FDA+EMA]; all - Waldenström macroglobulinaemia [FDA+EMA]) (AEL: 33.00)
- MYD88-P11R VUS in a driver (AEL: 1.62) ;
- BTK wild-type target (AEL: 18.29)

ZANUBRUTINIB (lymph node - mantle cell lymphoma [FDA]) (AEL: 27.68)
- MYD88-P11R VUS in a driver (AEL: 1.62) ;
- BTK wild-type target (AEL: 18.29)

OLAPARIB (breast - all [FDA+EMA]; prostate - all [FDA+EMA]; ovary - all [FDA+EMA]; peritoneum - all [FDA+EMA]; pancreas - all [FDA+EMA]; fallopian tube - all [FDA+EMA]) (AEL: 27.17)
- STAG2-E403D VUS in a driver (AEL: 4.32) ;
- STAG2-H1191Y VUS in a driver (AEL: 4.32) ;
- PARP1 wild-type target (AEL: 13.74)

DRUGS IN CLINICAL DEVELOPMENT

10 selected from 145

PYROTINIB (AEL: 2740.20)
- ERBB2 wild-type target (AEL: 1628.06) ;
- ERBB2-A775_G776insYVMA driver (AEL: 1042.51)

POZIOTINIB (AEL: 2691.97)
- ERBB2-A775_G776insYVMA driver (AEL: 1042.51) ;
- ERBB2 wild-type target (AEL: 1628.06)

CANERTINIB (AEL: 2691.97)
- ERBB2-A775_G776insYVMA driver (AEL: 1042.51) ;
- ERBB2 wild-type target (AEL: 1628.06)

RIVICICLIB (AEL: 228.22)
- CDK1 wild-type target (AEL: 56.89) ;
- CDK4 wild-type target (AEL: 57.54) ;
- CDK9 wild-type target (AEL: 56.89) ;

DRUGS NEGATIVELY ASSOCIATED

DRUGS IN CLINICAL USE

10 selected from 34

DACOMITINIB (lung - non-small cell carcinoma [FDA+EMA]; lung - adenocarcinoma [FDA+EMA]; lung - squamous cell carcinoma [FDA+EMA]) (AEL: -2161.06)
- ERBB2-A775_G776insYVMA driver (AEL: -1042.51) ;
- EGFR wild-type target (AEL: -1049.01)

OSIMERTINIB (lung - adenocarcinoma [FDA+EMA]; lung - squamous cell carcinoma [FDA+EMA]; lung - non-small cell carcinoma [FDA+EMA]) (AEL: -2091.63)
- ERBB2-A775_G776insYVMA driver (AEL: -1042.51) ;
- EGFR wild-type target (AEL: -1049.01)

PANITUMUMAB (rectum - all [FDA+EMA]; colon - all [FDA+EMA]) (AEL: -2091.28)
- EGFR wild-type target (AEL: -1049.01) ;
- ERBB2-A775_G776insYVMA driver (AEL: -1042.51)

FULVESTRANT (breast - all [FDA+EMA]) (AEL: -1053.19)
- ERBB2-A775_G776insYVMA driver (AEL: -1042.51)

TAMOXIFEN (breast - carcinoma [FDA]) (AEL: -1052.96)
- ERBB2-A775_G776insYVMA driver (AEL: -1042.51)

CEMIPLIMAB (lung - adenocarcinoma [FDA+EMA]; lung - squamous cell carcinoma [FDA+EMA]; skin - squamous cell carcinoma [FDA+EMA]; lung - non-small cell carcinoma [FDA+EMA]; skin - basal cell carcinoma [FDA+EMA]) (AEL: -1044.12)
- PDCD1 wild-type target (AEL: -1044.25)

DOSTARLIMAB (all - endometrioid carcinoma [EMA]; all - endometrial carcinoma [FDA]; endometrium - all [FDA+EMA]) (AEL: -1044.05)
- PDCD1 wild-type target (AEL: -1044.25)

AVELUMAB (skin - Merkel cell carcinoma (MCC) [FDA+EMA]; ureter - all [FDA+EMA]; bladder - urothelial carcinoma [FDA+EMA]; bladder - all [FDA+EMA]; kidney - renal cell carcinoma [FDA+EMA]) (AEL: -1033.03)
- CD274 wild-type target (AEL: -1035.27)

DURVALUMAB (all - urothelial carcinoma [FDA]; lung - non-small cell carcinoma [FDA+EMA]; lung - small cell carcinoma [FDA+EMA]) (AEL: -1023.07)
- CD274 wild-type target (AEL: -1035.27)

PEMBROLIZUMAB (all - urothelial carcinoma [FDA+EMA]; breast - all [FDA]; liver - hepatocellular carcinoma [FDA]; skin - squamous cell carcinoma [FDA]; lung - adenocarcinoma [FDA+EMA]; head-neck - squamous cell carcinoma [FDA+EMA]; esophagus - squamous cell carcinoma [FDA+EMA]; all - Hodgkin lymphoma [FDA+EMA]; skin - Merkel cell carcinoma (MCC) [FDA]; esophagus - carcinoma [FDA+EMA]; all - mediastinal B-cell lymphoma [FDA]; rectum - all [FDA+EMA]; all - endometrioid carcinoma [FDA]; lung - non-small cell carcinoma [FDA+EMA]; colon - all [FDA+EMA]; gastroesophageal junction - adenocarcinoma [FDA+EMA]; endometrium - all [FDA]; cervix - all [FDA]; gastric - adenocarcinoma [FDA]; all - renal cell carcinoma [FDA+EMA]; all - malignant melanoma [FDA+EMA]) (AEL: -1017.18)
- PDCD1 wild-type target (AEL: -1044.25)

DRUGS IN CLINICAL DEVELOPMENT

10 selected from 31

AEE788 (AEL: -3719.58)
- ERBB2-A775_G776insYVMA driver (AEL: -1042.51) ;
- EGFR wild-type target (AEL: -1049.01) ;
- ERBB2 wild-type target (AEL: -1628.06)

TAK-285 (AEL: -2091.52)
- ERBB2-A775_G776insYVMA driver (AEL: -1042.51) ;
- ERBB2 wild-type target (AEL: 0.00) ;
- EGFR wild-type target (AEL: -1049.01)

BRILANESTRANT (AEL: -1053.19)
- ERBB2-A775_G776insYVMA driver (AEL: -1042.51)

MEHD7945A (AEL: -1049.01)
- EGFR wild-type target (AEL: -1049.01)

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DRUGS POSITIVELY ASSOCIATED	DRUGS NEGATIVELY ASSOCIATED
• CDK2 wild-type target (AEL: 56.89) RGB-286638 (AEL: 228.22) • CDK2 wild-type target (AEL: 56.89) ; • CDK9 wild-type target (AEL: 56.89) ; • CDK4 wild-type target (AEL: 57.54) ; • CDK1 wild-type target (AEL: 56.89) RONICICLIB (AEL: 228.22) • CDK1 wild-type target (AEL: 56.89) ; • CDK9 wild-type target (AEL: 56.89) ; • CDK2 wild-type target (AEL: 56.89) ; • CDK4 wild-type target (AEL: 57.54) EPRENETAPOPT (AEL: 197.40) • TP53-R267W driver (AEL: 56.56) ; • TP53 mutant gene target (AEL: 125.68) M3814 (AEL: 123.54) • TP53-R267W driver (AEL: 56.56) ; • PRKDC wild-type target (AEL: 66.58) ADAVOSERTIB (AEL: 120.83) • WEE1 wild-type target (AEL: 60.36) ; • TP53-R267W driver (AEL: 56.56) MK-8776 (AEL: 117.24) • CHEK1 wild-type target (AEL: 58.34) ; • TP53-R267W driver (AEL: 56.56)	ABBV-181 (AEL: -1044.25) • PDCD1 wild-type target (AEL: -1044.25) TORIPALIMAB (AEL: -1044.25) • PDCD1 wild-type target (AEL: -1044.25) GEPTANOLIMAB (AEL: -1044.05) • PDCD1 wild-type target (AEL: -1044.25) ROCILETINIB (AEL: -1042.94) • ERBB2-A775_G776insYVMA driver (AEL: -1042.51) NAZARTINIB (AEL: -1042.94) • ERBB2-A775_G776insYVMA driver (AEL: -1042.51) MDX-1105 (AEL: -1035.27) • CD274 wild-type target (AEL: -1035.27)

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

ASXL1-G653R, BCL6-R459C, ERBB2-A775_G776INSYVMA, FANCL-T23I, MYD88-P11R, SETD2-D699G, SPEN-N2957D, STAG2-E403D, STAG2-H1191Y, TP53-R267W, TYRO3-P266R

WILD TYPE GENES

ABL1, ACVR1B, AKT1, AKT2, AKT3, ALK, ALOX12B, AMER1, APC, AR, ARAF, ARFRP1, ARID1A, ATM, ATR, ATRX, AURKA, AURKB, AXIN1, AXL, BAP1, BARD1, BCL2, BCL2L1, BCL2L2, 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, CDH1, 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, ERBB3, ERBB4, ERCC4, ERG, ERRFI1, ESR1, EZH2, FAM46C, FANCA, FANCC, FANCG, 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, KDR, KEAP1, KEL, KIT, KLHL6, KMT2A, KMT2D, KRAS, LTK, LYN, MAF, MAP2K1, MAP2K2, MAP2K4, MAP3K1, MAP3K13, MAPK1, MCL1, MDM2, MDM4, MED12, MEF2B, MEN1, MERTK, MET, MITF, MKNK1, MLH1, MPL, MRE11A, MSH2, MSH3, MSH6, MST1R, MTAP, MTOR, MUTYH, MYC, MYCL, MYCN, NBN, NF1, NF2, NFE2L2, NFKBIA, NKX2-1, NOTCH1, NOTCH2, 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, SF3B1, SGK1, SMAD2, SMAD4, SMARCA4, SMARCB1, SMO, SNCAIP, SOCS1, SOX2, SOX9, SPOP, SRC, STAT3, STK11, SUFU, SYK, TBX3, TEK, TET2, TGFBR2, TIPARP, TNFAIP3, TNFRSF14, TSC1, TSC2, U2AF1, VEGFA, VHL, WHSC1, WT1, XPO1, XRCC2, ZNF217, ZNF703

FISH/CNA/IHC POSITIVE GENES	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

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DETAILED MOLECULAR PROFILE

	ABSENCE, NUTM1 TRANSLOCATION ABSENCE, PDGFRA TRANSLOCATION ABSENCE, PDL1 PROTEIN NORMAL, 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

BIOMEDICAL INTERPRETATION

MOLECULAR ALTERATIONS

ERBB2-A775_G776insYVMA driver (AEL: 1042.51, AF/TR: NA/NA),
TP53-R267W driver (AEL: 56.56, AF/TR: NA/NA),
STAG2-E403D VUS in a driver gene (AEL: 4.32, AF/TR: NA/NA),
STAG2-H1191Y VUS in a driver gene (AEL: 4.32, AF/TR: NA/NA),
MYD88-P11R VUS in a driver gene (AEL: 1.62, AF/TR: NA/NA),
ASXL1-G653R VUS in a driver gene (AEL: 1.21, AF/TR: NA/NA),
SETD2-D699G VUS in a driver gene (AEL: 0.24, AF/TR: NA/NA),
FANCL-T23I driver (AEL: 0.15, AF/TR: NA/NA),
SPEN-N2957D VUS in a driver gene (AEL: 0.12, AF/TR: NA/NA),
KRAS wild-type biomarker (AEL: 0.00),
BCL6-R459C conflicting driver (AEL: 0.00, AF/TR: NA/NA),
TYRO3-P266R variant of unknown significance (AEL: 0.00, AF/TR: NA /NA)

TARGET GENES

ERBB2 wild-type (AEL: 1628.06),
- ERBB2-A775_G776insYVMA driver (AEL: 1042.51)

TP53 mutant gene (AEL: 125.68),
- TP53-R267W driver (AEL: 56.56)

ATR wild-type (AEL: 67.52),
- TP53-R267W driver (AEL: 56.56) ;
- STAG2-H1191Y VUS in a driver (AEL: 4.32) ;
- STAG2-E403D VUS in a driver (AEL: 4.32)

PRKDC wild-type (AEL: 66.58),
- STAG2-E403D VUS in a driver (AEL: 4.32) ;
- STAG2-H1191Y VUS in a driver (AEL: 4.32) ;
- TP53-R267W driver (AEL: 56.56)

WEE1 wild-type (AEL: 60.36),
- TP53-R267W driver (AEL: 56.56)

CHEK1 wild-type (AEL: 58.34),
- TP53-R267W driver (AEL: 56.56)

CDK4 wild-type (AEL: 57.54),
- TP53-R267W driver (AEL: 56.56)

RARG wild-type (AEL: 57.45),
- TP53-R267W driver (AEL: 56.56)

PLK1 wild-type (AEL: 57.04),
- TP53-R267W driver (AEL: 56.56)

CDK9 wild-type (AEL: 56.89),
- TP53-R267W driver (AEL: 56.56)

CDK1 wild-type (AEL: 56.89),
- TP53-R267W driver (AEL: 56.56)

CDK2 wild-type (AEL: 56.89),
- TP53-R267W driver (AEL: 56.56)

AURKB wild-type (AEL: 56.85),
- TP53-R267W driver (AEL: 56.56)

BTK wild-type (AEL: 18.29),
- MYD88-P11R VUS in a driver (AEL: 1.62)

PARP1 wild-type (AEL: 13.74),
- STAG2-E403D VUS in a driver (AEL: 4.32) ;
- FANCL-T23I driver (AEL: 0.15) ;
- STAG2-H1191Y VUS in a driver (AEL: 4.32)

STAG1 wild-type (AEL: 12.07),
- STAG2-H1191Y VUS in a driver (AEL: 4.32) ;
- STAG2-E403D VUS in a driver (AEL: 4.32)

XRCC5 wild-type (AEL: 9.62),
- STAG2-E403D VUS in a driver (AEL: 4.32) ;
- STAG2-H1191Y VUS in a driver (AEL: 4.32)

BRCA1 wild-type (AEL: 9.62),
- STAG2-H1191Y VUS in a driver (AEL: 4.32) ;
- STAG2-E403D VUS in a driver (AEL: 4.32)

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DETAILED MOLECULAR PROFILE

	RAD51 wild-type (AEL: 9.62), • STAG2-H1191Y VUS in a driver (AEL: 4.32) ; • STAG2-E403D VUS in a driver (AEL: 4.32) HCK wild-type (AEL: 3.52), • MYD88-P11R VUS in a driver (AEL: 1.62) BRD4 wild-type (AEL: 2.16), • ASXL1-G653R VUS in a driver (AEL: 1.21) PIK3CB wild-type (AEL: 1.29) • SETD2-D699G VUS in a driver (AEL: 0.24)

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.

ERBB2-A775_G776insYVMA

The HER2 exon 20 insertion is listed in the COSMIC database (n> 50), according to the ClinVar database, it is a likely pathogenic alteration. ERBB2-A775_G776insYVMA is the most common HER2 exon 20 insertion and also occurs in the literature under the following names: ERBB2-Y772_A775dup, M774_A775insAYVM, E770delinsEAYVM.
According to preclinical data, it is an activating mutation (1, 2) and it is sensitive to neratinib (1) and poziotinib, but it was shown to be less sensitive to lapatinib, dacomitinib, and afatinib compared to wild-type EGFR (2).
In one study, 11 NSCLC patients, carrying the ERBB2-A775_G776insYVMA mutation, were treated with afatinib. A partial response was achieved in two patients and a stable disease in one (3). Additional case studies also report the efficacy of afatinib therapy in patients carrying the ERBB2-A775_G776insYVMA mutation (4, 5).
The efficacy of erlotinib, trastuzumab, afatinib and/or sirolimus in mutant xenografts was investigated in a preclinical trial. The most effective inhibitory effect was elicited by afatinib + sirolimus therapy (6).
In another study, partial response to dacomitinib was not achieved in patients carrying the mutation, but survival of more than 10 months in 6 of 13 patients was measured using this therapy (7).

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BIOMEDICAL INTERPRETATION

In another study, the efficacy of afatinib was investigated. Patients with this mutation (n=10) had a median TTF of 9.6 months compared to 2.9 in the whole group (n=28). In patients with response data available (6 in patients with this mutation, and 16 carrying other HER2 mutations) diseas control rate (DCR) was 100%, and 69% respectively (8).
Contradictory, a study also looking at the efficacy of afatinib, found that the objective response rates with afatinib were 0% (n=14) in patients with the ERBB2-A775_G776insYVMA mutation (9).
In one patient with HER2 + and Y772_A775dup mutation, T-DM1 therapy resulted in an immediate partial response (10).
Tumor response to trastuzumab deruxtecan was found in 6 of 8 HER2 exon 20 insertion mutant NSCLC patients, although specific mutations are not detailed in the article (11).
Adding neratinib to T-DM1 or trastuzumab deruxtecan has been shown to be synergetic in ERBB2-A775_G776insYVMA mutant breast cancer modells, as neratinib increases the endocytosis of these drugs (12).

References:

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ERBB2 (HER2) mutant gene - targets

HER2 inhibitors can be beneficial in HER2 mutant tumors (1). HER2 inhibitors in clinical use are TRASTUZUMAB, PERTUZUMAB, LAPATINIB, T-DM1, AFATINIB, MARGETUXIMAB and NERATINIB. The HER2 inhibitor TUCATINIB, and the anti-HER2 and topoisomerase-I inhibitor antibody-drug conjugate, TRASTUZUMAB DERUXTECAN, are approved by the FDA and receieved conditional marketing authorization from the EMA.
HER2 activation causes resistance against EGFR inhibitor monotherapies and endocrine therapies.
In a phase II trial, TRASTUZUMAB DERUXTECAN showed efficacy in patients with central nervous system metastases (CNS subgroup: ORR: 58.3%, mPFS: 18.1 months) (2).

References:

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ERBB2 (HER2) mutant NSCLC

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BIOMEDICAL INTERPRETATION

HER2-mutant non-small cell lung cancer (NSCLC) patients were treated with trastuzumab deruxtecan in a phase I study. The response rate was 72.7% (8/11), and median progression-free survival (PFS) was 11.3 months (1). In a phase II clinical trial HER2-mutant NSCLC patients (HER2 mutations were predominantly in the kinase domain) were treated with trastuzumab deruxtecan. The objective response rate was 61.9%, the disease control rate was 90.5% and the estimated median PFS was 14.0 months (2).

TDM-1 therapy reached 44% response rate in HER2 mutant NSCLC patients. The median PFS was 5 months (3).

Afatinib therapy resulted in 19% response rate, and 69% disease control rate in heavily pretreated HER2 mutant NSCLC patients (4). In a prospective trial, afatinib resulted in 53,8% disease control rate at 12 weeks in HER2 mutant NSCLC patients (5).

Neratinib + temsirolimus therapy reached 19% response rate in a phase II trail in HER2 mutant lung cancer patients. The median PFS was 4.1 months and the median overall survival was 15.8 months (6).

HER2 mutant NSCLC patients had 7% response rate on checkpoint inhibitors according to a retrospective study, that is lower compared to the general population. The authors recommend considering immunotherapies only after receiving targeted therapies, and chemotherapies to patients with actionable driver alterations (7).

References:

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TP53-R267W

The variant is listed in the COSMIC database. According to the IARC TP53 database it is a non-functional, deleterious variant. In the ClinVar database, it is mentioned as a pathogenic / likely pathogenic variant. According to preclinical studies the mutation results in partial loss-of-function of the TP53 gene (1, 2).

References:

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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.

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BIOMEDICAL INTERPRETATION

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).

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FANCL-T23I

This variant is listed in the COSMIC database with low frequency (n<5). Functional effect of this mutation is not discussed in the scientific literature.

Lung adenocarcinoma - EGFR inhibitors

The EGFR pathway is frequently activated in lung cancers (1).
In patients with tumors without EGFR activating mutations, ERLOTINIB is indicated when other treatment options are not considered suitable. Erlotinib has been shown to has some activity in EGFR wild type lung adenocarcinoma population as well (2). Erlotinib is not recommended by the NCCN guideline for patients without EGFR driver mutations.
Erlotinib treatment resulted in improved median overall survival (OS) compared to placebo (6.7 vs 4.7 months) in non-selected non-small cell lung cancer (NSCLC) patients (3).
In non-selected patient population, docetaxel resulted in longer OS than erlotinib in EGFR wild-type patients (8.2 months vs 5.4 months) (4). Resistance mechanisms were not tested in this study.
Erlotinib resulted in 1.2% complete response rate, 20.2% partial response rate, and 48.8% stable disease rate in KRAS wild-type lung adenocarcinoma patients (5).

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Cetuximab combined with chemotherapy resulted in 25.7% overall response rate (ORR) in NSCLC patients, while the ORR was 17.2% for chemotherapy alone (6).

OSIMERTINIB is approved for the adjuvant treatment of NSCLC patients with EGFR exon 19 deletions or exon 21 L858R mutations. The approval was based on the results of the ADAURA phase III trial (NCT02511106). OSIMERTINIB is also approved for the first-line treatment of NSCLC with EGFR activating mutations, and previously treated NSCLC with EGFR-T790M mutation.

In a phase I/II study patients with EGFR-mutated (L858R or del19) NSCLC received combination therapy with osimertinib and gefitinib as first-line treatment. The ORR was 85.2%, and at 14.8 months median follow up the median progression free survival (PFS) was not yet reached (7).

NRAS, KRAS, BRAF, gain-of-function PIK3CA, and loss-of-function PTEN mutations can cause resistance to EGFR inhibitors (8).

Based on preclinical data, lung cancer cells with acquired TKI resistance, are sensitive to combined TKI and PARPi treatment, independent of the particular TKI resistance mechanism, through the redox regulatory function of PARP (9). A phase I clinical trial combining a PARPi with an EGFR TKI in TKI-resistant EGFR mutant NSCLC is ongoing (NCT03891615).

In a phase III clinical trial patients with untreated, EGFR-mutated (exon 19 deletion or L858R mutation), advanced NSCLC were treated with ramucirumab plus erlotinib (n=224) or placebo plus erlotinib. The PFS was significantly longer in the ramucirumab plus erlotinib group than in the placebo plus erlotinib group (19.4 months vs. 12.4) (10).

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Lung adenocarcinoma - immunotherapy regardless of PD-L1 status

Immunotherapeutic agents used in non-small cell lung cancer (NSCLC) indication irrespective of PD-L1 expression status are NIVOLUMAB (PD-1 inhibitor), ATEZOLIZUMAB (PD-L1 inhibitor), and, as a combinational treatment, PEMBROLIZUMAB (PD-1 inhibitor).

NIVOLUMAB (PD-1 inhibitor) is approved for NSCLC patients after systematic treatment. NIVOLUMAB is also approved in combination with IPILUMUMAB (CTLA-4 monoclonal antibody) and platinum-based chemotherapy as a first-line treatment for metastatic or recurrent NSCLC patients with no EGFR or ALK mutations. ATEZOLIZUMAB (PD-L1 inhibitor) is approved for the treatment of patients with locally advanced or metastatic NSCLC after they have been previously treated with chemotherapy or as a first-line treatment combined with bevacizumab and chemotherapy. PEMBROLIZUMAB (PD-1 inhibitor) in combination with first-line chemotherapy (carboplatin + pemetrexed) is approved for the treatment of non-squamous NSCLC patients.

In a randomized, international phase III study, patients were enrolled with non-squamous NSCLC to receive nivolumab or docetaxel. The median overall survival (OS) was 12.2 months among 292 patients in the nivolumab group and 9.4 months among 290 patients in the docetaxel group (1). In a phase III clinical trial, first-line treatment with nivolumab plus ipilimumab resulted in a longer median overall survival than chemotherapy (17.1 vs 13.9 months) in patients with NSCLC, irrespective of PD-L1 expression level (2). Furthermore, according to a post-hoc analysis, nivolumab + ipilimumab as first-line treatment provided similar benefit in patients with and without brain metastases (3). According to the interim analysis of

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the CheckMate-9LA phase III trial, nivolumab and ipilimumab combined with 2 cycles of platinum-doublet chemotherapy (chemo) resulted in improved responses (PFS, ORR, OS) compared with 4 cycles chemo as first-line treatment for NSCLC patients (n=719). The median OS was 15.6 versus 10.9 months, respectively (4).
Atezolizumab significantly improved survival compared with docetaxel (4.2 months vs 2.9 months) according to the OAK and POPLAR clinical trials, involving 1137 NSCLC patients (5, 6).
Addition of atezolizumab to bevacizumab + chemotherapy significantly increased progression-free survival (PFS) (8.3 vs 6.8 month) and OS (19.2 vs 14.7 month) in patients with metastatic non-squamous NSCLC, independent of PD-L1 status and EGFR or ALK alterations as a first-line therapy (7).
Pembrolizumab in combination with pemetrexed and platinum therapy is approved as a first-line therapy irrespective of PD-L1 expression in non-squamous NSCLC indication. This combination resulted in improved median PFS compared with pemetrexed and platinum therapy (8.8 vs 4.9 months) regardless of PD-L1 status in a phase III trial (8). After a median follow-up of 23.1 months, the median PFS and OS were 9.0 and 22.0 months in the pembrolizumab combination group, and 4.9 and 10.7 months in the placebo combination (placebo+pemetrexed+platinum therapy) group (9).
In a phase II study, the combination of pembrolizumab and docetaxel resulted in improved ORR and PFS compared with docetaxel monotherapy in patients with advanced NSCLC who had previous progression after platinum-based chemotherapy, regardless of PD-L1 and EGFR status (10).
According to a meta-analysis, second-line nivolumab, pembrolizumab, or atezolizumab resulted in longer survival than docetaxel in the EGFR wild-type and in the KRAS mutant subgroups, but not in the EGFR mutant or KRAS wild-type ones (11).
In a phase III clinical trial NSCLC patients were treated with atezolizumab plus chemotherapy (carboplatin plus nab-paclitaxel) or chemotherapy alone. The median PFS and the median OS were significantly longer in the atezolizumab plus chemotherapy group than in the chemotherapy group (PFS: 7.0 vs 5.5 months, OS: 18.6 vs 13.9 months) (12).
In the COSMIC-021 phase Ib trial, atezolizumab in combination with cabozantinib therapy resulted in an ORR of 23% (7/30), a DCR of 83%, and a median DOR of 5.6 months among non-squamous NSCLC patients who had progressed after prior ICI therapy (13).

In a phase III trial, sintilimab (PD-1 inhibitor) in combination with pemetrexed and platinum therapy resulted in improved median PFS compared with chemotherapy alone (8.9 vs 5.0 months) as a first-line therapy in patients with non-squamous NSCLC, regardless of PD-L1 status. Though, PFS benefit correlated with the level of PD-L1 expression (14).
Tislelizumab (PD-1 antibody) in combination with platinum-based chemotherapy demonstrated antitumor activity as a first-line treatment for NSCLC patients (NCT03432598). Efficacy of tislelizumab is currently tested compared to docetaxel in second or third-line treatment setting for NSCLC patients in the RATIONALE 303 phase III trial (NCT03358875). According to preliminary results, the study met its primary end point of OS.

Eftilagimod alpha is a soluble LAG3 protein, that participates in mediating the stimulation of the dendritic cells and T-cell recruitment. In the phase II TACTI-002 trial, initial results showed promising antitumor activity of eftilagimod alpha and pembrolizumab as a first-line treatment for NSCLC patients irrespective of PD-L1 expression (15).
According to a study, statin use improved the response to anti-PD1 agents as second line therapy in NSCLC patients (n=36 and n=94). Statin use was associated with improved ORR (40% vs 22%) and longer median PFS (7.8 vs 3.6 months) compared (16).

In a phase Ib/II study pepinemab (SEMA4D monoclonal antibody) was investigated in combination with avelumab in NSCLC patients. According to the interim results among 29 patients who progressed during or following immunotherapy, two experienced confirmed partial response (PR), and 15 additional patients experienced stable disease (SD). Among 21 immunotherapy-naive patients, 5 experienced PR, and the disease control rate (DCR) was 81% (17).

In a phase III clinical trial the anti-PD-L1 monoclonal antibody CS1001 in combination with chemotherapy reached significantly longer PFS compared to chemotherapy + placebo among previously untreated NSCLC patients (7.8 vs. 4.9 months). The ORR was 61.4% and 39.2% in the two arms (18).

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Lung adenocarcinoma - angiogenesis inhibitors

RAMUCIRUMAB (VEGFR-2 inhibitor) is not associated with the patient's molecular profile, but it is a registered compound in non-small-cell lung cancer (NSCLC) indication in combination with docetaxel after prior platinum-containing chemotherapy. BEVACIZUMAB (VEGF inhibitor) and NINTEDANIB (receptor tyrosine kinase inhibitor) are registered drugs in lung adenocarcinoma. They are indicated in combination with chemotherapy in first or second line, respectively.

The addition of bevacizumab to paclitaxel plus carboplatin in the treatment of selected patients with NSCLC has a significant survival benefit. The median survival (OS) was 12.3 months in the group assigned to chemotherapy plus bevacizumab, as compared with 10.3 months in the chemotherapy-alone group (1).

According to a study, involving 1314 patients, nintedanib in combination with docetaxel is an effective second-line option for patients with advanced NSCLC previously treated with one line of platinum-based therapy, especially for patients with adenocarcinoma. Progression-free survival (PFS) was significantly improved in the docetaxel plus nintedanib group compared with the docetaxel plus placebo group (median 3.4 months vs 2.7 months (2).

Ramucirumab plus docetaxel improves survival as second-line treatment of patients with stage IV NSCLC. Median OS was 10.5 months for 628 patients allocated ramucirumab plus docetaxel and 9.1 months for 625 patients who received placebo plus docetaxel (3).

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SPEN-N2957D	Wellcome Sanger Institute

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HCK wild-type	Yang G, Buhrlage SJ, Tan L, Liu X, Chen J, Xu L, Tsakmaklis N, Chen JG, Patterson CJ, Brown JR, Castillo JJ, Zhang W, Zhang X, Liu S, Cohen P, Hunter ZR, Gray N, Treon SP. HCK is a survival determinant transactivated by mutated MYD88, and a direct target of ibrutinib. Blood. 2016 Jun 23;127(25):3237-52. doi: 10.1182/blood-2016-01-695098. Epub 2016 May 3. PubMed PMID: 27143257.
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ASXL1	Probable Polycomb group (PcG) protein involved in transcriptional regulation mediated by ligand-bound nuclear hormone receptors, such as retinoic acid receptors (RARs) and peroxisome proliferator-activated receptor gamma (PPARG). Acts as coactivator of RARA and RXRA through association with NCOA1. Acts as corepressor through recruitment of KDM1A and CBX5 to target genes in a cell-type specific manner; the function seems to involve differential recruitment of methylated histone H3 to respective promoters. Acts as corepressor for PPARG and suppresses its adipocyte differentiation-inducing activity (By similarity). Non-catalytic component of the PR-DUB complex, a complex that specifically mediates deubiquitination of histone H2A monoubiquitinated at Lys-119 (H2AK119ub1).
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.
ERBB2	Protein tyrosine kinase that is part of several cell surface receptor complexes, but that apparently needs a coreceptor for ligand binding. Essential component of a neuregulin-receptor complex, although neuregulins do not interact with it alone. GP30 is a potential ligand for this receptor. Regulates outgrowth and stabilization of peripheral microtubules (MTs). Upon ERBB2 activation, the MEMO1-RHOA-DIAPH1 signaling pathway elicits the phosphorylation and thus the inhibition of GSK3B at cell membrane. This prevents the phosphorylation of APC and CLASP2, allowing its association with the cell membrane. In turn, membrane-bound APC allows the localization of MACF1 to the cell membrane, which is required for microtubule capture and stabilization In the nucleus is involved in transcriptional regulation. Associates with the 5-TCAAATTC-3 sequence in the PTGS2/COX-2 promoter and activates its transcription. Implicated in transcriptional activation of CDKN1A; the function involves STAT3 and SRC. Involved in the transcription of rRNA genes by RNA Pol I and enhances protein synthesis and cell growth
FANCL	Ubiquitin ligase protein that mediates monoubiquitination of FANCD2, a key step in the DNA damage pathway. Also mediates monoubiquitination of FANCI. May stimulate the ubiquitin release from UBE2W. May be required for proper primordial germ cell proliferation in the embryonic stage, whereas it is probably not needed for spermatogonial proliferation after birth.
KRAS	Ras proteins bind GDP/GTP and possess intrinsic GTPase activity. Plays an important role in the regulation of cell proliferation (PubMed:23698361, PubMed:22711838). Plays a role in promoting oncogenic events by inducing transcriptional silencing of tumor suppressor genes (TSGs) in colorectal cancer (CRC) cells in a ZNF304-dependent manner (PubMed:24623306). Enzyme regulation : Alternates between an inactive form bound to GDP and an active form bound to GTP. Activated by a guanine nucleotide-exchange factor (GEF) and inactivated by a GTPase-activating protein (GAP). Interaction with SOS1 promotes exchange of bound GDP by GTP.
MYD88	Adapter protein involved in the Toll-like receptor and IL-1 receptor signaling pathway in the innate immune response. Acts via IRAK1, IRAK2, IRF7 and TRAF6, leading to NF-kappa-B activation, cytokine secretion and the inflammatory response. Increases IL-8 transcription. Involved in IL-18-mediated signaling pathway. Activates IRF1 resulting in its rapid migration into the nucleus to mediate an efficient induction of IFN-beta, NOS2/INOS, and IL12A genes. MyD88-mediated signaling in intestinal epithelial cells is crucial for maintenance of gut homeostasis and controls the expression of the antimicrobial lectin REG3G in the small intestine.
SETD2	Histone methyltransferase that specifically trimethylates Lys-36 of histone H3 (H3K36me3) using dimethylated Lys-36 (H3K36me2) as substrate. Represents the main enzyme generating H3K36me3, a specific tag for epigenetic transcriptional activation. Plays a role in chromatin structure modulation during elongation by coordinating recruitment of the FACT complex and by interacting with hyperphosphorylated POLR2A. Acts as a key regulator of DNA mismatch repair in G1 and early S phase by generating H3K36me3, a mark required to recruit MSH6 subunit of the MutS alpha complex: early recruitment of the MutS alpha complex to chromatin to be replicated allows a quick identification of mismatch DNA to initiate the mismatch repair reaction. H3K36me3 also plays an essential role in the maintenance of a heterochromatic state, by recruiting DNA methyltransferase DNMT3A. H3K36me3 is also enhanced in intron-containing genes, suggesting that SETD2 recruitment is enhanced by splicing and that splicing is coupled to recruitment of elongating RNA polymerase. Required during angiogenesis. Recruited to the promoters of adenovirus 12 E1A gene in case of infection, possibly leading to regulate its expression.
SPEN	May serve as a nuclear matrix platform that organizes and integrates transcriptional responses. In osteoblasts, supports transcription activation: synergizes with RUNX2 to enhance FGFR2-mediated activation of the osteocalcin FGF-responsive element (OCFRE) (By similarity). Has also been shown to be an essential corepressor protein, which probably regulates different key pathways such as the Notch pathway. Negative regulator of the Notch pathway via its interaction with RBPSUH, which prevents the association between NOTCH1 and RBPSUH, and therefore suppresses the transactivation activity of Notch signaling. Blocks the differentiation of precursor B-cells into marginal zone B-cells. Probably represses transcription via the recruitment of large complexes containing histone deacetylase proteins. May bind both to DNA and RNA.
STAG2	Component of cohesin complex, a complex required for the cohesion of sister chromatids after DNA replication. The cohesin complex apparently forms a large proteinaceous ring within which sister chromatids can be trapped. At

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	anaphase, the complex is cleaved and dissociates from chromatin, allowing sister chromatids to segregate. The cohesin complex may also play a role in spindle pole assembly during mitosis.
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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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.
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 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.
BRCA1	E3 ubiquitin-protein ligase that specifically mediates the formation of Lys-6-linked polyubiquitin chains and plays a central role in DNA repair by facilitating cellular responses to DNA damage. It is unclear whether it also mediates the formation of other types of polyubiquitin chains. The E3 ubiquitin-protein ligase activity is required for its tumor suppressor function. The BRCA1-BARD1 heterodimer coordinates a diverse range of cellular pathways such as DNA damage repair, ubiquitination and transcriptional regulation to maintain genomic stability. Regulates centrosomal microtubule nucleation. Required for normal cell cycle progression from G2 to mitosis. Required for appropriate cell cycle arrests after ionizing irradiation in both the S-phase and the G2 phase of the cell cycle. Involved in transcriptional regulation of P21 in response to DNA damage. Required for FANCD2 targeting to sites of DNA damage. May function as a transcriptional regulator. Inhibits lipid synthesis by binding to inactive phosphorylated ACACA and preventing its dephosphorylation. Contributes to homologous recombination repair (HRR) via its direct interaction with PALB2, fine-tunes recombinational repair partly through its modulatory role in the PALB2-dependent loading of BRCA2-RAD51 repair machinery at DNA breaks. Component of the BRCA1-RBBP8 complex which regulates CHEK1 activation and controls cell cycle G2/M checkpoints on DNA damage via BRCA1-mediated ubiquitination of RBBP8.
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

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	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
BTK	Non-receptor tyrosine kinase indispensable for B lymphocyte development, differentiation and signaling. Binding of antigen to the B-cell antigen receptor (BCR) triggers signaling that ultimately leads to B-cell activation. After BCR engagement and activation at the plasma membrane, phosphorylates PLCG2 at several sites, igniting the downstream signaling pathway through calcium mobilization, followed by activation of the protein kinase C (PKC) family members. PLCG2 phosphorylation is performed in close cooperation with the adapter protein B-cell linker protein BLNK. BTK acts as a platform to bring together a diverse array of signaling proteins and is implicated in cytokine receptor signaling pathways. Plays an important role in the function of immune cells of innate as well as adaptive immunity, as a component of the Toll-like receptors (TLR) pathway. The TLR pathway acts as a primary surveillance system for the detection of pathogens and are crucial to the activation of host defense. Especially, is a critical molecule in regulating TLR9 activation in splenic B-cells. Within the TLR pathway, induces tyrosine phosphorylation of TIRAP which leads to TIRAP degradation. BTK plays also a critical role in transcription regulation. Induces the activity of NF-kappa-B, which is involved in regulating the expression of hundreds of genes. BTK is involved on the signaling pathway linking TLR8 and TLR9 to NF-kappa-B. Transiently phosphorylates transcription factor GTF2I on tyrosine residues in response to BCR. GTF2I then translocates to the nucleus to bind regulatory enhancer elements to modulate gene expression. ARID3A and NFAT are other transcriptional target of BTK. BTK is required for the formation of functional ARID3A DNA-binding complexes. There is however no evidence that BTK itself binds directly to DNA. BTK has a dual role in the regulation of apoptosis.
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.
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 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

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	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
ERBB2	Protein tyrosine kinase that is part of several cell surface receptor complexes, but that apparently needs a coreceptor for ligand binding. Essential component of a neuregulin-receptor complex, although neuregulins do not interact with it alone. GP30 is a potential ligand for this receptor. Regulates outgrowth and stabilization of peripheral microtubules (MTs). Upon ERBB2 activation, the MEMO1-RHOA-DIAPH1 signaling pathway elicits the phosphorylation and thus the inhibition of GSK3B at cell membrane. This prevents the phosphorylation of APC and CLASP2, allowing its association with the cell membrane. In turn, membrane-bound APC allows the localization of MACF1 to the cell membrane, which is required for microtubule capture and stabilization In the nucleus is involved in transcriptional regulation. Associates with the 5-TCAAATTC-3 sequence in the PTGS2/COX-2 promoter and activates its transcription. Implicated in transcriptional activation of CDKN1A; the function involves STAT3 and SRC. Involved in the transcription of rRNA genes by RNA Pol I and enhances protein synthesis and cell growth
HCK	Non-receptor tyrosine-protein kinase found in hematopoietic cells that transmits signals from cell surface receptors and plays an important role in the regulation of innate immune responses, including neutrophil, monocyte, macrophage and mast cell functions, phagocytosis, cell survival and proliferation, cell adhesion and migration. Acts downstream of receptors that bind the Fc region of immunoglobulins, such as FCGR1A and FCGR2A, but also CSF3R, PLAUR, the receptors for IFNG, IL2, IL6 and IL8, and integrins, such as ITGB1 and ITGB2. During the phagocytic process, mediates mobilization of secretory lysosomes, degranulation, and activation of NADPH oxidase to bring about the respiratory burst. Plays a role in the release of inflammatory molecules. Promotes reorganization of the actin cytoskeleton and actin polymerization, formation of podosomes and cell protrusions. Inhibits TP73-mediated transcription activation and TP73-mediated apoptosis. Phosphorylates CBL in response to activation of immunoglobulin gamma Fc region receptors. Phosphorylates ADAM15, BCR, ELMO1, FCGR2A, GAB1, GAB2, RAPGEF1, STAT5B, TP73, VAV1 and WAS.
PARP1	

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DETAILED DESCRIPTION OF DRIVER AND TARGET GENES

TARGET GENES

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

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DETAILED DESCRIPTION OF DRIVER AND TARGET GENES

TARGET GENES

Name	Description
	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.
RAD51	Participates in a common DNA damage response pathway associated with the activation of homologous recombination and double-strand break repair. Binds to single and double-stranded DNA and exhibits DNA-dependent ATPase activity. Underwinds duplex DNA and forms helical nucleoprotein filaments. Part of a PALB2-scaffolded HR complex containing BRCA2 and RAD51C and which is thought to play a role in DNA repair by HR. Plays a role in regulating mitochondrial DNA copy number under conditions of oxidative stress in the presence of RAD51C and XRCC3.
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).
STAG1	This gene is a member of the SCC3 family and is expressed in the nucleus. It encodes a component of cohesin, a multisubunit protein complex that provides sister chromatid cohesion along the length of a chromosome from DNA replication through prophase and prometaphase, after which it is dissociated in preparation for segregation during anaphase. [provided by RefSeq, Jul 2008]
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).
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-

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APPENDIX

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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