Patient name *****
Patient ID
Case ID
Date of birth *****

Diagnosis Metastasiertes Prostatakarzinom
ICD-10-CM code —
MeSH ID/term D064129 (Prostatic Neoplasms, Castration-Resistant)
Additional MeSH IDs —

Sex	Male	Sample type	—	Labtest	VCF OCAv3 (unpaired) SIP	General dataset ID	108301296939
Ethnicity	EUR	Tumor cellularity	0%	Organizational unit	SIP-UK-Frankfurt-PHI	CVI dataset ID	108301296939
Country	DE					Software version	4.3.5

SUMMARY

Overview of potential treatment impacts
15 Effective | 9 Ineffective | 0 Safety

Overview of prognostic and diagnostic findings
0 Prognostic | 4 Diagnostic

Clinical trials found
3 Trials

Potential impact	Treatment	Drug approval	Biomarker	VAF#	Biomarker score		Trials
Effective	Olaparib	Approved	BRCA2 p.T2399fs (del)	59.48%	AMP Tier I A	7 Clinically Approved	1
Effective	Rucaparib	Off-label	BRCA2 p.T2399fs (del)	59.48%	AMP Tier I A	7 Clinically Approved	0
Effective	Trametinib	Off-label	NF1 p.C680fs (indel)	9.84%	AMP n/a	1 Preclinical	1
			BRAF p.K601E (SNV)	31.55%	AMP Tier II C	5 Clinical	
Effective ⚠	Palbociclib	Off-label	CDK4 Copy number GAIN (CNA)	GCN: 5.48	AMP Tier II D	4 Clinical	0
Effective ⚠	Idasanutlin Palbociclib	Other Off-label	CDK4 Copy number GAIN (CNA)	GCN: 5.48	AMP Tier II D	3 Preclinical	0
Effective	Abemaciclib	Off-label	CDK4 Copy number GAIN (CNA)	GCN: 5.48	AMP n/a	2 Preclinical	0
Effective ⚠	Trametinib Dabrafenib	Off-label Off-label	NF1 p.C680fs (indel)	9.84%	AMP n/a	1 Preclinical	1
Effective ⚠	Erlotinib Trametinib	Off-label Off-label	NF1 p.C680fs (indel)	9.84%	AMP n/a	1 Preclinical	1
Effective	Imatinib	Off-label	NF1 p.C680fs (indel)	9.84%	AMP n/a	1 Preclinical	0
Effective ⚠	Erlotinib Selumetinib	Off-label Other	NF1 p.C680fs (indel)	9.84%	AMP n/a	1 Preclinical	0
Effective	Selumetinib	Other	NF1 p.C680fs (indel)	9.84%	AMP n/a	1 Preclinical	0
Effective	Sirolimus	Other	NF1 p.C680fs (indel)	9.84%	AMP n/a	1 Preclinical	0
Effective	Tranilast	Other	NF1 p.C680fs (indel)	9.84%	AMP n/a	1 Preclinical	0

Potential impact	Treatment	Drug approval	Biomarker	VAF[#]	Biomarker score		Trials
Effective ⚠	CDK inhibitors	Other	CDK4 Copy number GAIN (CNA)	GCN: 5.48	AMP n/a	n/a	0
Effective	PARP inhibitors	Other	BRCA2 p.T2399fs (del)	59.48%	AMP n/a	n/a	2
Ineffective ⚠	Dabrafenib	Off-label	BRAF p.K601E (SNV)	31.55%	AMP Tier II D	4 Clinical	—
Ineffective	Vemurafenib	Off-label	BRAF p.K601E (SNV)	31.55%	AMP Tier II D	4 Clinical	—
			NF1 p.C680fs (indel)	9.84%	AMP n/a	1 Preclinical	
Ineffective	Crizotinib	Off-label	MET p.N375S (SNV)	60.43%	AMP Tier III	4 Clinical	—
Ineffective	Ribociclib	Off-label	RB1 p.D578fs (del)	9.93%	AMP n/a	2 Preclinical	—
Ineffective ⚠	Palbociclib	Off-label	RB1 p.D578fs (del)	9.93%	AMP n/a	2 Preclinical	—
Ineffective	Gefitinib	Off-label	NF1 p.C680fs (indel)	9.84%	AMP n/a	1 Preclinical	—
Ineffective	Afatinib	Off-label	NF1 p.C680fs (indel)	9.84%	AMP n/a	1 Preclinical	—
Ineffective ⚠	Erlotinib	Off-label	NF1 p.C680fs (indel)	9.84%	AMP n/a	1 Preclinical	—
Ineffective ⚠	CDK inhibitors	Other	RB1 p.D578fs (del)	9.93%	AMP n/a	n/a	—
Diagnostic	—	—	ERG/TMPRSS2 (fusion)	—	AMP Tier II D	6 Clinical	—
Diagnostic	—	—	RB1 p.D578fs (del)	9.93%	AMP Tier II D	6 Clinical	—
Diagnostic	—	—	CDK4 Copy number GAIN (CNA)	GCN: 5.48	AMP n/a	6 Clinical	—
Diagnostic	—	—	ATM p.D1853V (SNV)	54.13%	AMP Tier IV	3 Preclinical	—

* the drug is approved for the cancer type but either none of the currently approved biomarkers for this drug were identified, or an approved resistance biomarker for the drug was identified in this patient. Therefore, the drug label may not cover the analyzed patient.

[#] the VAF column shows variant allele frequency (VAF). For CNAs, the gene copy number (GCN) is shown. Fold change (FC) is shown for CNAs from Illumina panels.

Biomarker score: AMP score and CVI score. **Clinically approved:** Approved biomarker (by the FDA, EMA, or NCCN) to predict a specific effect in the patient's disease. **Clinical:** Not yet approved biomarker for the patient's disease. Observed in clinical studies as a potential biomarker to predict a specific effect of the drug. **Preclinical:** This biomarker has not yet been observed/tested in patients to predict a specific effect of the drug. It is supported by preclinical evidence or

translational data.
You can find more details on the biomarker score (AMP and CVI score) in the glossary.

BIOMARKER DETAILS

BRCA2 p.T2399fs (del)

The BRCA2 protein is required for the repair of DNA double-strand breaks by homologous recombination. Frameshift mutations in BRCA2 are likely to disrupt gene function and result in defective DNA repair. Both preclinical and clinical studies show that defects in BRCA2 can sensitize cancer cells to PARP inhibitors. Preclinical and clinical studies have shown that defects in BRCA2 can sensitize cancer cells to PARP inhibitors. Rucaparib is indicated for the treatment of patients with a deleterious BRCA mutation-associated metastatic castration-resistant prostate cancer (mCRPC). After progression on enzalutamide or abiraterone, olaparib is indicated in mCRPC with deleterious germline or somatic alterations in homologous recombination repair genes, such as BRCA1 and BRCA2.

PubMed ID
32343890, 15829967, 28540598

Potential impact	Treatment	Drug approval	Biomarker score	
Effective	Olaparib	Approved	AMP Tier I A	7 Clinically Approved
Effective	Rucaparib	Off-label	AMP Tier I A	7 Clinically Approved
Effective	PARP inhibitors	Other	AMP n/a	n/a

* the drug is approved for the cancer type but either none of the currently approved biomarkers for this drug were identified, or an approved resistance biomarker for the drug was identified in this patient. Therefore, the drug label may not cover the analyzed patient.

NF1 p.C680fs (indel)

[The information provided in this CVI should be carefully reviewed for clinical relevance since no specific match with the patient's disease term was detected.] The GTPase activating protein neurofibromin (NF1) is a negative regulator of RAS and inactivates the RAS/MAPK signaling pathway to inhibit cell proliferation. Loss of function of NF1 due to damaging mutations or biallelic copy loss can activate the RAS/RAF/MEK/ERK pathway and is a known contributor to oncogenesis in many tumor types. Inherited mutations in the NF1 gene are causative of neurofibromatosis type 1 (NF1) which is an autosomal dominantly inherited tumor predisposition syndrome. A clinical study has shown an objective response rate of 26% to imatinib in NF1 patients (N=23) with germline NF1 mutation and one type of peripheral nerve sheath tumors, plexiform neurofibroma (PNs). Although neurofibromatosis type 1 (NF1) associated progressive PNs have not responded to sirolimus in terms of tumor shrinkage in an uncontrolled clinical study, patients treated with sirolimus had a slightly longer time to progression (TTP) compared to untreated PN patients in a previous study with similar eligibility criteria. Another clinical study suggested that children with neurofibromatosis type 1 and inoperable plexiform neurofibromas benefited from long-term dose-adjusted treatment with selumetinib. Treatment with selumetinib resulted in partial tumor responses in 17 of 24 children and this observation was supported by preclinical data in xenograft mice. Trametinib treatment leads to a dramatic clinical improvement of the symptoms of a neurofibromatosis patient. In vitro, NF1 deficient cells were more efficiently suppressed by tranilast than NF1 proficient cells. Somatic NF1 mutations are frequently seen (~11%) in lung adenocarcinoma. Clinical cases of EGFR-driven lung cancer have shown that the tumor with loss of NF1 expression was resistant to EGFR inhibitor erlotinib, gefitinib or afatinib. Preclinical EGFR-driven lung cancer models revealed that a tumor with diminished NF1 expression remains sensitive to combination therapy with erlotinib and MEK inhibitor trametinib or selumetinib. Another preclinical observation in lung cancer cells has shown that NF1 loss indicates trametinib sensitivity but might reduce sensitivity to tyrosine kinase inhibitor dasatinib. Somatic mutations in NF1 are common in melanomas, specifically in the desmoplastic subtype. Loss of NF1 in cutaneous melanoma is associated with RAS activation and MEK-dependence. The BRAF mutated tumors of four melanoma patients, one with a nonsense and three with splice site NF1 mutations, have shown resistance to vemurafenib. However, one case report of a melanoma tumor with BRAF.V600E and NF1.R440* mutation showed a complete response to trametinib and dabrafenib combination therapy. Preclinical studies in melanoma cell lines are resistant to BRAF inhibitor vemurafenib and have reduced sensitivity to MEK inhibitor selumetinib, but sensitivity to trametinib.

PubMed ID
24296828, 24576830, 24535670, 26076063, 23288408, 23171796, 26861459, 25314964, 23099009, 24851266, 24500418, 28230061

Potential impact	Treatment	Drug approval	Biomarker score
Effective	Trametinib	Off-label	AMP n/a · 1 Preclinical
Effective ⚠	Trametinib + Dabrafenib	Off-label, Off-label	AMP n/a · 1 Preclinical
Effective ⚠	Erlotinib + Trametinib	Off-label, Off-label	AMP n/a · 1 Preclinical
Effective	Imatinib	Off-label	AMP n/a · 1 Preclinical
Effective ⚠	Erlotinib + Selumetinib	Off-label, Other	AMP n/a · 1 Preclinical
Effective	Selumetinib	Other	AMP n/a · 1 Preclinical
Effective	Sirolimus	Other	AMP n/a · 1 Preclinical
Effective	Tranilast	Other	AMP n/a · 1 Preclinical
Ineffective	Vemurafenib	Off-label	AMP n/a · 1 Preclinical
Ineffective	Gefitinib	Off-label	AMP n/a · 1 Preclinical
Ineffective	Afatinib	Off-label	AMP n/a · 1 Preclinical
Ineffective ⚠	Erlotinib	Off-label	AMP n/a · 1 Preclinical

* the drug is approved for the cancer type but either none of the currently approved biomarkers for this drug were identified, or an approved resistance biomarker for the drug was identified in this patient. Therefore, the drug label may not cover the analyzed patient.

BRAF p.K601E (SNV)

[The information provided in this CVI should be carefully reviewed for clinical relevance since no specific match with the patient's disease term was detected.] The serine/threonine-protein kinase BRAF activates the RAS/MAPK signaling pathway to promote cell proliferation and survival. This mutation, located in the activation segment, confers high kinase activity. Preclinical data have shown that this BRAF mutation renders cancer cells resistant to BRAF inhibitors such as dabrafenib or vemurafenib. These preclinical findings were confirmed by some lung cancer patients with this mutation whose tumors progressed on vemurafenib or dabrafenib treatment. Tumor responses in melanoma patients with this mutation have been observed with the MEK inhibitor trametinib. Preclinical data support sensitivity to trametinib.

PubMed ID
28783719, 24933606, 22798288, 29076950, 23248257, 27911979, 22355009, 27790118, 28344857

Potential impact	Treatment	Drug approval	Biomarker score
Effective	Trametinib	Off-label	AMP Tier II C; 5 Clinical
Ineffective ⚠	Dabrafenib	Off-label	AMP Tier II D; 4 Clinical
Ineffective	Vemurafenib	Off-label	AMP Tier II D; 4 Clinical

* the drug is approved for the cancer type but either none of the currently approved biomarkers for this drug were identified, or an approved resistance biomarker for the drug was identified in this patient. Therefore, the drug label may not cover the analyzed patient.

CDK4 Copy number GAIN (CNA)

[The information provided in this CVI should be carefully reviewed for clinical relevance since no specific match with the patient's disease term was detected.] The cyclin-dependent kinase 4 (CDK4) upregulates the CDK4/6-Rb pathway, thus promoting cell cycle progression. Dysregulation of the CDK4/6-Rb axis is common in many cancer types. Amplification of CDK4 is seen in more than 90% of well-differentiated/dedifferentiated liposarcomas (WD/DDLPS). Clinical studies of CDK4 amplified patients with WD/DDLPS whose tumors had previously progressed on systemic therapy reported an 18-week median progression-free survival after treatment with palbociclib. However, an objective response was documented only in 2 out of 60 patients and it has yet to be established whether CDK4 amplification is a biomarker of palbociclib response. Preclinical dedifferentiated liposarcoma models with CDK4 amplification showed sensitivity and a synergistic effect to the combination regimen of palbociclib and the MDM2 antagonist idasanutlin. Preliminary results from clinical studies of patients with DDLPS indicate that tumors with CDK4 amplification might respond to abemaciclib.

PubMed ID
25028469, 26528855, 27124835, 23569312, 29250486, 29372852, 28629371, 29731991, 16160477

Potential impact	Treatment	Drug approval	Biomarker score
Effective ⚠	Palbociclib	Off-label	AMP Tier II D; 4 Clinical
Effective ⚠	Idasanutlin + Palbociclib	Other, Off-label	AMP Tier II D; 3 Preclinical
Effective	Abemaciclib	Off-label	AMP n/a; 2 Preclinical
Effective ⚠	CDK inhibitors	Other	AMP n/a; n/a
Diagnostic	—	—	AMP n/a; 6 Clinical

* the drug is approved for the cancer type but either none of the currently approved biomarkers for this drug were identified, or an approved resistance biomarker for the drug was identified in this patient. Therefore, the drug label may not cover the analyzed patient.

MET p.N375S (SNV)

[The information provided in this CVI should be carefully reviewed for clinical relevance since no specific match with the patient's disease term was detected.] [Clinical data based on rare patient cases with lack of preclinical validation have to be considered with caution.] The hepatocyte growth factor receptor MET is a receptor tyrosine kinase that activates the RAS/MAPK, PI3K/AKT, PLC/PKC, and JAK/STAT signaling pathways to promote cell proliferation, survival, and invasion. The N375S mutation exhibits weaker affinity to its ligand (HGF) and lacks transforming abilities. This mutation was identified in a head

and neck tumor that rapidly progressed on crizotinib treatment.

PubMed ID
19723643, 28514312

Potential impact	Treatment	Drug approval	Biomarker score
Ineffective	Crizotinib	Off-label	AMP Tier III; 4 Clinical

* the drug is approved for the cancer type but either none of the currently approved biomarkers for this drug were identified, or an approved resistance biomarker for the drug was identified in this patient. Therefore, the drug label may not cover the analyzed patient.

RB1 p.D578fs (del)

[The information provided in this CVI should be carefully reviewed for clinical relevance since no specific match with the patient's disease term was detected.]   The tumor suppressor gene RB1 (retinoblastoma 1) is a negative regulator of the cell cycle. This frameshift mutation leads to premature termination of gene transcription and likely renders the protein non-functional. Loss of RB1 function confers cell cycle deregulation. Mutations in the RB1 gene are a cause of a relatively common childhood cancer (retinoblastoma) and, if found in a patient's germline, also confer an increased risk of developing secondary cancers later in life, including breast, bladder and prostate cancers, melanomas and sarcomas. There is strong mechanistic rationale suggesting that effective inhibition of cancer cell proliferation through CDK4/6 inhibitors depends on functional RB1. This is supported by preclinical evidence demonstrating that, in the absence of functional RB1, tumor cell-lines and mouse xenografts from several cancer types (including breast cancer, liposarcoma, and hepatocellular carcinoma) are resistant to treatment with the CDK4/6 inhibitors palbociclib as well as ribocilib. Emerging clinical data elicited that resistance to CDK4/6 inhibitors correlates with mutations in RB1 conferring loss of functions.

PubMed ID
22767154, 31396487, 26923330, 27020857

The well-characterized tumor suppressor RB1 (retinoblastoma 1) is a negative regulator of the cell cycle. This frameshift mutation leads to premature termination of gene transcription and likely renders the protein non-functional. Nonsense mutations in the RB1 gene induced cell cycle deregulation and are a cause of a relatively common childhood cancer (retinoblastoma). Patients with hereditary retinoblastoma (RB1 mutations in the germline) have an increased risk of developing secondary cancers later in life, including melanoma, soft-tissue cancers, bladder, lung, and prostate cancers, as well as sarcomas.

PubMed ID
8651278, 16269091, 24433356, 24740996

Potential impact	Treatment	Drug approval	Biomarker score
Ineffective	Ribociclib	Off-label	AMP n/a; 2 Preclinical
Ineffective ⚠	Palbociclib	Off-label	AMP n/a; 2 Preclinical
Ineffective ⚠	CDK inhibitors	Other	AMP n/a; n/a
Diagnostic	—	—	AMP Tier II D; 6 Clinical

* the drug is approved for the cancer type but either none of the currently approved biomarkers for this drug were identified, or an approved resistance biomarker for the drug was identified in this patient. Therefore, the drug label may not cover the analyzed patient.

ERG/TMPRSS2 (fusion)

ERG (ETS-related gene) is a transcription factor that prevents the activation of pro-inflammatory genes and promotes vasculogenesis, angiogenesis, haematopoiesis, and bone development. Translocation with TMPRSS2 leads to increased expression of ERG and upregulation of the TGF-beta signaling pathway. This mutation is specific to and highly associated with (>50% of patients) prostate cancer.

PubMed ID
24266818, 19395877, 30459527, 18065961, 30680235, 20473283, 28445989

Potential impact	Treatment	Drug approval	Biomarker score
Diagnostic	—	—	AMP Tier II D; 6 Clinical

* the drug is approved for the cancer type but either none of the currently approved biomarkers for this drug were identified, or an approved resistance biomarker for the drug was identified in this patient. Therefore, the drug label may not cover the analyzed patient.

ATM p.D1853V (SNV)

The serine-protein kinase ATM is a serine/threonine kinase that activates the checkpoint signaling pathway upon double-strand breaks and genotoxic stress. In experimental models, this variant was shown to be functionally neutral.

PubMed ID
19431188, 23585524, 18634022, 11805335, 14970866

Potential impact	Treatment	Drug approval	Biomarker score
Diagnostic	—	—	AMP Tier IV; 3 Preclinical

* the drug is approved for the cancer type but either none of the currently approved biomarkers for this drug were identified, or an approved resistance biomarker for the drug was identified in this patient. Therefore, the drug label may not cover the analyzed patient.
Biomarker score: AMP score and CVI score. **Clinically approved:** Approved biomarker (by the FDA, EMA, or NCCN) to predict a specific effect in the patient's disease. **Clinical:** Not yet approved biomarker for the patient's disease. Observed in clinical studies as a potential biomarker to predict a specific effect of the drug. **Preclinical:** This biomarker has not yet been observed/tested in patients to predict a specific effect of the drug. It is supported by preclinical evidence or translational data.
You can find more details on the biomarker score (AMP and CVI score) in the glossary.

TREATMENT DETAILS

Potentially effective treatments

The drugs listed as drug-drug interactions may interact with elements of the treatment. Such interactions can negatively affect the effectiveness and/or safety of this treatment. It is recommended that current and future medications be carefully assessed against this list. If necessary, appropriate changes can be considered in consultation with your pharmacist. As the DrugBank database and the MH Guide database are updated asynchronously, this list may not be complete.

Olaparib — Drug approval in patient disease: Approved

Olaparib is an inhibitor of poly (ADP-ribose) polymerase (PARP) enzymes, including PARP1, PARP2, and PARP3. PARP enzymes are involved in normal cellular homeostasis, such as DNA transcription, cell cycle regulation, and DNA repair. Olaparib has been shown to inhibit growth of select tumor cell lines in vitro and decrease tumor growth in mouse xenograft models of human cancer both as monotherapy or following platinum-based chemotherapy. Increased cytotoxicity and anti-tumor activity following treatment with olaparib were noted in cell lines and mouse tumor models with deficiencies in BRCA. In vitro studies have shown that olaparib-induced cytotoxicity may involve inhibition of PARP enzymatic activity and increased formation of PARP-DNA complex, resulting in disruption of cellular homeostasis and cell death.
Olaparib is available as oral tablets marketed under the brand name Lynparza and was initially indicated as a maintenance therapy or monotherapy for the treatment of adult patients with recurrent epithelial ovarian, fallopian tube or primary peritoneal cancer. On January 12, 2018, FDA expanded the approved use of Lynparza to include chemotherapy-experienced patients with germline breast cancer susceptibility gene (BRCA) mutated, human epidermal growth factor receptor 2 (HER2)-negative metastatic breast cancer. In a randomized clinical trial involving patients with HER2-negative metastatic breast cancer with a germline BRCA mutation, the median progression-free survival for patients taking Lynparza was 7 months compared to 4.2 months for patients taking chemotherapy only. Patient selection for this newly-approved indication can be performed based on an FDA-approved genetic test, called the BRACAnalysis CDx.
Moreover, in December of 2018 the FDA further approved the categorization and use of Lynparza (olaparib) as frontline maintenance therapy in ovarian cancer, making the medication the first time a PARP inhibitor has been approved in the first-line maintenance setting [L5086]. This new approval for frontline maintenance now allows patients who have had surgery and complete or partial response to platinum-based therapy after being first diagnosed with the cancer to be treated with olaparib to decrease the risk of recurrence or delay it significantly [L5086]. This approval is based on findings from the phase 3 SOLO-1 trial for olaparib, which demonstrated the capacity for the agent to reduce the risk of disease progression or death by 70% in patients with BRCA-mutant advanced ovarian cancer who were in complete or partial response to platinum-based chemotherapy [L5086]. It is expected that the ability to offer this important first-line maintenance treatment option to eligible patients may slow down or even stop the natural course of disease progression [L5086].(DB09074)

Detected variants supporting this treatment effect:
BRCA2 p.T2399fs (del)

Drug-drug interactions
/ **2**-Methoxyethanol / **4**-Hydroxycoumarin / **5**-Fluorouracil / **6**-Mercaptopurine / **9**-(N-Methyl-L-Isoleucine)-Cyclosporin A
/ **A**betimus, Acteoside, Adenovirus Type 7 Vaccine Live, Aldesleukin, Aldosterone, Alefacept, Alemtuzumab, Alfentanil, Alprazolam, Altretamine, Amiodarone Hydrochloride, Amitriptyline Hydrochloride, Amsacrine, Anthrax Vaccine, Antilymphocyte Immunoglobulin (Horse), Antithymocyte Immunoglobulin (Rabbit), Argatroban, Arsenic Trioxide, Astemizole, Avanafil, Azacitidine, Azathioprine
/ **B**acillus Calmette-Guerin Substrain Connaught Live Antigen, Bacillus Calmette-Guerin Substrain Danish 1331 Live Antigen, Bacillus Calmette-Guerin Substrain Tice Live Antigen, Baf-312, Baricitinib, Basiliximab, Bcg Vaccine, Beclomethasone Dipropionate, Begelomab, Belatacept, Belimumab, Belinostat, Bendamustine, Betamethasone, Bevacizumab, Bexarotene, Bleomycin, Bleselumab, Blinatumomab, Bortezomib, Bosutinib, Brentuximab Vedotin, Brequinar, Briakinumab, Brodalumab, Bromocriptine Mesylate, Budesonide, Buspirone Hydrochloride, Busulfan
/ **C**abazitaxel, Capecitabine, Carbamazepine, Carboplatin, Carfilzomib, Carmustine, Castanospermine, Cepeginterferon Alfa-2b, Cerebyx, Chlorambucil, Chloramphenicol, Ciclesonide, Cisapride, Cisplatin, Cladribine, Clindamycin Hydrochloride, Clobetasol, Clofarabine, Clomipramine Hydrochloride, Clonidine, Cloprednol, Clorindione, Corticotropin, Cortisone Acetate, Cortivazol, Cyclobenzaprine Hydrochloride, Cyclophosphamide, Cyclosporine, Cytarabine
/ **D**acarbazine, Daclizumab, Dactinomycin, Darifenacin, Dasatinib, Daunorubicin, Decitabine, Deflazacort, Deoxyspergualin, Desipramine Hydrochloride, Dexamethasone, Dexamethasone Isonicotinate, Dexrazoxane, Digitoxin, Dihydroergotamine Mesylate, Dimethyl Fumarate, Dinutuximab, Diphenadione, Dipyrone, Docetaxel, Dofetilide, Dothiepin, Doxepin Hydrochloride, Doxifluridine, Doxorubicin
/ **E**bastine, Eculizumab, Efalizumab, Eletriptan Hydrobromide, Eliglustat Tartrate, Epirubicin, Eplerenone, Eribulin, Esketamine Hydrochloride, Estramustine, Ethosuximide, Ethyl Biscoumacetate, Etoposide, Everolimus
/ **F**elodipine, Fentanyl, Floxuridine, Fluclorolone, Flucytosine, Fludarabine, Fludrocortisone, Fluindione, Flunisolide, Fluocinolone Acetonide, Fluocortin, Fluocortolone, Fluperolone, Fluprednidene, Fluprednisolone, Fluticasone, Fluticasone Furoate, Fluticasone Propionate, Formocortal, Fosaprepitant Dimeglumine
/ **G**allium Nitrate (Anhydrous), Gemcitabine, Gemtuzumab Ozogamicin, Glatiramer Acetate, Guselkumab, Gusperimus
/ **H**alometasone, Human Adenovirus E Serotype 4 Strain Cl-68578 Antigen, Hydrocodone Bitartrate, Hydrocortisone Aceponate, Hydrocortisone Acetate, Hydrocortisone Succinate, Hydroxychloroquine, Hydroxyurea, Hypericin
/ **I**britumomab Tiuxetan, Idarubicin, Ifosfamide, Imatinib, Indinavir Sulfate, Indomethacin, Interferon Alfa, Interferon Alfa-2a, Recombinant, Interferon Alfa-2b, Interferon Alfa-N1, Interferon Alfa-N3, Interferon Alfacon-1, Interferon Beta-1b, Interferon Gamma-1b, Irinotecan, Ixabepilone, Ixekizumab

/ **L**atuda, Lenalidomide, Levacetylmethadol, Levothyroxine Sodium, Linezolid, Lipegfilgrastim, Lofepramine Hydrochloride, Lomustine
/ **M**araviroc, Mechlorethamine, Melengestrol, Melitracen, Melphalan, Meperidine Hydrochloride, Mepolizumab, Meprednisone, Methotrexate, Methylprednisolone Sodium Succinate, Methysergide, Mitomycin C, Mitoxantrone Hydrochloride, Mizoribine, Mometasone, Mometasone Furoate, Monomethyl Fumarate, Muromonab, Mycophenolate Mofetil, Mycophenolic Acid
/ **N**aloxegol, Nelarabine, Nelfinavir Mesylate, Nisoldipine, Nortriptyline Hydrochloride / **O**binutuzumab, Ocrelizumab, Omega Interferon, Oxaliplatin, Ozanimod
/ **P**aclitaxel, Palbociclib, Panobinostat, Paramethasone, Pazopanib, Peficitinib, Pegaspargase, Peginterferon Alfa-2a, Peginterferon Beta-1a, Pemetrexed, Penicillamine, Pentostatin, Phenprocoumon, Phenylalanine, Pimecrolimus, Pimozide, Pirarubicin, Pirfenidone, Pomalidomide, Ponatinib, Pralatrexate, Prednisolone, Prednisone, Prednylidene, Procarbazine, Propylthiouracil
/ **Q**uinidine / **R**altitrexed, Ravulizumab, Rilpivirine, Risankizumab, Rituximab, Rivaroxaban, Rozanolixizumab, Rubella Virus Vaccine, Ruxolitinib
/ **S**arilumab, Sildenafil, Simvastatin, Sirolimus, Sirukumab, Sorafenib, Stepronin, Streptozocin, Sulfasalazine, Sunitinib
/ **T**adalafil, Tedizolid Phosphate, Temozolomide, Temsirolimus, Teniposide, Tepoxalin, Teriflunomide, Tetrandrine, Thalidomide, Theophylline, Thioguanine, Thiotepa, Tianeptine, Ticagrelor, Tixocortol, Tofranil, Tolvaptan, Topotecan, Tositumomab, Trabectedin, Trastuzumab Emtansine, Tretinoin, Triamcinolone Hexacetonide, Triazolam, Trifluridine, Trilostane, Trimipramine Maleate, Triptolide, Trofosfamide, Typhoid Vaccine Live
/ **V**aricella Zoster Vaccine (Live/Attenuated), Vedolizumab, Vibrio Cholerae Cvd 103-Hgr Strain Live Antigen, Vilanterol, Vinblastine, Vincristine, Vindesine, Vinorelbine, Voclosporin, Vorinostat
/ **W**artmannin / **Y**ellow Fever Vaccine / **Z**idovudine, Zolpidem

Rucaparib

Drug approval in patient disease: Off-label

Rucaparib is a potent mammalian poly(ADP-ribose) polymerase (PARP) 1, 2 and 3 inhibitor with anticancer properties. PPAR is an enzyme that plays an essential role in DNA repair by activating response pathways and facilitating repair [A18745], and defects in these repair mechanisms have been demonstrated in various malignancies, including cancer. Regulation of repair pathways is critical in promoting necessary cell death. BRCA genes are tumor suppressor genes mediate several cellular process including DNA replication, transcription regulation, cell cycle checkpoints, apoptosis, chromatin structuring and homologous recombination (HR). Homologous recombination deficiency (HRD), along with PPAR inhibition, is a vulnerability that enhances the cell death pathway when the single mutations alone would permit viability. Ovarian cancer commonly possesses defects in DNA repair pathways such as HRD due to BRCA mutations or otherwise.
There are three main types of ovarian cancer: epithelial (90%), germ cell (5%) and sex cord stromal cell (5%). Epithelial ovarian, being the most common, fifth leading cause of cancer-related deaths in women in the United States. Advanced ovarian cancer particularly poses challenges due to reduced therapeutic response rates from standard platinum-based chemotherapy and overall survival rates. Rucaparib has shown to induce cytotoxicity in tumor cell lines with deficiencies in BRCA1/2 and other DNA repair genes [FDA Label]. Of all the BRCA1/2 mutations in ovarian cancer, most are due to germline mutations (18%), and approximately 7% represent somatic mutations acquired within the tumor [A31354].
The indication of rucaparib as an oral monotherapy in patients with deleterious BRCA mutation (germline and/or somatic) associated advanced ovarian cancer was granted accelerated approval in 2016 for selected patients who have previously received greater than two lines of platinum-based therapy. It is currently marketed in the US under the brand name Rubraca that contains rucaparib camsylate as the active ingredient. The identification of patients who are eligible for rucaparib therapy is performed via *in vitro* diagnostic tests to detect the presence of a deleterious BRCA mutation (germline and/or somatic). The FDA-approved test qualitatively detects sequence alterations in BRCA1 and BRCA2 (BRCA1/2) genes. More information can be found on the FDA Website [L1047].
While rucaparib is indicated for deleterious BRCA mutation (germline and/or somatic)-associated advanced ovarian cancer, there is evidence that its antitumor activity is also clinically effective against ovarian tumors with high homologous recombination deficiency (HRD) loss of heterozygosity (LOH) [A31354].(DB12332)

Detected variants supporting this treatment effect:
BRCA2 p.T2399fs (del)

Drug-drug interactions
/ **4**-Hydroxycoumarin / **A**bemaciclib, Alfentanil, Alprazolam, Aprepitant, Argatroban, Avanafil
/ **B**af-312, Baricitinib, Bromocriptine Mesylate, Budesonide, Bupropion Hydrochloride, Busulfan
/ **C**arbamazepine, Cerebyx, Chembl372638, Cinacalcet Hydrochloride, Ciprofloxacin, Cisapride, Clinafloxacin, Clindamycin Hydrochloride, Clorindione, Conivaptan Hydrochloride, Cyclobenzaprine Hydrochloride
/ **D**arunavir, Dasatinib, Dicumarol, Digitoxin, Dihydroergotamine Mesylate, Diphenadione, Dofetilide
/ **E**bastine, Eliglustat Tartrate, Enoxacin, Eplerenone, Ergotamine Tartrate, Esketamine Hydrochloride, Ethosuximide, Ethyl Biscoumacetate
/ **F**elodipine, Fentanyl, Fluindione, Fosaprepitant Dimeglumine / **G**lycerol Phenylbutyrate, Guanidine Hydrochloride
/ **H**alofantrine Hydrochloride, Hydrocodone Bitartrate / **I**ndinavir Sulfate, Irinotecan / **L**atuda, Levacetylmethadol, Levothyroxine Sodium, Lumateperone
/ **M**araviroc, Methysergide, Midostaurin, Mycophenolic Acid / **N**isoldipine / **O**rphenadrine / **P**aclitaxel, Phenobarbital, Phenprocoumon, Primidone
/ **R**evefenacin, Rifampin, Rilpivirine, Rivaroxaban, Rofecoxib / **S**aquinavir, Sirolimus
/ **T**adalafil, Technetium Tc-99m Ciprofloxacin, Temsirolimus, Theophylline, Thiopental Sodium, Tianeptine, Tolvaptan, Triazolam / **V**alproic Acid / **Z**afirlukast

Trametinib

Drug approval in patient disease: Off-label

Trametinib dimethyl sulfoxide is a kinase inhibitor. Each 1-mg tablet contains 1.127 mg trametinib dimethyl sulfoxide equivalent to 1 mg of trametinib non-solvated parent. FDA approved on May 29, 2013 [L2727].
The U.S. Food and Drug Administration approved [DB08912](Tafilnar) and Mekinist (trametinib), administered together, for the treatment of anaplastic

thyroid cancer (ATC) that cannot be removed by surgery or has spread to other parts of the body (metastatic), and has a type of abnormal gene, BRAF V600E (BRAF V600E mutation-positive) [L2726].
Thyroid cancer is a disease in which cancer cells form in the tissues of the thyroid. Anaplastic thyroid cancer is a rare, aggressive type of thyroid cancer. The National Institutes of Health (NIH) estimates there will be 53,990 new cases of thyroid cancer and an estimated 2,060 deaths from the disease in the United States in 2018. Anaplastic thyroid cancer accounts for approximately 1 to 2 percent of all thyroid cancers [L2726].(DB08911)

Detected variants supporting this treatment effect:
BRAF p.K601E (SNV), NF1 p.C680fs (indel)

Drug-drug interactions
/ **4**-Hydroxycoumarin / **5**-Fluorouracil
/ **A**lfentanil, Almotriptan Malate, Alprazolam, Aminophenazone, Amiodarone Hydrochloride, Amitriptyline Hydrochloride, Amodiaquine Hydrochloride, Anastrozole, Apixaban, Aprepitant, Astemizole, Atorvastatin Calcium, Avanafil, Azelastine Hydrochloride
/ **B**af-312, Balaglitazone, Benzyl Alcohol, Beraprost, Brigatinib, Bromocriptine Mesylate, Budesonide, Buprenorphine, Buspirone Hydrochloride, Busulfan
/ **C**abazitaxel, Capravirine, Carbamazepine, Celecoxib, Cerebyx, Cerivastatin Sodium, Chloroquine, Ciglitazone, Cisapride, Clindamycin Hydrochloride, Clomipramine Hydrochloride, Clonidine, Clorindione, Colchicine, Conivaptan Hydrochloride, Cyclobenzaprine Hydrochloride, Cyclophosphamide, Cyclosporine
/ **D**apsone, Darbepoietin, Darifenacin, Darunavir, Dasabuvir, Dasatinib, Dexibuprofen, Diclofenac, Diethylstilbestrol, Digitoxin, Dihydroergotamine Mesylate, Diltiazem Hydrochloride, Diphenadione, Dofetilide, Domperidone, Doxepin Hydrochloride, Dronedarone
/ **E**bastine, Elagolix Sodium, Eletriptan Hydrobromide, Eliglustat Tartrate, Eltrombopag, Enasidenib, Entrectinib, Enzalutamide, Eplerenone, Ergotamine Tartrate, Esketamine Hydrochloride, Esomeprazole Magnesium, Estradiol, Estradiol Benzoate, Estradiol Cypionate, Estradiol Dienanthate, Estradiol Valerate, Eszopiclone, Ethinylestradiol, Ethosuximide, Ethyl Biscoumacetate, Everolimus
/ **F**elodipine, Femring, Fentanyl, Fluindione, Fluvastatin Sodium, Fosaprepitant Dimeglumine / **G**lasdegib / **H**alofantrine Hydrochloride
/ **I**brutinib, Ibuprofen, Imatinib, Indinavir Sulfate, Irbesartan, Isavuconazole, Istradefylline, Ixazomib / **J**uxtapid
/ **K**etamine Hydrochloride, Ketobemidone, Ketorolac Tromethamine
/ **L**ansoprazole, Lapatinib, Latuda, Levacetylmethadol, Levothyroxine Sodium, Licofelone, Livalo, Lobeglitazone, Loperamide, Lopinavir, Lorlatinib, Lovastatin, Lumateperone
/ **M**araviroc, Meperidine Hydrochloride, Mephenytoin, Mestranol, Methadone Hydrochloride, Methysergide, Midazolam, Montelukast Sodium, Morphine, Muraglitazar, Mycophenolate Mofetil
/ **N**aloxegol, Naproxen, Netoglitazone, Nicardipine Hydrochloride, Nicotine, Nisoldipine, Nortriptyline Hydrochloride
/ **O**danacatib, Olodaterol Hydrochloride, Ombitasvir
/ **P**aclitaxel, Paramethadione, Pazopanib, Perospirone, Phenazone, Phenprocoumon, Phenytoin, Pimozide, Piroxicam, Ponatinib, Propacetamol Hydrochloride, Propofol
/ **Q**uinidine, Quinine Sulfate / **R**anolazine, Repaglinide, Rilpivirine, Riociguat, Rivaroxaban, Rivoglitazone, Rosiglitazone
/ **S**aquinavir, Selegiline, Selexipag, Seratrodast, Sildenafil, Simvastatin, Sirolimus, Sitagliptin, Sorafenib, Sulfadiazine
/ **T**acrolimus, Tadalafil, Tazarotene, Tegafur, Temsirolimus, Terbinafine, Terfenadine, Testosterone Enanthate, Testosterone Undecanoate, Theophylline, Tianeptine, Ticagrelor, Tipranavir, Tofranil, Tolbutamide, Tolvaptan, Torsemide, Tretinoin, Triazolam, Trimethadione, Trimethoprim, Troglitazone
/ **V**ardenafil Hydrochloride, Velpatasvir, Verapamil Hydrochloride, Vortioxetine, Voxilaprevir / **Z**afirlukast, Zidovudine

Palbociclib ⚠

Drug approval in patient disease: Off-label

Palbociclib is a piperazine pyridopyrimidine[A176792] that acts in the cell cycle machinery. It is a second generation cyclin-dependent kinase inhibitor[A176798] selected from a group of pyridopyrimidine compounds due to its favorable physical and pharmaceutical properties.[A176810] Palbociclib was developed by Pfizer Inc after the discovery that identified the cyclin-dependent kinases as key regulators of cell growth.[L5867] It was originally FDA approved on March 2015 for the treatment of HR-positive, HER2-negative advanced or metastatic breast cancer and its indications were updated in April 2019 to include male patients based on findings from postmarketing reports and electronic health records demonstrating safety and clinical efficacy.[L4894](DB09073)

Detected variants supporting this treatment effect:
CDK4 Copy number GAIN (CNA)

Drug-drug interactions
/ **2**-Methoxyethanol / **4**-Hydroxycoumarin / **5**-Fluorouracil / **6**-Mercaptopurine / **9**-(N-Methyl-L-Isoleucine)-Cyclosporin A
/ **A**batacept, Abetimus, Acteoside, Adalimumab, Adenovirus Type 7 Vaccine Live, Afelimomab, Aldesleukin, Aldosterone, Alefacept, Alemtuzumab, Alfentanil, Alprazolam, Altretamine, Amiodarone Hydrochloride, Amitriptyline Hydrochloride, Amsacrine, Anakinra, Anthrax Vaccine, Antilymphocyte Immunoglobulin (Horse), Antithymocyte Immunoglobulin (Rabbit), Apremilast, Aprepitant, Arsenic Trioxide, Astemizole, Avanafil, Azacitidine, Azathioprine
/ **B**acillus Calmette-Guerin Substrain Connaught Live Antigen, Bacillus Calmette-Guerin Substrain Danish 1331 Live Antigen, Bacillus Calmette-Guerin Substrain Tice Live Antigen, Baf-312, Baricitinib, Basiliximab, Bcg Vaccine, Beclomethasone Dipropionate, Begelomab, Belatacept, Belimumab, Belinostat, Bendamustine, Betamethasone, Bevacizumab, Bexarotene, Bleomycin, Bleselumab, Blinatumomab, Bortezomib, Brequinar, Briakinumab, Brodalumab, Bromocriptine Mesylate, Budesonide, Buspirone Hydrochloride, Busulfan
/ **C**abazitaxel, Canakinumab, Capecitabine, Carbamazepine, Carboplatin, Carfilzomib, Carmustine, Castanospermine, Cepeginterferon Alfa-2b, Cerebyx, Certolizumab Pegol, Chlorambucil, Chloramphenicol, Ciclesonide, Cisapride, Cisplatin, Cladribine, Clindamycin Hydrochloride, Clobetasol, Clofarabine, Clomipramine Hydrochloride, Clonidine, Cloprednol, Clorindione, Corticotropin, Cortisone Acetate, Cortivazol, Cyclobenzaprine Hydrochloride, Cyclophosphamide, Cyclosporine, Cytarabine

/ **D**acarbazine, Daclizumab, Dactinomycin, Darifenacin, Dasatinib, Daunorubicin, Decitabine, Deflazacort, Deoxyspergualin, Dexamethasone, Dexamethasone Isonicotinate, Dexrazoxane, Digitoxin, Dihydroergotamine Mesylate, Dimethyl Fumarate, Dinutuximab, Diphenadione, Dipyrone, Docetaxel, Dofetilide, Doxepin Hydrochloride, Doxifluridine, Dronedarone
/ **E**bastine, Eculizumab, Efalizumab, Eletriptan Hydrobromide, Eliglustat Tartrate, Emapalumab, Epirubicin, Eplerenone, Eribulin, Esketamine Hydrochloride, Estramustine, Etanercept, Ethosuximide, Ethyl Biscoumacetate, Etoposide
/ **F**elodipine, Fentanyl, Floxuridine, Fluclorolone, Flucytosine, Fludarabine, Fludrocortisone, Fluindione, Flunisolide, Fluocinolone Acetonide, Fluocortin, Fluocortolone, Fluperolone, Fluprednidene, Fluprednisolone, Fluticasone, Fluticasone Furoate, Fluticasone Propionate, Formocortal, Fosaprepitant Dimeglumine
/ **G**allium Nitrate (Anhydrous), Gemcitabine, Gemtuzumab Ozogamicin, Glatiramer Acetate, Golimumab, Guselkumab, Gusperimus
/ **H**alometasone, Human Adenovirus E Serotype 4 Strain Cl-68578 Antigen, Hydrocodone Bitartrate, Hydrocortisone Aceponate, Hydrocortisone Acetate, Hydrocortisone Succinate, Hydroxychloroquine, Hydroxyurea, Hypericin
/ **I**britumomab Tiuxetan, Idarubicin, Ifosfamide, Imatinib, Indinavir Sulfate, Indomethacin, Infliximab, Interferon Alfa, Interferon Alfa-2a, Recombinant, Interferon Alfa-2b, Interferon Alfa-N1, Interferon Alfa-N3, Interferon Alfacon-1, Interferon Beta-1b, Interferon Gamma-1b, Irinotecan, Ixabepilone, Ixekizumab
/ **L**atuda, Lenalidomide, Levacetylmethadol, Levothyroxine Sodium, Linezolid, Lipegfilgrastim, Lomustine
/ **M**araviroc, Mechlorethamine, Melengestrol, Melphalan, Meperidine Hydrochloride, Mepolizumab, Meprednisone, Methotrexate, Methylprednisolone Sodium Succinate, Methysergide, Mitomycin C, Mitoxantrone Hydrochloride, Mizoribine, Mometasone, Mometasone Furoate, Monomethyl Fumarate, Muromonab, Mycophenolate Mofetil, Mycophenolic Acid
/ **N**elarabine, Nisoldipine, Nortriptyline Hydrochloride / **O**binutuzumab, Ocrelizumab, Olaparib, Omega Interferon, Oxaliplatin, Ozanimod
/ **P**aclitaxel, Panobinostat, Paramethasone, Peficitinib, Pegaspargase, Peginterferon Alfa-2a, Peginterferon Beta-1a, Pemetrexed, Penicillamine, Pentostatin, Phenobarbital, Phenprocoumon, Phenylalanine, Phenytoin, Pimecrolimus, Pimozide, Pirarubicin, Pirfenidone, Pomalidomide, Ponatinib, Pralatrexate, Prednisolone, Prednisone, Prednylidene, Procarbazine, Propylthiouracil
/ **Q**uinidine
/ **R**altitrexed, Ravulizumab, Rifampin, Rilonacept, Rilpivirine, Risankizumab, Rituximab, Rivaroxaban, Rozanolixizumab, Rubella Virus Vaccine, Ruxolitinib
/ **S**arilumab, Secukinumab, Sildenafil, Siltuximab, Simvastatin, Sirolimus, Sirukumab, Sorafenib, Stepronin, Streptozocin, Sulfasalazine, Sunitinib
/ **T**adalafil, Tedizolid Phosphate, Temozolomide, Temsirolimus, Teniposide, Tepoxalin, Teriflunomide, Tetrandrine, Thalidomide, Theophylline, Thioguanine, Thiotepa, Tianeptine, Ticagrelor, Tixocortol, Tocilizumab, Tofranil, Tolvaptan, Tositumomab, Trabectedin, Trastuzumab Emtansine, Tretinoin, Triamcinolone Hexacetonide, Triazolam, Trifluridine, Trilostane, Trimipramine Maleate, Triptolide, Trofosfamide, Typhoid Vaccine Live
/ **V**aricella Zoster Vaccine (Live/Attenuated), Vedolizumab, Vibrio Cholerae Cvd 103-Hgr Strain Live Antigen, Vilanterol, Vinblastine, Vindesine, Vinorelbine, Voclosporin, Vorinostat
/ **W**artmannin / **Y**ellow Fever Vaccine / **Z**idovudine, Zolpidem

Idasanutlin ⚠	Drug approval in patient disease: Other
Palbociclib ⚠	Drug approval in patient disease: Off-label

Idasanutlin has been used in trials studying the treatment of Neoplasms, Non-Hodgkin's Lymphoma, Leukemia, Myeloid, Acute, Recurrent Plasma Cell Myeloma, and Neoplasms, Leukemia, Acute Myeloid Leukemia.(DB12325)
Palbociclib is a piperazine pyridopyrimidine[A176792] that acts in the cell cycle machinery. It is a second generation cyclin-dependent kinase inhibitor[A176798] selected from a group of pyridopyrimidine compounds due to its favorable physical and pharmaceutical properties.[A176810] Palbociclib was developed by Pfizer Inc after the discovery that identified the cyclin-dependent kinases as key regulators of cell growth.[L5867] It was originally FDA approved on March 2015 for the treatment of HR-positive, HER2-negative advanced or metastatic breast cancer and its indications were updated in April 2019 to include male patients based on findings from postmarketing reports and electronic health records demonstrating safety and clinical efficacy.[L4894](DB09073)

Detected variants supporting this treatment effect:
CDK4 Copy number GAIN (CNA)

Drug-drug interactions
/ **2**-Methoxyethanol / **4**-Hydroxycoumarin / **5**-Fluorouracil / **6**-Mercaptopurine / **9**-(N-Methyl-L-Isoleucine)-Cyclosporin A
/ **A**batacept, Abetimus, Acteoside, Adalimumab, Adenovirus Type 7 Vaccine Live, Afelimomab, Aldesleukin, Aldosterone, Alefacept, Alemtuzumab, Alfentanil, Alprazolam, Altretamine, Amiodarone Hydrochloride, Amitriptyline Hydrochloride, Amsacrine, Anakinra, Anthrax Vaccine, Antilymphocyte Immunoglobulin (Horse), Antithymocyte Immunoglobulin (Rabbit), Apremilast, Aprepitant, Arsenic Trioxide, Astemizole, Avanafil, Azacitidine, Azathioprine
/ **B**acillus Calmette-Guerin Substrain Connaught Live Antigen, Bacillus Calmette-Guerin Substrain Danish 1331 Live Antigen, Bacillus Calmette-Guerin Substrain Tice Live Antigen, Baf-312, Baricitinib, Basiliximab, Bcg Vaccine, Beclomethasone Dipropionate, Begelomab, Belatacept, Belimumab, Belinostat, Bendamustine, Betamethasone, Bevacizumab, Bexarotene, Bleomycin, Bleselumab, Blinatumomab, Bortezomib, Brequinar, Briakinumab, Brodalumab, Bromocriptine Mesylate, Budesonide, Buspirone Hydrochloride, Busulfan
/ **C**abazitaxel, Canakinumab, Capecitabine, Carbamazepine, Carboplatin, Carfilzomib, Carmustine, Castanospermine, Cepeginterferon Alfa-2b, Cerebyx, Certolizumab Pegol, Chlorambucil, Chloramphenicol, Ciclesonide, Cisapride, Cisplatin, Cladribine, Clindamycin Hydrochloride, Clobetasol, Clofarabine, Clomipramine Hydrochloride, Clonidine, Cloprednol, Clorindione, Corticotropin, Cortisone Acetate, Cortivazol, Cyclobenzaprine Hydrochloride, Cyclophosphamide, Cyclosporine, Cytarabine
/ **D**acarbazine, Daclizumab, Dactinomycin, Darifenacin, Dasatinib, Daunorubicin, Decitabine, Deflazacort, Deoxyspergualin, Dexamethasone, Dexamethasone Isonicotinate, Dexrazoxane, Digitoxin, Dihydroergotamine Mesylate, Dimethyl Fumarate, Dinutuximab, Diphenadione, Dipyrone, Docetaxel, Dofetilide, Doxepin Hydrochloride, Doxifluridine, Dronedarone

/ **E**bastine, Eculizumab, Efalizumab, Eletriptan Hydrobromide, Eliglustat Tartrate, Emapalumab, Epirubicin, Eplerenone, Eribulin, Esketamine Hydrochloride, Estramustine, Etanercept, Ethosuximide, Ethyl Biscoumacetate, Etoposide
/ **F**elodipine, Fentanyl, Floxuridine, Fluclorolone, Flucytosine, Fludarabine, Fludrocortisone, Fluindione, Flunisolide, Fluocinolone Acetonide, Fluocortin, Fluocortolone, Fluperolone, Fluprednidene, Fluprednisolone, Fluticasone, Fluticasone Furoate, Fluticasone Propionate, Formocortal, Fosaprepitant Dimeglumine
/ **G**allium Nitrate (Anhydrous), Gemcitabine, Gemtuzumab Ozogamicin, Glatiramer Acetate, Golimumab, Guselkumab, Gusperimus
/ **H**alometasone, Human Adenovirus E Serotype 4 Strain CI-68578 Antigen, Hydrocodone Bitartrate, Hydrocortisone Aceponate, Hydrocortisone Acetate, Hydrocortisone Succinate, Hydroxychloroquine, Hydroxyurea, Hypericin
/ **I**britumomab Tiuxetan, Idarubicin, Ifosfamide, Imatinib, Indinavir Sulfate, Indomethacin, Infliximab, Interferon Alfa, Interferon Alfa-2a, Recombinant, Interferon Alfa-2b, Interferon Alfa-N1, Interferon Alfa-N3, Interferon Alfacon-1, Interferon Beta-1b, Interferon Gamma-1b, Irinotecan, Ixabepilone, Ixekizumab
/ **L**atuda, Lenalidomide, Levacetylmethadol, Levothyroxine Sodium, Linezolid, Lipegfilgrastim, Lomustine
/ **M**araviroc, Mechlorethamine, Melengestrol, Melphalan, Meperidine Hydrochloride, Mepolizumab, Meprednisone, Methotrexate, Methylprednisolone Sodium Succinate, Methysergide, Mitomycin C, Mitoxantrone Hydrochloride, Mizoribine, Mometasone, Mometasone Furoate, Monomethyl Fumarate, Muromonab, Mycophenolate Mofetil, Mycophenolic Acid
/ **N**elarabine, Nisoldipine, Nortriptyline Hydrochloride / **O**binutuzumab, Ocrelizumab, Olaparib, Omega Interferon, Oxaliplatin, Ozanimod
/ **P**aclitaxel, Panobinostat, Paramethasone, Peficitinib, Pegaspargase, Peginterferon Alfa-2a, Peginterferon Beta-1a, Pemetrexed, Penicillamine, Pentostatin, Phenobarbital, Phenprocoumon, Phenylalanine, Phenytoin, Pimecrolimus, Pimozide, Pirarubicin, Pirfenidone, Pomalidomide, Ponatinib, Pralatrexate, Prednisolone, Prednisone, Prednylidene, Procarbazine, Propylthiouracil
/ **Q**uinidine
/ **R**altitrexed, Ravulizumab, Rifampin, Rilonacept, Rilpivirine, Risankizumab, Rituximab, Rivaroxaban, Rozanolixizumab, Rubella Virus Vaccine, Ruxolitinib
/ **S**arilumab, Secukinumab, Sildenafil, Siltuximab, Simvastatin, Sirolimus, Sirukumab, Sorafenib, Stepronin, Streptozocin, Sulfasalazine, Sunitinib
/ **T**adalafil, Tedizolid Phosphate, Temozolomide, Temsirolimus, Teniposide, Tepoxalin, Teriflunomide, Tetrandrine, Thalidomide, Theophylline, Thioguanine, Thiotepa, Tianeptine, Ticagrelor, Tixocortol, Tocilizumab, Tofranil, Tolvaptan, Tositumomab, Trabectedin, Trastuzumab Emtansine, Tretinoin, Triamcinolone Hexacetonide, Triazolam, Trifluridine, Trilostane, Trimipramine Maleate, Triptolide, Trofosfamide, Typhoid Vaccine Live
/ **V**aricella Zoster Vaccine (Live/Attenuated), Vedolizumab, Vibrio Cholerae Cvd 103-Hgr Strain Live Antigen, Vilanterol, Vinblastine, Vindesine, Vinorelbine, Voclosporin, Vorinostat
/ **W**artmannin / **Y**ellow Fever Vaccine / **Z**idovudine, Zolpidem

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Abemaciclib — Drug approval in patient disease: Off-label

Abemaciclib is an antitumor agent and dual inhibitor of cyclin-dependent kinases 4 (CDK4) and 6 (CDK6) that are involved in the cell cycle and promotion of cancer cell growth in case of unregulated activity. On September 28, 2017, FDA granted approval of abemaciclib treatment under the market name Verzenio for the treatment of HR-positive and HER2-negative advanced or metastatic breast cancer that has progressed after unsuccessful endocrine therapy. It is either given alone in patients who has undergone endocrine therapy and chemotherapy after the metastasis of cancer, or in combination with [DB00947]. Following oral treatment in patients with HR-positive, HER2-negative breast cancer, abemaciclib demonstrated increased progression-free survival rates and objective response rates. Abemaciclib has been used in trials studying the treatment of melanoma, lymphoma, neoplasm, solid tumor, and glioblastoma.(DB12001)

Detected variants supporting this treatment effect:
CDK4 Copy number GAIN (CNA)

Drug-drug interactions
/ **A**cyclovir, Amitriptyline Hydrochloride / **B**aricitinib, Bictegravir, Brigatinib
/ **C**arbamazepine, Cephalexin, Cephradine, Cimetidine, Ciprofloxacin, Clonidine, Cyclosporine / **D**igitoxin / **E**mtricitabine, Estropipate
/ **F**edratinib, Flecainide Acetate / **G**anciclovir, Gilteritinib, Glasdegib, Guanidine Hydrochloride / **I**stradefylline / **L**evofloxacin, Lofexidine Hydrochloride
/ **M**etformin Hydrochloride / **N**-Methylnicotinamide, Nadolol
/ **P**aclitaxel, Pexidartinib, Phenobarbital, Phenytoin, Plazomicin Sulfate, Procainamide Hydrochloride, Pyrimethamine / **Q**uinidine
/ **R**elebactam, Rifampin, Rifamycin Sodium, Rucaparib / **S**irolimus, Solriamfetol
/ **T**acrolimus, Tafenoquine, Tazemetostat, Temsirolimus, Tetraethylammonium, Tipiracil, Tofranil, Trimipramine Maleate / **V**erapamil Hydrochloride

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Trametinib — Drug approval in patient disease: Off-label
Dabrafenib — Drug approval in patient disease: Off-label

Trametinib dimethyl sulfoxide is a kinase inhibitor. Each 1-mg tablet contains 1.127 mg trametinib dimethyl sulfoxide equivalent to 1 mg of trametinib non-solvated parent. FDA approved on May 29, 2013 [L2727].
The U.S. Food and Drug Administration approved [DB08912](Tafilnar) and Mekinist (trametinib), administered together, for the treatment of anaplastic thyroid cancer (ATC) that cannot be removed by surgery or has spread to other parts of the body (metastatic), and has a type of abnormal gene, BRAF V600E (BRAF V600E mutation-positive) [L2726].
Thyroid cancer is a disease in which cancer cells form in the tissues of the thyroid. Anaplastic thyroid cancer is a rare, aggressive type of thyroid cancer. The National Institutes of Health (NIH) estimates there will be 53,990 new cases of thyroid cancer and an estimated 2,060 deaths from the disease in the United States in 2018. Anaplastic thyroid cancer accounts for approximately 1 to 2 percent of all thyroid cancers [L2726].(DB08911)
Dabrafenib mesylate (Tafinlar) is a reversible ATP-competitive kinase inhibitor and targets the MAPK pathway. It was approved on May 29, 2013 for the

treatment of melanoma [L2718].
In May 2018, Tafinlar (dabrafenib) and Mekinist ([DB08911]) in combination have been approved to treat anaplastic thyroid cancer caused by an abnormal BRAF V600E gene [L2714].(DB08912)

Detected variants supporting this treatment effect:
NF1 p.C680fs (indel)

Drug-drug interactions
/ **4**-Hydroxycoumarin / **5**-Fluorouracil
/ **A**cetohexamide, Acetylsalicylic Acid, Alfentanil, Almotriptan Malate, Alosetron Hydrochloride, Alprazolam, Aminophenazone, Amiodarone Hydrochloride, Amitriptyline Hydrochloride, Amodiaquine Hydrochloride, Amprenavir, Anastrozole, Apixaban, Aprepitant, Arachidonic Acid, Arformoterol Tartrate, Astemizole, Asunaprevir, Atazanavir Sulfate, Atorvastatin Calcium, Avanafil, Avapritinib, Azelastine Hydrochloride
/ **B**af-312, Balaglitazone, Benzyl Alcohol, Beraprost, Bexarotene, Bortezomib, Bosentan, Brigatinib, Brivaracetam, Bromocriptine Mesylate, Budesonide, Buprenorphine, Bupropion Hydrochloride, Buspirone Hydrochloride, Busulfan
/ **C**abazitaxel, Cabozantinib, Candesartan, Candesartan Cilexetil, Cannabidiol, Capravirine, Carbamazepine, Carbutamide, Carvedilol, Celecoxib, Cerebyx, Cerivastatin Sodium, Chloroquine, Chlorpropamide, Ciglitazone, Cinnarizine, Cisapride, Clindamycin Hydrochloride, Clomipramine Hydrochloride, Clonidine, Clorindione, Clozapine, Colchicine, Conivaptan Hydrochloride, Coumarin, Cyclobenzaprine Hydrochloride, Cyclophosphamide, Cyclosporine
/ **D**acomitinib, Dapagliflozin, Dapsone, Darbepoietin, Darifenacin, Darunavir, Dasabuvir, Dasatinib, Deflazacort, Desipramine Hydrochloride, Desogestrel, Dexibuprofen, Dextromethorphan, Diclofenac, Dicumarol, Diethylstilbestrol, Digitoxin, Dihydroergotamine Mesylate, Diltiazem Hydrochloride, Diphenadione, Diphenhydramine Hydrochloride, Doconexent, Dofetilide, Domperidone, Donepezil Hydrochloride, Dothiepin, Doxepin Hydrochloride, Dronedarone, Duloxetine Hydrochloride
/ **E**bastine, Elagolix Sodium, Eletriptan Hydrobromide, Eliglustat Tartrate, Eltrombopag, Enasidenib, Entrectinib, Enzalutamide, Eplerenone, Ergotamine Tartrate, Esketamine Hydrochloride, Esomeprazole Magnesium, Estradiol, Estradiol Benzoate, Estradiol Cypionate, Estradiol Dienanthate, Estradiol Valerate, Estropipate, Eszopiclone, Ethinylestradiol, Ethosuximide, Ethyl Biscoumacetate, Etodolac, Etoricoxib, Everolimus
/ **F**elodipine, Femring, Fentanyl, Fluindione, Flunarizine, Flunitrazepam, Flurbiprofen, Fluticasone, Fluticasone Furoate, Fluticasone Propionate, Fluvastatin Sodium, Formoterol Fumarate, Fosaprepitant Dimeglumine
/ **G**emfibrozil, Glasdegib, Glibornuride, Gliclazide, Glimepiride, Glipizide, Gliquidone, Glisoxepid
/ **H**alofantrine Hydrochloride, Haloperidol, Halothane, Hydromorphone Hydrochloride, Hydroxyzine
/ **I**brutinib, Ibuprofen, Idarubicin, Imatinib, Indinavir Sulfate, Indisulam, Indomethacin, Irbesartan, Isavuconazole, Istradefylline, Ixazomib / **J**uxtapid
/ **K**etamine Hydrochloride, Ketobemidone, Ketorolac Tromethamine
/ **L**ansoprazole, Lapatinib, Latuda, Lefamulin Acetate, Leflunomide, Lesinurad, Levacetylmethadol, Levothyroxine Sodium, Licofelone, Livalo, Lobeglitazone, Lofepramine Hydrochloride, Loperamide, Lopinavir, Lorlatinib, Lornoxicam, Losartan Potassium, Lovastatin, Lumateperone, Lumiracoxib
/ **M**araviroc, Medical Cannabis, Mefenamic Acid, Melatonin, Melitracen, Meloxicam, Meperidine Hydrochloride, Mephenytoin, Mestranol, Metahexamide, Methadone Hydrochloride, Methoxyflurane, Methysergide, Midazolam, Moclobemide, Mometasone Furoate, Montelukast Sodium, Morphine, Muraglitazar, Mycophenolate Mofetil
/ **N**abiximols, Nabumetone, Naloxegol, Naproxen, Nateglinide, Netoglitazone, Netupitant, Nevirapine, Nicardipine Hydrochloride, Niclosamide, Nicotine, Nisoldipine, Nortriptyline Hydrochloride
/ **O**danacatib, Olodaterol Hydrochloride, Ombitasvir, Ondansetron, Ospemifene
/ **P**aclitaxel, Paramethadione, Parecoxib, Pazopanib, Perospirone, Phenacetin, Phenazone, Phenprocoumon, Phenylbutazone, Phenytoin, Pimozide, Piperaquine, Piroxicam, Ponatinib, Prasugrel, Promazine Hydrochloride, Propacetamol Hydrochloride, Propofol
/ **Q**uazepam, Quinidine, Quinine Sulfate
/ **R**anolazine, Repaglinide, Revefenacin, Rifampin, Rilpivirine, Riociguat, Ritonavir, Rivaroxaban, Rivoglitazone, Rofecoxib, Rosiglitazone, Rosuvastatin Calcium, Rupatadine
/ **S**alicylic Acid, Salmeterol, Saquinavir, Secobarbital Sodium, Selegiline, Selexipag, Seratrodast, Sildenafil, Simvastatin, Sirolimus, Sitagliptin, Sitaxentan, Sorafenib, Sulfadiazine, Sulfamethoxazole
/ **T**acrolimus, Tadalafil, Tapentadol, Tazarotene, Tegafur, Temsirolimus, Tenoxicam, Terbinafine, Terfenadine, Testosterone Enanthate, Testosterone Undecanoate, Tetrahydrocannabinol, Thalidomide, Theophylline, Thiamylal Sodium, Tianeptine, Ticagrelor, Tipranavir, Tofranil, Tolazamide, Tolbutamide, Tolterodine Tartrate, Tolvaptan, Torsemide, Trabectedin, Tranilast, Trazodone Hydrochloride, Tretinoin, Triazolam, Trimethadione, Trimethoprim, Trimipramine Maleate, Troglitazone
/ **V**aldecoxib, Valproic Acid, Valsartan, Vardenafil Hydrochloride, Velpatasvir, Venlafaxine Hydrochloride, Verapamil Hydrochloride, Vicriviroc, Vismodegib, Vortioxetine, Voxilaprevir
/ **X**imelagatran / **Z**afirlukast, Zaltoprofen, Zanubrutinib, Zidovudine, Zileuton

Erlotinib ⚠	Drug approval in patient disease: Off-label
Trametinib ⚠	Drug approval in patient disease: Off-label

Erlotinib is an inhibitor of the epidermal growth factor receptor (EGFR) tyrosine kinase that is used in the treatment of non-small cell lung cancer, pancreatic cancer and several other types of cancer. It is typically marketed under the trade name Tarceva. Erlotinib binds to the epidermal growth factor receptor (EGFR) tyrosine kinase in a reversible fashion at the adenosine triphosphate (ATP) binding site of the receptor. Recent studies demonstrate that erlotinib is also a potent inhibitor of JAK2V617F, which is a mutant form of tyrosine kinase JAK2 found in most patients with polycythemia vera (PV) and a substantial proportion of patients with idiopathic myelofibrosis or essential thrombocythemia. This finding introduces the potential use of erlotinib in the treatment of JAK2V617F-positive PV and other myeloproliferative disorders.(DB00530)
Trametinib dimethyl sulfoxide is a kinase inhibitor. Each 1-mg tablet contains 1.127 mg trametinib dimethyl sulfoxide equivalent to 1 mg of trametinib

non-solvated parent. FDA approved on May 29, 2013 [L2727].
The U.S. Food and Drug Administration approved [DB08912](Tafilnar) and Mekinist (trametinib), administered together, for the treatment of anaplastic thyroid cancer (ATC) that cannot be removed by surgery or has spread to other parts of the body (metastatic), and has a type of abnormal gene, BRAF V600E (BRAF V600E mutation-positive) [L2726].
Thyroid cancer is a disease in which cancer cells form in the tissues of the thyroid. Anaplastic thyroid cancer is a rare, aggressive type of thyroid cancer. The National Institutes of Health (NIH) estimates there will be 53,990 new cases of thyroid cancer and an estimated 2,060 deaths from the disease in the United States in 2018. Anaplastic thyroid cancer accounts for approximately 1 to 2 percent of all thyroid cancers [L2726].(DB08911)

Detected variants supporting this treatment effect:
NF1 p.C680fs (indel)

Drug-drug interactions
/ **1**63253-35-8 / **4**-Hydroxycoumarin / **5**-Fluorouracil
/ **A**bexinostat, Acebutolol Hydrochloride, Acepromethazine, Adenosine, Alfentanil, Almotriptan Malate, Alprazolam, Amifampridine, Aminophenazone, Amiodarone Hydrochloride, Amitriptyline Hydrochloride, Amodiaquine Hydrochloride, Amoxapine, Anagrelide, Anastrozole, Antazoline, Apixaban, Aprepitant, Argatroban, Arsenic Trioxide, Astemizole, Atorvastatin Calcium, Atropine, Avanafil, Azelastine Hydrochloride, Azimilide Hydrochloride, Azithromycin
/ **B**af-312, Balaglitazone, Benidipine, Benzyl Alcohol, Bepridil Hydrochloride, Beraprost, Brigatinib, Bromocriptine Mesylate, Budesonide, Bunaftine, Buprenorphine, Bupropion Hydrochloride, Buspirone Hydrochloride, Busulfan, Butriptyline
/ **C**abazitaxel, Candesartan Cilexetil, Capravirine, Carbamazepine, Carbinoxamine Maleate, Celecoxib, Cerebyx, Ceritinib, Cerivastatin Sodium, Chembl372638, Chloroquine, Chlorpheniramine Maleate, Ciglitazone, Cinacalcet Hydrochloride, Cinnarizine, Cinoxacin, Cisapride, Citalopram Hydrobromide, Clemastine Fumarate, Clinafloxacin, Clindamycin Hydrochloride, Clomipramine Hydrochloride, Clonidine, Clorindione, Cocaine Hydrochloride, Colchicine, Conivaptan Hydrochloride, Crizotinib, Cudc-101, Cyclobenzaprine Hydrochloride, Cyclophosphamide, Cyclosporine
/ **D**acomitinib, Dapsone, Darbepoietin, Darifenacin, Darunavir, Dasabuvir, Dasatinib, Desloratadine, Deutetrabenazine, Dexibuprofen, Diclofenac, Diethylstilbestrol, Digitoxin, Dihydroergotamine Mesylate, Diltiazem Hydrochloride, Dimenhydrinate, Diphenadione, Disopyramide Phosphate, Dofetilide, Dolasetron, Domperidone, Doxepin Hydrochloride, Dronedarone, Droperidol
/ **E**bastine, Elagolix Sodium, Eletriptan Hydrobromide, Eliglustat Tartrate, Eltrombopag, Enasidenib, Enoxacin, Entinostat, Entrectinib, Enzalutamide, Eperisone, Eplerenone, Ergotamine Tartrate, Erythromycin, Esketamine Hydrochloride, Esomeprazole Magnesium, Estradiol, Estradiol Benzoate, Estradiol Cypionate, Estradiol Dienanthate, Estradiol Valerate, Eszopiclone, Ethinylestradiol, Ethosuximide, Ethyl Biscoumacetate, Everolimus
/ **F**elodipine, Femring, Fendiline, Fentanyl, Fetzima, Flecainide Acetate, Fluindione, Fluoxetine, Flupentixol, Fluspirilene, Fluticasone, Fluticasone Furoate, Fluticasone Propionate, Fluvastatin Sodium, Fosaprepitant Dimeglumine
/ **G**adobenate Dimeglumine, Garenoxacin, Gemfibrozil, Gemifloxacin Mesylate, Gilteritinib, Glasdegib, Goserelin, Granisetron, Grepafloxacin Hydrochloride
/ **H**alofantrine Hydrochloride, Haloperidol, Hydrocodone Bitartrate, Hydroxyzine
/ **I**brutinib, Ibuprofen, Ibutilide Fumarate, Imatinib, Indenolol, Indinavir Sulfate, Irbesartan, Irinotecan, Isavuconazole, Istradefylline, Ivabradine, Ixazomib
/ **J**uxtapid / **K**etamine Hydrochloride, Ketobemidone, Ketorolac Tromethamine
/ **L**ansoprazole, Lapatinib, Latuda, Lefamulin Acetate, Leuprolide, Levacetylmethadol, Levobetaxolol Hydrochloride, Levofloxacin, Levomepromazine, Levosimendan, Levothyroxine Sodium, Licofelone, Lithium Cation, Livalo, Lobeglitazone, Lofexidine Hydrochloride, Lomefloxacin Hydrochloride, Loperamide, Lopinavir, Lorcainide, Lorlatinib, Lovastatin, Lumateperone
/ **M**acimorelin Acetate, Maraviroc, Melperone, Meperidine Hydrochloride, Mephenytoin, Mestranol, Methadone Hydrochloride, Methysergide, Mevastatin, Mibefradil, Midazolam, Mizolastine, Mocetinostat, Mometasone Furoate, Montelukast Sodium, Morphine, Muraglitazar, Mycophenolate Mofetil, Mycophenolic Acid
/ **N**alidixic Acid, Naloxegol, Naproxen, Nelfinavir Mesylate, Nemonoxacin, Netoglitazone, Nicardipine Hydrochloride, Nicotine, Nilvadipine, Nimodipine, Nisoldipine, Nizofenone Fumarate, Nortriptyline Hydrochloride
/ **O**danacatib, Ofloxacin, Olodaterol Hydrochloride, Ombitasvir, Ondansetron, Opipramol, Orphenadrine, Otilonium Bromide, Oxaliplatin, Oxatomide, Oxprenolol Hydrochloride
/ **P**aclitaxel, Paliperidone, Papaverine, Parамethadione, Paroxetine, Pazopanib, Penfluridol, Pentamidine, Perflutren, Perospirone, Phenazone, Phenprocoumon, Phenytoin, Pimozide, Piroxicam, Plavix, Ponatinib, Pracinostat, Pravastatin, Prenylamine, Probucol, Procainamide Hydrochloride, Prochlorperazine, Promazine Hydrochloride, Propacetamol Hydrochloride, Propafenone Hydrochloride, Propofol, Propranolol, Protriptyline Hydrochloride
/ **Q**uetiapine Fumarate, Quinidine, Quinine Sulfate
/ **R**anolazine, Repaglinide, Ricolinostat, Rilpivirine, Riociguat, Rivaroxaban, Rivoglitazone, Romidepsin, Rosiglitazone, Rosuvastatin Calcium, Roxithromycin
/ **S**almeterol, Saquinavir, Selegiline, Selexipag, Seratrodast, Serentil, Sildenafil, Simvastatin, Sirolimus, Sirturo, Sitagliptin, Sorafenib, Sotalol Hydrochloride, Sparfloxacin, Sulfadiazine, Sulfisoxazole, Sulpiride, Sultopride
/ **T**acrolimus, Tadalafil, Tazarotene, Technetium Tc-99m Ciprofloxacin, Tedisamil, Tegafur, Telavancin, Temafloxacin, Temsirolimus, Terbinafine, Terfenadine, Terlipressin, Terodiline, Testosterone Enanthate, Testosterone Undecanoate, Tetrabenazine, Theophylline, Thioridazine, Tianeptine, Ticagrelor, Tipranavir, Tofranil, Tolbutamide, Tolvaptan, Toremifene, Torsemide, Trazodone Hydrochloride, Tretinoin, Triazolam, Trimethadione, Trimethoprim, Trimipramine Maleate, Troglitazone, Trovafloxacin Mesylate, Tucidinostat
/ **V**alproic Acid, Vandetanib, Vardenafil Hydrochloride, Velpatasvir, Verapamil Hydrochloride, Vigamox, Vortioxetine, Voxilaprevir
/ **Z**afirlukast, Zidovudine, Ziprasidone Hydrochloride, Zolpidem, Zuclopenthixol

Imatinib — Drug approval in patient disease: Off-label

Imatinib is a small molecule kinase inhibitor used to treat certain types of cancer. It is currently marketed by Novartis as Gleevec (USA) or Glivec (Europe/ Australia) as its mesylate salt, imatinib mesilate (INN). It is occasionally referred to as CGP57148B or STI571 (especially in older publications). It is used in treating chronic myelogenous leukemia (CML), gastrointestinal stromal tumors (GISTs) and a number of other malignancies.

It is the first member of a new class of agents that act by inhibiting particular tyrosine kinase enzymes, instead of non-specifically inhibiting rapidly dividing cells.(DB00619)

Detected variants supporting this treatment effect:
NF1 p.C680fs (indel)

Drug-drug interactions
/ **1**63253-35-8 / **2**-Methoxyethanol / **4**-Aminopyridine, 4-Hydroxycoumarin / **5**-Fluorouracil / **6**-Mercaptopurine / **9**-(N-Methyl-L-Isoleucine)-Cyclosporin A
/ **A**betimus, Abexinostat, Acebutolol Hydrochloride, Aceprometazine, Acteoside, Adenosine, Adenovirus Type 7 Vaccine Live, Agmatine, Aldesleukin, Aldosterone, Alefacept, Alemtuzumab, Alfentanil, Alprazolam, Altretamine, Amantadine Hydrochloride, Amifampridine, Amiodarone Hydrochloride, Amoxapine, Amsacrine, Anagrelide, Antazoline, Anthrax Vaccine, Antilymphocyte Immunoglobulin (Horse), Antithymocyte Immunoglobulin (Rabbit), Aprepitant, Argatroban, Arsenic Trioxide, Artemether, Asenapine, Astemizole, Atropine, Avanafil, Azacitidine, Azathioprine, Azimilide Hydrochloride, Azithromycin
/ **B**acillus Calmette-Guerin Substrain Connaught Live Antigen, Bacillus Calmette-Guerin Substrain Danish 1331 Live Antigen, Bacillus Calmette-Guerin Substrain Tice Live Antigen, Baf-312, Baricitinib, Basiliximab, Bcg Vaccine, Beclomethasone Dipropionate, Begelomab, Belatacept, Belimumab, Belinostat, Bendamustine, Benidipine, Bepridil Hydrochloride, Betamethasone, Bevacizumab, Bexarotene, Bleomycin, Bleselumab, Blinatumomab, Boceprevir, Bortezomib, Brequinar, Briakinumab, Brodalumab, Bromocriptine Mesylate, Budesonide, Bunaftine, Bupropion Hydrochloride, Buspirone Hydrochloride, Busulfan, Butriptyline
/ **C**abazitaxel, Candesartan Cilexetil, Capecitabine, Carbinoxamine Maleate, Carboplatin, Carfilzomib, Carmustine, Castanospermine, Cepeginterferon Alfa-2b, Ceritinib, Chembl372638, Chlorambucil, Chloramphenicol, Chlorpheniramine Maleate, Choline, Ciclesonide, Cinacalcet Hydrochloride, Cinnarizine, Cinoxacin, Ciprofloxacin, Cisapride, Cisplatin, Citalopram Hydrobromide, Cladribine, Clarithromycin, Clemastine Fumarate, Clinafloxacin, Clindamycin Hydrochloride, Clobetasol, Clofarabine, Clomipramine Hydrochloride, Clonidine, Cloprednol, Clorindione, Cobicistat, Cocaine Hydrochloride, Conivaptan Hydrochloride, Corticotropin, Cortisone Acetate, Cortivazol, Crizotinib, Cudc-101, Cyclobenzaprine Hydrochloride, Cyclophosphamide, Cytarabine
/ **D**abrafenib, Dacarbazine, Daclizumab, Dacomitinib, Dactinomycin, Darunavir, Dasatinib, Daunorubicin, Decitabine, Deflazacort, Deoxyspergualin, Desloratadine, Deutetrabenazine, Dexamethasone Isonicotinate, Dexrazoxane, Dicumarol, Digitoxin, Dihydroergotamine Mesylate, Diltiazem Hydrochloride, Dimenhydrinate, Dimethyl Fumarate, Dinutuximab, Diphenadione, Dipyrone, Disopyramide Phosphate, Docetaxel, Dofetilide, Dolasetron, Domperidone, Dopamine Hydrochloride, Doxepin Hydrochloride, Doxifluridine, Dronedarone, Droperidol
/ **E**bastine, Eculizumab, Efalizumab, Efavirenz, Eletriptan Hydrobromide, Eliglustat Tartrate, Enoxacin, Entinostat, Eperisone, Epinephrine, Epirubicin, Eplerenone, Ergotamine Tartrate, Eribulin, Erlotinib, Erythromycin, Esketamine Hydrochloride, Estramustine, Ethosuximide, Ethyl Biscoumacetate, Etoposide
/ **F**elodipine, Fendiline, Fentanyl, Flecainide Acetate, Floxuridine, Fluclorolone, Fluconazole, Flucytosine, Fludrocortisone, Fluindione, Flunisolide, Fluocinolone Acetonide, Fluocortin, Fluocortolone, Fluoxetine, Flupentixol, Fluperolone, Fluprednidene, Fluprednisolone, Fluspirilene, Fluticasone, Fluticasone Furoate, Fluticasone Propionate, Formocortal, Fosaprepitant Dimeglumine
/ **G**adobenate Dimeglumine, Gallium Nitrate (Anhydrous), Garenoxacin, Gemcitabine, Gemfibrozil, Gemifloxacin Mesylate, Gemtuzumab Ozogamicin, Gilteritinib, Glasdegib, Glatiramer Acetate, Glycerol Phenylbutyrate, Goserelin, Granisetron, Grepafloxacin Hydrochloride, Guselkumab, Gusperimus
/ **H**alofantrine Hydrochloride, Halometasone, Haloperidol, Histamine Phosphate, Human Adenovirus E Serotype 4 Strain Cl-68578 Antigen, Hydrocodone Bitartrate, Hydrocortisone Aceponate, Hydrocortisone Acetate, Hydrocortisone Succinate, Hydroxychloroquine, Hydroxyurea, Hydroxyzine, Hypericin
/ **I**britumomab Tiuxetan, Ibutilide Fumarate, Idarubicin, Idelalisib, Ifosfamide, Indenolol, Indinavir Sulfate, Indomethacin, Interferon Alfa, Interferon Alfa-2a, Recombinant, Interferon Alfa-2b, Interferon Alfa-N1, Interferon Alfa-N3, Interferon Alfacon-1, Interferon Beta-1b, Interferon Gamma-1b, Irinotecan, Itraconazole, Ivabradine, Ivosidenib, Ixabepilone, Ixekizumab
/ **J**uxtapid
/ **L**amivudine, Latuda, Lefamulin Acetate, Lenalidomide, Lenvatinib, Leuprolide, Levacetylmethadol, Levobetaxolol Hydrochloride, Levofloxacin, Levomepromazine, Levosimendan, Linagliptin, Linezolid, Lipegfilgrastim, Lithium Cation, Lofexidine Hydrochloride, Lomefloxacin Hydrochloride, Lomustine, Loperamide, Lorcainide
/ **M**acimorelin Acetate, Maraviroc, Mechlorethamine, Melengestrol, Melperone, Melphalan, Memantine Hydrochloride, Meperidine Hydrochloride, Mephenytoin, Mepolizumab, Meprednisone, Metformin Hydrochloride, Methadone Hydrochloride, Methotrexate, Methylprednisolone Sodium Succinate, Methysergide, Mibefradil, Miconazole, Mitomycin C, Mitoxantrone Hydrochloride, Mizolastine, Mizoribine, Mocetinostat, Mometasone, Mometasone Furoate, Monomethyl Fumarate, Muromonab, Mycophenolate Mofetil, Mycophenolic Acid
/ **N**afamostat, Nalidixic Acid, Nelarabine, Nelfinavir Mesylate, Nemonoxacin, Nifedipine, Nilvadipine, Nimodipine, Nisoldipine, Nizofenone Fumarate, Norepinephrine, Nortriptyline Hydrochloride
/ **O**binutuzumab, Ocrelizumab, Ofloxacin, Olaparib, Omega Interferon, Ondansetron, Opipramol, Orphenadrine, Otilonium Bromide, Oxaliplatin, Oxatomide, Oxprenolol Hydrochloride, Ozanimod
/ **P**aclitaxel, Palbociclib, Paliperidone, Papaverine, Paramethasone, Paroxetine, Peficitinib, Peginterferon Alfa-2a, Peginterferon Beta-1a, Pemetrexed, Penfluridol, Penicillamine, Pentamidine, Pentostatin, Perflutren, Phenprocoumon, Phenylalanine, Pimecrolimus, Pimozide, Pirarubicin, Pirfenidone, Plavix, Pomalidomide, Ponatinib, Pracinostat, Pralatrexate, Pramipexole Dihydrochloride, Prednisolone, Prednisone, Prednylidene, Prenylamine, Probucol, Procainamide Hydrochloride, Procarbazine, Prochlorperazine, Promazine Hydrochloride, Propafenone Hydrochloride, Propranolol, Protriptyline Hydrochloride
/ **Q**uetiapine Fumarate, Quinidine
/ **R**altitrexed, Ravulizumab, Reserpine, Ribociclib, Ricolinostat, Rilpivirine, Risankizumab, Rituximab, Rivaroxaban, Rofecoxib, Romidepsin, Roxithromycin, Rozanolixizumab, Rubella Virus Vaccine, Ruxolitinib
/ **S**almeterol, Saquinavir, Sarilumab, Secobarbital Sodium, Serentil, Sildenafil, Sirolimus, Sirturo, Sirukumab, Sorafenib, Sotalol Hydrochloride, Sparfloxacin, Stepronin, Streptozocin, Sulfasalazine, Sulfisoxazole, Sultopride, Sunitinib

/ **T**adalafil, Technetium Tc-99m Ciprofloxacin, Tedisamil, Tedizolid Phosphate, Telavancin, Telithromycin, Temafloxacin, Temozolomide, Temsirolimus, Teniposide, Tepoxalin, Terlipressin, Terodiline, Tetrabenazine, Tetraethylammonium, Tetrandrine, Thalidomide, Theophylline, Thioguanine, Thioridazine, Thiotepa, Tianeptine, Tixocortol, Tolvaptan, Toremifene, Tositumomab, Trabectedin, Trametinib, Trastuzumab Emtansine, Trazodone Hydrochloride, Tretinoin, Triamcinolone Hexacetonide, Triazolam, Trifluridine, Trilostane, Trimipramine Maleate, Triptolide, Trofosfamide, Troleandomycin, Trovafloxacin Mesylate, Tucidinostat, Typhoid Vaccine Live
/ **V**alproic Acid, Vandetanib, Varicella Zoster Vaccine (Live/Attenuated), Vedolizumab, Verapamil Hydrochloride, Vibrio Cholerae Cvd 103-Hgr Strain Live Antigen, Vigamox, Vilanterol, Vinblastine, Vindesine, Vinorelbine, Voclosporin, Vorinostat
/ **W**artmannin / **Y**ellow Fever Vaccine / **Z**afirlukast, Zidovudine, Ziprasidone Hydrochloride, Zolpidem, Zuclopenthixol

Erlotinib ⚠	Drug approval in patient disease: Off-label
Selumetinib ⚠	Drug approval in patient disease: Other

Erlotinib is an inhibitor of the epidermal growth factor receptor (EGFR) tyrosine kinase that is used in the treatment of non-small cell lung cancer, pancreatic cancer and several other types of cancer. It is typically marketed under the trade name Tarceva. Erlotinib binds to the epidermal growth factor receptor (EGFR) tyrosine kinase in a reversible fashion at the adenosine triphosphate (ATP) binding site of the receptor. Recent studies demonstrate that erlotinib is also a potent inhibitor of JAK2V617F, which is a mutant form of tyrosine kinase JAK2 found in most patients with polycythemia vera (PV) and a substantial proportion of patients with idiopathic myelofibrosis or essential thrombocythemia. This finding introduces the potential use of erlotinib in the treatment of JAK2V617F-positive PV and other myeloproliferative disorders.(DB00530)
Selumetinib is under investigation for the treatment of Carcinoma, Thymic, Non-Small Cell Lung Cancer, and Carcinoma, Small Cell Lung. AZD6244 has been investigated for the treatment and basic science of Melanoma, Solid Tumours, Breast Cancer, Non Small Cell Lung Cancer, and Non Small Cell Lung Carcinoma, among others.(DB11689)

Detected variants supporting this treatment effect:
NF1 p.C680fs (indel)

Drug-drug interactions
/ **1**63253-35-8 / **5**-Fluorouracil
/ **A**bexinostat, Acebutolol Hydrochloride, Acepromethazine, Adenosine, Alfentanil, Almotriptan Malate, Alprazolam, Amifampridine, Aminophenazone, Amiodarone Hydrochloride, Amitriptyline Hydrochloride, Amodiaquine Hydrochloride, Amoxapine, Anagrelide, Anastrozole, Antazoline, Apixaban, Aprepitant, Argatroban, Arsenic Trioxide, Astemizole, Atorvastatin Calcium, Atropine, Avanafil, Azelastine Hydrochloride, Azimilide Hydrochloride, Azithromycin
/ **B**af-312, Balaglitazone, Benidipine, Benzyl Alcohol, Bepridil Hydrochloride, Beraprost, Bromocriptine Mesylate, Bunaftine, Buprenorphine, Bupropion Hydrochloride, Buspirone Hydrochloride, Busulfan, Butriptyline
/ **C**abazitaxel, Candesartan Cilexetil, Capravirine, Carbinoxamine Maleate, Ceritinib, Cerivastatin Sodium, Chembl372638, Chlorpheniramine Maleate, Ciglitazone, Cinacalcet Hydrochloride, Cinnarizine, Cinoxacin, Cisapride, Citalopram Hydrobromide, Clemastine Fumarate, Clinafloxacin, Clindamycin Hydrochloride, Clomipramine Hydrochloride, Clonidine, Cocaine Hydrochloride, Crizotinib, Cudc-101, Cyclobenzaprine Hydrochloride
/ **D**acomitinib, Dapsone, Dasabuvir, Dasatinib, Desloratadine, Deutetrabenazine, Dexibuprofen, Diclofenac, Diethylstilbestrol, Digitoxin, Dihydroergotamine Mesylate, Diltiazem Hydrochloride, Dimenhydrinate, Disopyramide Phosphate, Dofetilide, Dolasetron, Domperidone, Dronedarone, Droperidol
/ **E**bastine, Elagolix Sodium, Eletriptan Hydrobromide, Eliglustat Tartrate, Eltrombopag, Enoxacin, Entinostat, Enzalutamide, Eperisone, Eplerenone, Erythromycin, Ethinylestradiol, Ethosuximide
/ **F**elodipine, Fendiline, Fentanyl, Fetzima, Flecainide Acetate, Fluoxetine, Flupentixol, Fluspirilene, Fluticasone, Fluticasone Furoate, Fluticasone Propionate, Fluvastatin Sodium
/ **G**adobenate Dimeglumine, Garenoxacin, Gemfibrozil, Gemifloxacin Mesylate, Gilteritinib, Glasdegib, Goserelin, Granisetron, Grepafloxacin Hydrochloride
/ **H**alofantrine Hydrochloride, Haloperidol, Hydrocodone Bitartrate, Hydroxyzine
/ **I**buprofen, Ibutilide Fumarate, Imatinib, Indenolol, Indinavir Sulfate, Irbesartan, Irinotecan, Istradefylline, Ivabradine, Ixazomib / **J**uxtapid
/ **K**etobemidone, Ketorolac Tromethamine
/ **L**apatinib, Latuda, Lefamulin Acetate, Leuprolide, Levacetylmethadol, Levobetaxolol Hydrochloride, Levofloxacin, Levomepromazine, Levosimendan, Licofelone, Lithium Cation, Livalo, Lobeglitazone, Lofexidine Hydrochloride, Lomefloxacin Hydrochloride, Lorcainide, Lovastatin, Lumateperone
/ **M**acimorelin Acetate, Maraviroc, Melperone, Mephenytoin, Mestranol, Methysergide, Mevastatin, Mibefradil, Mizolastine, Mocetinostat, Mometasone Furoate, Montelukast Sodium, Morphine, Muraglitazar, Mycophenolate Mofetil, Mycophenolic Acid
/ **N**alidixic Acid, Naproxen, Nelfinavir Mesylate, Nemonoxacin, Netoglitazone, Nicotine, Nilvadipine, Nimodipine, Nisoldipine, Nizofenone Fumarate, Nortriptyline Hydrochloride
/ **O**danacatib, Ofloxacin, Olodaterol Hydrochloride, Ombitasvir, Ondansetron, Opipramol, Orphenadrine, Otilonium Bromide, Oxaliplatin, Oxatomide, Oxprenolol Hydrochloride
/ **P**aliperidone, Papaverine, Paramethadione, Paroxetine, Penfluridol, Pentamidine, Perflutren, Perospirone, Phenazone, Pimozide, Piroxicam, Plavix, Ponatinib, Pracinostat, Pravastatin, Prenylamine, Probucol, Procainamide Hydrochloride, Prochlorperazine, Promazine Hydrochloride, Propacetamol Hydrochloride, Propafenone Hydrochloride, Propofol, Propranolol, Protriptyline Hydrochloride
/ **Q**uetiapine Fumarate, Quinidine
/ **R**epaglinide, Ricolinostat, Rilpivirine, Riociguat, Rivaroxaban, Rivoglitazone, Romidepsin, Rosiglitazone, Rosuvastatin Calcium, Roxithromycin
/ **S**almeterol, Selegiline, Selexipag, Serentil, Sildenafil, Simvastatin, Sirolimus, Sirturo, Sitagliptin, Sorafenib, Sotalol Hydrochloride, Sparfloxacin, Sulfadiazine, Sulfisoxazole, Sulpiride, Sultopride
/ **T**adalafil, Tazarotene, Technetium Tc-99m Ciprofloxacin, Tedisamil, Tegafur, Telavancin, Temafloxacin, Temsirolimus, Terlipressin, Terodiline, Tetrabenazine, Theophylline, Thioridazine, Tianeptine, Tolbutamide, Tolvaptan, Toremifene, Torsemide, Trazodone Hydrochloride, Tretinoin, Triazolam, Trimethadione, Trimethoprim, Trimipramine Maleate, Trovafloxacin Mesylate, Tucidinostat

/ **V**alproic Acid, Vandetanib, Velpatasvir, Verapamil Hydrochloride, Vigamox, Vortioxetine, Voxilaprevir
/ **Z**afirlukast, Zidovudine, Ziprasidone Hydrochloride, Zolpidem, Zuclopenthixol

Selumetinib

Drug approval in patient disease: Other

Selumetinib is under investigation for the treatment of Carcinoma, Thymic, Non-Small Cell Lung Cancer, and Carcinoma, Small Cell Lung. AZD6244 has been investigated for the treatment and basic science of Melanoma, Solid Tumours, Breast Cancer, Non Small Cell Lung Cancer, and Non Small Cell Lung Carcinoma, among others.(DB11689)

Detected variants supporting this treatment effect:
NF1 p.C680fs (indel)

Drug-drug interactions
There are no drug-drug interactions available for this treatment

Sirolimus

Drug approval in patient disease: Other

A macrolide compound obtained from Streptomyces hygroscopicus that acts by selectively blocking the transcriptional activation of cytokines thereby inhibiting cytokine production. It is bioactive only when bound to immunophilins. Sirolimus is a potent immunosuppressant and possesses both antifungal and antineoplastic properties.(DB00877)

Detected variants supporting this treatment effect:
NF1 p.C680fs (indel)

Drug-drug interactions
/ **1**67354-41-8 / **2**-Methoxyethanol / **5**-Fluorouracil / **6**-Mercaptopurine / **9**-(N-Methyl-L-Isoleucine)-Cyclosporin A
/ **A**batacept, Abemaciclib, Abetimus, Acalabrutinib, Acetaminophen, Acetazolamide, Acetylsalicylic Acid, Acteoside, Adalimumab, Adenovirus Type 7 Vaccine Live, Afelimomab, Albendazole, Aldesleukin, Aldosterone, Alectinib, Alefacept, Alemtuzumab, Alpelisib, Altretamine, Ambrisentan, Aminoglutethimide, Amitriptyline Hydrochloride, Amobarbital, Amodiaquine Hydrochloride, Amoxapine, Amphotericin B, Amprenavir, Amsacrine, Anakinra, Annamycin, Anthrax Vaccine, Antilymphocyte Immunoglobulin (Horse), Antithymocyte Immunoglobulin (Rabbit), Apixaban, Apremilast, Aprepitant, Aprobarbital, Argatroban, Aripiprazole, Aripiprazole Lauroxil, Arsenic Trioxide, Artemether, Astemizole, Asunaprevir, Atazanavir Sulfate, Atovaquone, Avasimibe, Axitinib, Azacitidine, Azathioprine, Azelastine Hydrochloride, Azimilide Hydrochloride, Azithromycin
/ **B**acillus Calmette-Guerin Substrain Connaught Live Antigen, Bacillus Calmette-Guerin Substrain Danish 1331 Live Antigen, Bacillus Calmette-Guerin Substrain Tice Live Antigen, Baf-312, Bafilomycin A1, Bafilomycin B1, Barbexaclone, Barbital, Baricitinib, Basiliximab, Beclomethasone Dipropionate, Begelomab, Belatacept, Belimumab, Belinostat, Bendamustine, Benzquinamide, Benzyl Alcohol, Betamethasone, Betamethasone Sodium Phosphate, Bevacizumab, Bexarotene, Bicalutamide, Bifonazole, Biricodar, Bisoprolol Fumarate, Black Cohosh, Bleomycin, Bleselumab, Blinatumomab, Boceprevir, Bortezomib, Bosentan, Brequinar, Briakinumab, Brigatinib, Brodalumab, Bromocriptine Mesylate, Budesonide, Buprenorphine, Busulfan, Butalbital
/ **C**abazitaxel, Cabergoline, Calcitriol, Canagliflozin, Canakinumab, Candesartan, Candesartan Cilexetil, Cannabidiol, Capecitabine, Capsaicin, Carboplatin, Carfilzomib, Carmustine, Caspofungin Acetate, Castanospermine, Cefoperazone, Cepeginterferon Alfa-2b, Cephradine, Cerebyx, Ceritinib, Cerivastatin Sodium, Certolizumab Pegol, Cetirizine, Chlorambucil, Chloramphenicol, Chloroform, Chloroquine, Chlorpheniramine Maleate, Chlorpromazine, Cholesterol, Cholic Acid, Ciclesonide, Cilostazol, Cimetidine, Ciprofloxacin, Cisapride, Cisplatin, Citalopram Hydrobromide, Cladribine, Clobazam, Clobetasol, Clocortolone Acetate, Clofarabine, Clofazimin, Clofibrate, Clomipramine Hydrochloride, Clonidine, Cloprednol, Cobicistat, Cocaine Hydrochloride, Colforsin, Concanamycin A, Conivaptan Hydrochloride, Copanlisib, Corticotropin, Cortisone, Cortisone Acetate, Cortivazol, Curcumin, Curcumin Sulfate, Cyclophosphamide, Cyclosporine, Cyproterone Acetate, Cytarabine
/ **D**abigatran Etexilate, Dabrafenib, Dacarbazine, Daclatasvir Dihydrochloride, Daclizumab, Dacomitinib, Dactinomycin, Dalfopristin, Dalmane, Danazol, Danoprevir, Dapoxetine, Dapsone, Darbepoietin, Darunavir, Dasatinib, Daunorubicin, Decitabine, Deferasirox, Deflazacort, Delavirdine Mesylate, Deoxyspergualin, Desipramine Hydrochloride, Desloratadine, Desmethylsertraline, Desvenlafaxine, Deutetrabenazine, Dexamethasone, Dexamethasone Isonicotinate, Dexloxiglumide, Dexrazoxane, Dextromethorphan, Dhea Sulfate, Diazepam, Diclofenac, Dicloxacillin Sodium, Diethylstilbestrol, Digitoxin, Dihydroergocornine, Dihydroergocristine, Dihydroergocryptine, Dihydroergotamine Mesylate, Dimethyl Fumarate, Dimethyl Sulfoxide, Dinutuximab, Dipyridamole, Dipyrone, Disopyramide Phosphate, Disulfiram, Ditiocarb, Docetaxel, Dofequidar, Domperidone, Doravirine, Dovitinib, Doxazosin Mesylate, Doxifluridine, Doxorubicin, Doxycycline, Duloxetine Hydrochloride, Dutasteride
/ **E**chinacea, Eculizumab, Edetate Calcium Disodium, Efalizumab, Efavirenz, Elacridar, Elbasvir, Elexacaftor, Eliglustat Tartrate, Elvitegravir, Emapalumab, Enasidenib, Entrectinib, Enzalutamide, Epinephrine, Epirubicin, Eplerenone, Ergoloid Mesylates, Ergonovine, Ergotamine Tartrate, Eribulin, Erlotinib, Esketamine Hydrochloride, Eslicarbazepine, Eslicarbazepine Acetate, Esomeprazole Magnesium, Estradiol, Estradiol Benzoate, Estradiol Cypionate, Estradiol Dienanthate, Estradiol Valerate, Estramustine, Estriol, Etanercept, Ether, Ethotoin, Ethyl Alcohol, Etoposide, Etoricoxib, Etravirine
/ **F**edratinib, Felbamate, Femring, Fenofibrate, Fentanyl, Finasteride, Flibanserin, Floxacillin, Floxuridine, Fluclorolone, Fluconazole, Flucytosine, Fludarabine, Fludrocortisone, Flunisolide, Fluocinolone Acetonide, Fluocortin, Fluocortolone, Fluoxetine, Flupentixol, Fluperolone, Fluphenazine, Fluprednidene, Fluprednidene Acetate, Fluprednisolone, Flutamide, Fluticasone, Fluticasone Furoate, Fluticasone Propionate, Fluvastatin Sodium, Fluvoxamine Maleate, Formestane, Formocortal, Fosamprenavir Calcium, Fosaprepitant Dimeglumine, Fosnetupitant, Fostamatinib, Fusidic Acid
/ **G**allium Nitrate (Anhydrous), Gefitinib, Gemcitabine, Gemtuzumab Ozogamicin, Genistein, Gestodene, Glasdegib, Glatiramer Acetate, Glecaprevir, Glyburide, Glycerin, Glycerol Phenylbutyrate, Golimumab, Gpi-1485, Gramicidin, Grepafloxacin Hydrochloride, Griseofulvin, Guselkumab, Gusperimus

/ **H**alofantrine Hydrochloride, Halometasone, Haloperidol, Hm-30181, Human Adenovirus E Serotype 4 Strain Cl-68578 Antigen, Hycanthone, Hydralazine Hydrochloride, Hydrocortisone, Hydrocortisone Aceponate, Hydrocortisone Acetate, Hydrocortisone Cypionate, Hydrocortisone Sodium Phosphate, Hydrocortisone Succinate, Hydroxychloroquine, Hydroxyprogesterone Caproate, Hydroxyurea, Hydroxyzine, Hypericin
/ **I**britumomab Tiuxetan, Ibrutinib, Ibuprofen, Icotinib, Idarubicin, Idelalisib, Ifosfamide, Iloperidone, Imatinib, Indalpine, Indinavir Sulfate, Indisulam, Indomethacin, Infliximab, Interferon Alfa, Interferon Alfa-2a, Recombinant, Interferon Alfa-2b, Interferon Alfa-N1, Interferon Alfa-N3, Interferon Alfacon-1, Interferon Beta-1b, Interferon Gamma-1b, Irbesartan, Irinotecan, Isavuconazonium Sulfate, Isoniazid, Istradefylline, Ivacaftor, Ivermectine, Ivosidenib, Ixekizumab
/ **J**uxtapid / **K**etamine Hydrochloride, Ketazolam
/ **L**aniquidar, Lanreotide, Lansoprazole, Lapatinib, Ledipasvir, Lemborexant, Lenalidomide, Lenvatinib, Lesinurad, Lestaurtinib, Letermovir, Levacetylmethadol, Levamlodipine, Levofloxacin, Levothyroxine Sodium, Lidocaine, Linezolid, Liothyronine Sodium, Liotrix, Lipegfilgrastim, Lisuride, Lomustine, Lonafarnib, Lopinavir, Lorlatinib, Losartan Potassium, Lovastatin, Loxapine, Lumefantrine, Lusutrombopag, Lysergide
/ **M**agnacort, Mechlorethamine, Medical Cannabis, Medroxyprogesterone Acetate, Mefloquine Hydrochloride, Megestrol Acetate, Melengestrol, Melengestrol Acetate, Melphalan, Mepacrine, Meperidine Hydrochloride, Mepolizumab, Meprednisone, Mequitazine, Metergoline, Methadone Hydrochloride, Methimazole, Methohexital Sodium, Methotrexate, Methylergonovine, Methylphenobarbital, Methylprednisolone Sodium Succinate, Methysergide, Metronidazole, Metyrapone, Miconazole, Midostaurin, Mifepristone, Milnacipran, Mirabegron, Miralax, Mirtazapine, Mitomycin C, Mitotane, Mitoxantrone Hydrochloride, Mizoribine, Mometasone, Mometasone Furoate, Monensin, Monomethyl Fumarate, Muromonab, Mycophenolate Mofetil, Mycophenolic Acid
/ **N**abiximols, Nafcillin Sodium, Naloxone, Naproxen, Nateglinide, Nefazodone Hydrochloride, Nelarabine, Nelfinavir Mesylate, Neratinib, Netupitant, Nevirapine, Niacin, Nicergoline, Nigericin, Nilotinib, Nitric Oxide, Nk-012, Norethindrone, Norfloxacin, Norgestimate, Norgestrel, Nortriptyline Hydrochloride, Noscapine
/ **O**binutuzumab, Ocrelizumab, Octreotide Acetate, Olaparib, Omega Interferon, Ondansetron, Ont-093, Oritavancin, Orlistat, Orphenadrine, Osimertinib, Oxaliplatin, Oxcarbazepine, Oxethazaine, Oxybutynin, Oxycodone Hydrochloride, Oxymetholone, Ozanimod
/ **P**aclitaxel, Palbociclib, Panobinostat, Paramethasone, Paritaprevir, Paroxetine, Pasireotide, Peficitinib, Pegaspargase, Peginterferon Alfa-2a, Peginterferon Beta-1a, Pegvisomant, Pemetrexed, Penicillamine, Pentamidine, Pentazocine Hydrochloride, Pentobarbital, Pentostatin, Peppermint Oil, Perampanel, Pergolide Mesylate, Phenelzine Sulfate, Phenobarbital, Phenylalanine, Phenylbutazone, Phenytoin, Pibrentasvir, Pilocarpine, Pimecrolimus, Pimozide, Piperaquine, Piperine, Pirarubicin, Pirfenidone, Platelet Activating Factor, Plavix, Pomalidomide, Ponatinib, Posaconazole, Pralatrexate, Praziquantel, Prazosin Hydrochloride, Prednisolone, Prednisolone Hemisuccinate, Prednisolone Sodium Phosphate, Prednisone, Prednisone Acetate, Prednylidene, Primaquine, Primidone, Probenecid, Procarbazine, Progesterone, Promethazine, Propafenone Hydrochloride, Propofol, Propoxyphene Hydrochloride, Propranolol, Propylthiouracil, Protonix, Protriptyline Hydrochloride
/ **Q**uercetin, Quetiapine Fumarate, Quinidine, Quinine Sulfate, Quinupristin
/ **R**abeprazole, Raloxifene, Raltitrexed, Ranitidine, Ravulizumab, Reboxetine, Regorafenib, Remacemide, Reserpine, Resveratrol, Revefenacin, Reversin 121, Ribociclib, Rifabutin, Rifampin, Rifamycin Sodium, Rifapentine, Rilonacept, Rilpivirine, Risankizumab, Risperidone, Ritonavir, Rituximab, Rivaroxaban, Rocephin, Rofecoxib, Rolapitant, Romidepsin, Rosuvastatin Calcium, Roxithromycin, Rozanolixizumab, Rubella Virus Vaccine, Rucaparib, Rufinamide, Rutin, Ruxolitinib
/ **S**afinamide Mesylate, Salinomycin, Salmeterol, Sapropterin Dihydrochloride, Saquinavir, Saracatinib, Sarecycline, Sarilumab, Saxagliptin, Scopolamine, Secobarbital Sodium, Secukinumab, Selegiline, Seproxetine, Seratrodast, Sildenafil, Siltuximab, Simeprevir, Simvastatin, Sirukumab, Sitaxentan, Sofosbuvir, Somatostatin, Sorafenib, Spironolactone, St. John'S Wort, Staurosporine, Stepronin, Stiripentol, Streptozocin, Sulfasalazine, Sulfinpyrazone, Sunitinib, Suvorexant
/ **T**acrolimus, Tadalafil, Tamoxifen, Taractan, Tariquidar, Taurocholic Acid, Tedizolid Phosphate, Tegafur, Telmisartan, Temozolomide, Teniposide, Tenofovir Disoproxil Fumarate, Tepoxalin, Terazosin Hydrochloride, Terbinafine, Terfenadine, Terguride, Teriflunomide, Tesmilifene, Testosterone, Testosterone Enanthate, Testosterone Undecanoate, Tetracycline, Tezacaftor, Thalidomide, Thiamylal Sodium, Thioguanine, Thiopental Sodium, Thiotepa, Ticagrelor, Tipifarnib, Tipranavir, Tixocortol, Tocilizumab, Tofisopam, Tofranil, Tolvaptan, Topiramate, Topiroxostat, Toremifene, Tositumomab, Trabectedin, Trametinib, Tranylcypromine Sulfate, Trastuzumab Emtansine, Trazodone Hydrochloride, Tretinoin, Triclabendazole, Trifluoperazine, Triflupromazine, Trifluridine, Trilostane, Trimethoprim, Trimipramine Maleate, Triptolide, Trofosfamide, Troglitazone, Typhoid Vaccine Live
/ **U**denafil
/ **V**albenazine, Valinomycin, Valproic Acid, Valspodar, Vandetanib, Vapreotide, Vardenafil Hydrochloride, Varicella Zoster Vaccine (Live/Attenuated), Vedolizumab, Velpatasvir, Venetoclax, Venlafaxine Hydrochloride, Vibrio Cholerae Cvd 103-Hgr Strain Live Antigen, Vicriviroc, Vilanterol, Vinblastine, Vincristine, Vindesine, Vinorelbine, Vitamin E, Voacamine, Voclosporin, Voriconazole, Vorinostat, Vortioxetine, Voxelotor, Voxilaprevir
/ **W**artmannin / **Y**ellow Fever Vaccine, Yohimbine / **Z**afirlukast, Zaleplon, Zidovudine, Zimeldine, Ziprasidone Hydrochloride, Zoloft, Zomepirac, Zontivity

Tranilast

Drug approval in patient disease: Other

Tranilast is an antiallergic drug developed by Kissei Pharmaceuticals. In 1982, it was approved in Japan and South Korea for the management of bronchial asthma. Indications for keloid and hypertrophic scar were added in 1993. It has been used for the treatment of allergic disorders such as asthma, allergic rhinitis and atopic dermatitis.(DB07615)

Detected variants supporting this treatment effect:
NF1 p.C680fs (indel)

Drug-drug interactions
/ **B**af-312 / **C**apecitabine, Cerebyx, Clonidine, Curcumin / **D**abrafenib, Dantrolene Sodium, Delavirdine Mesylate, Doxepin Hydrochloride
/ **F**loxuridine, Fluconazole / **G**emfibrozil / **M**iconazole / **P**henytoin / **S**orafenib, Sulfaphenazole / **V**alproic Acid

CDK inhibitors ⚠ Drug approval in patient disease: Other

Abemaciclib, Palbociclib, Trilaciclib, Ribociclib

Detected variants supporting this treatment effect:
CDK4 Copy number GAIN (CNA)

Drug-drug interactions
There are no drug-drug interactions available for this treatment

PARP inhibitors Drug approval in patient disease: Other

Olaparib, Niraparib, Rucaparib, Veliparib, Talazoparib

Detected variants supporting this treatment effect:
BRCA2 p.T2399fs (del)

Drug-drug interactions
There are no drug-drug interactions available for this treatment

Potentially ineffective treatments

Dabrafenib ⚠ Drug approval in patient disease: Off-label

Dabrafenib mesylate (Tafinlar) is a reversible ATP-competitive kinase inhibitor and targets the MAPK pathway. It was approved on May 29, 2013 for the treatment of melanoma [L2718].
In May 2018, Tafinlar (dabrafenib) and Mekinist ([DB08911]) in combination have been approved to treat anaplastic thyroid cancer caused by an abnormal BRAF V600E gene [L2714].(DB08912)

Detected variants supporting this treatment effect:
BRAF p.K601E (SNV)

Vemurafenib Drug approval in patient disease: Off-label

Vemurafenib is a competitive kinase inhibitor with activity against BRAF kinase with mutations like V600E.[A31269] It exerts its function by binding to the ATP-binding domain of the mutant BRAF.[A31270] Vemurafenib was co-developed by Roche and Plexxikon and it obtained its FDA approval on August 17, 2011, under the company Hoffmann La Roche. After approval, Roche in collaboration with Genentech launched a broad development program. [L1012](DB08881)

Detected variants supporting this treatment effect:
BRAF p.K601E (SNV), NF1 p.C680fs (indel)

Crizotinib Drug approval in patient disease: Off-label

Crizotinib an inhibitor of receptor tyrosine kinase for the treatment of non-small cell lung cancer (NSCLC). Verification of the presence of ALK fusion gene is done by Abbott Molecular's Vysis ALK Break Apart FISH Probe Kit. This verification is used to select for patients suitable for treatment. FDA approved in August 26, 2011.(DB08865)

Detected variants supporting this treatment effect:
MET p.N375S (SNV)

Ribociclib Drug approval in patient disease: Off-label

Ribociclib is a selective cyclin-dependent kinase inhibitor, a class of drugs that help slow the progression of cancer by inhibiting two proteins called cyclin-dependent kinase 4 and 6 (CDK4/6). These proteins, when over-activated, can enable cancer cells to grow and divide too quickly. Targeting CDK4/6 with enhanced precision may play a role in ensuring that cancer cells do not continue to replicate uncontrollably. Ribociclib was approved by the U.S. FDA in March, 2017 as Kisqali.(DB11730)

Detected variants supporting this treatment effect:
RB1 p.D578fs (del)

Palbociclib ⚠ Drug approval in patient disease: Off-label

Palbociclib is a piperazine pyridopyrimidine[A176792] that acts in the cell cycle machinery. It is a second generation cyclin-dependent kinase inhibitor[A176798] selected from a group of pyridopyrimidine compounds due to its favorable physical and pharmaceutical properties.[A176810] Palbociclib was developed by Pfizer Inc after the discovery that identified the cyclin-dependent kinases as key regulators of cell growth.[L5867] It was originally FDA approved on March 2015 for the treatment of HR-positive, HER2-negative advanced or metastatic breast cancer and its indications were updated in April 2019 to include male patients based on findings from postmarketing reports and electronic health records demonstrating safety and clinical efficacy.[L4894](DB09073)

Detected variants supporting this treatment effect:
RB1 p.D578fs (del)

Gefitinib Drug approval in patient disease: Off-label

Gefitinib (originally coded ZD1839) is a drug used in the treatment of certain types of cancer. Acting in a similar manner to erlotinib (marketed as Tarceva), gefitinib selectively targets the mutant proteins in malignant cells. It is marketed by AstraZeneca under the trade name Iressa.(DB00317)

Detected variants supporting this treatment effect:
NF1 p.C680fs (indel)

Afatinib Drug approval in patient disease: Off-label

Afatinib is a 4-anilinoquinazoline tyrosine kinase inhibitor in the form of a dimaleate salt available as Boehringer Ingelheim's brand name Gilotrif [FDA Label]. For oral use, afatinib tablets are a first-line (initial) treatment for patients with metastatic non-small cell lung cancer (NSCLC) with common epidermal growth factor receptor (EGFR) mutations as detected by an FDA-approved test [L2939]. Gilotrif (afatinib) is the first FDA-approved oncology product from Boehringer Ingelheim [L2939].(DB08916)

Detected variants supporting this treatment effect:
NF1 p.C680fs (indel)

Erlotinib ⚠ Drug approval in patient disease: Off-label

Erlotinib is an inhibitor of the epidermal growth factor receptor (EGFR) tyrosine kinase that is used in the treatment of non-small cell lung cancer, pancreatic cancer and several other types of cancer. It is typically marketed under the trade name Tarceva. Erlotinib binds to the epidermal growth factor receptor (EGFR) tyrosine kinase in a reversible fashion at the adenosine triphosphate (ATP) binding site of the receptor. Recent studies demonstrate that erlotinib is also a potent inhibitor of JAK2V617F, which is a mutant form of tyrosine kinase JAK2 found in most patients with polycythemia vera (PV) and a substantial proportion of patients with idiopathic myelofibrosis or essential thrombocythemia. This finding introduces the potential use of erlotinib in the treatment of JAK2V617F-positive PV and other myeloproliferative disorders.(DB00530)

Detected variants supporting this treatment effect:
NF1 p.C680fs (indel)

CDK inhibitors ⚠ Drug approval in patient disease: Other

Abemaciclib, Palbociclib, Trilaciclib, Ribociclib

Detected variants supporting this treatment effect:
RB1 p.D578fs (del)

Treatments with potential for adverse reaction

No treatments with potential for adverse reaction reported

TUMOR MUTATIONAL BURDEN (TMB), BASED ON RELEVANT SOMATIC VARIANTS

The following table summarizes the number of somatic variants identified as potentially relevant in the patient sample in total, and relative to the analyzed coding target region of the assay. A TMB calculated on a coding target region size smaller than 1 MB might not be reliable.

Variant type	Variant count	mut/Mb
Non-synonymous SNVs	3	n/a
Synonymous SNVs	0	n/a
Deletions, Insertions, Indels	5	n/a

DETECTED VARIANTS

This section provides details on all detected variants matching the filter criteria. PF = population frequency. The VAF column shows variant allele frequency (VAF). For CNAs, the gene copy number (GCN) is shown. Fold change (FC) is shown for CNAs from Illumina panels.

Protein	Coding DNA	Genomic	Type	Total reads	VAF	PF	AMP score
ARID1A p.Q1334del	ENST00000324856.7 c.3999_4001del	chr1 g.27100203_27100205del	del	1889	5.98%	0.02%	—
ATM p.D1853V	ENST00000278616.4 c.5558A>T	chr11 g.108175463A>T	SNV	1999	54.13%	0.48%	Tier IV
BRAF p.K601E	ENST00000288602.6 c.1801A>G	chr7 g.140453134T>C	SNV	1981	31.55%	0%	Tier IIC
BRCA1	ENST00000357654.3 c.5277+77C>T	chr17 g.41208992G>A	SNV	1892	7.51%	—	—
BRCA2 p.T2399fs	ENST00000380152.3 c.7195del	chr13 g.32929185del	del	1994	59.48%	—	Tier IA
CDK4 Copy number GAIN	—	chr12 Chr12:58141510_58149796gain	CNA	—	GCN: 5.48	—	Tier IID
ERG/TMPRSS2 TMPRSS2	—	chr21 Chr21:39817544/Chr21:42880008	fusion	—	—	—	Tier IID
KLLN	ENST00000445946.3 c.-2071_-2054del	chr10 g.89624298_89624315del	del	10308	11.41%	—	—
MET p.N375S	ENST00000397752.3 c.1124A>G	chr7 g.116340262A>G	SNV	1999	60.43%	2.77%	Tier III
MET p.R359Q	ENST00000397752.3 c.1076G>A	chr7 g.116340214G>A	SNV	1998	38.79%	0.03%	—
NF1 p.C680fs	ENST00000358273.4 c.2034_2036delinsAA	chr17 g.29553485_29553487delinsAA	indel	1951	9.84%	—	—
NOTCH1	ENST00000277541.6 c.4014+33G>A	chr9 g.139400946C>T	SNV	2000	37.10%	0.25%	—
PIK3CA p.R115P	ENST00000263967.3 c.344G>C	chr3 g.178916957G>C	SNV	1997	7.66%	—	—
PTEN p.L25_T26del	ENST00000371953.3 c.74_79+12del	chr10 g.89624300_89624317del	del	10308	11.41%	—	—
RAD50	ENST00000265335.6 c.1052-34_1052-31delinsG	chr5 g.131924345_131924348delinsG	indel	191	95.81%	—	—
RAD51C p.T287A	ENST00000337432.4 c.859A>G	chr17 g.56798128A>G	SNV	1362	60.21%	0.58%	—
RB1 p.D578fs	ENST00000267163.4 c.1732del	chr13 g.49027165del	del	1994	9.93%	—	Tier IID

ADDITIONAL TEST RESULTS

No additional test results reported

CLINICAL TRIALS

The following trials are potentially best suited for your patient's indication, considering all reported treatment recommendations. See https://clinicaltrials.gov (clinical trials from NCT) or https://apps.who.int/trialsearch (clinical trials from other registries) for more information.

Title	Trial phase and ID	Intervention	Disease	Location	Age and sex
Study of Olaparib (MK-7339) in Combination With Pembrolizumab (MK-3475) in the Treatment of Homologous Recombination Repair Mutation (HRRm) and/or Homologous Recombination Deficiency (HRD)-Positive Advanced Cancer (MK-7339-007/KEYLYNK-007)	Phase 2; NCT04123366	Olaparib	Neoplasms; Solid tumor	Berlin, Koeln, Nordrhein-Westfalen, Muenchen, Bayern	Age: 18, Gender: Both
A Study to Test Different Doses of BI 1701963 Alone and Combined With Trametinib in Patients With Different Types of Advanced Cancer (Solid Tumours With KRAS Mutation) Eligibility criteria: **Inclusion:**KRAS mutation: activating mutation	Phase 1; NCT04111458	Trametinib	Neoplasms; Solid tumor	Frankfurt am Main, Köln	Age: 18, Gender: Both
A Study of Niraparib in Combination With Abiraterone Acetate and Prednisone Versus Abiraterone Acetate and Prednisone for Treatment of Participants With Metastatic Prostate Cancer (MAGNITUDE)	Phase 3; NCT03748641	Niraparib	Prostatic Neoplasms, Castration-Resistant	Braunschweig, Duisburg, Homburg, ...	Age: 18, Gender: Male

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DRUG CLASSES

The following drugs are members of drug classes that are part of reported treatments:

PARP inhibitors (effective)

The drug class PARP inhibitors includes the following drugs.
Niraparib Olaparib Rucaparib Talazoparib Veliparib

FILTERS AND RULESET SETTINGS

Number of variants

Here you see the total number of somatic and germline variant calls identified in the patient sample. The subset of variants identified as potentially clinically significant is highlighted in green. Variants that are filtered out (for example, false positives or potentially benign polymorphisms) are shown in gray. Variants can be automatically filtered out by the MH Guide filters and rulesets, or manually, based on the expertise of the certified user.

Identification of potentially relevant variants

An SNV variant is identified as a potential false positive if it was detected in more than 5 cases of the same labtest, has fewer than 3 references in COSMIC, has no matching CVI, and if it fulfills one of the following criteria: Population frequency (general) less than or equal to 0.10, Population frequency (ethnicity) less than or equal to 0.10, or Population frequency (max. ethnicity) less than or equal to 0.10.
An indel variant is identified as a potential false positive if it was detected in more than 5 cases of the same labtest, has fewer than 3 references in COSMIC, has no matching CVI, and if it fulfills one of the following criteria: Population frequency (general) less than or equal to 0.10, Population frequency (ethnicity) less than or equal to 0.10, or Population frequency (max. ethnicity) less than or equal to 0.10.
An SNV variant is identified as a potentially benign polymorphism and filtered out if no matching CVI of impact(s) Effective, Ineffective, Safety is available and if it fulfills one of the following criteria: Population frequency (general) greater than 1.00, Population frequency (ethnicity) greater than 1.00, or Population frequency (max. ethnicity) greater than 1.00.
An indel variant is identified as a potentially benign polymorphism and filtered out if no matching CVI of impact(s) Effective, Ineffective, Safety is available and if it fulfills one of the following criteria: Population frequency (general) greater than 1.00, Population frequency (ethnicity) greater than 1.00, or Population frequency (max. ethnicity) greater than 1.00.

The following thresholds were used for identification of relevant variants:

	Variant allele frequency [%]	Observation quality	Number of reads (primary)	Number of reads (control)
SNV	10.00	100.00	100.00	100.00
Indels	10.00	100.00	100.00	100.00
Fusions	—	0.00	100.00	—
CNAs	—	0.00	—	—

Additionally, other variants that do not meet the above thresholds may still be described as possibly relevant based on the following thresholds:

	Variant allele frequency [%]	Observation quality	Number of reads (primary)	Number of reads (control)
SNV	5.00	0.00	95.00	95.00
Indels	5.00	0.00	95.00	95.00
Fusions	—	-1.00	10.00	—
CNAs	—	0.05	—	—

DESCRIPTION KEY

- Potentially effective treatments. These treatment recommendations are based solely on tumor biology and do not override your oncologist's clinical treatment plan.
- Potentially ineffective treatments. These treatments, in combination with the biomarkers identified in the patient tumor, have been reported to predict lack of effectiveness. Treatment of a patient with any of these reported drugs may lead to disease progression.
- Treatments with potential to cause an adverse reaction. These treatments, in combination with the biomarkers identified in the patient tumor, have been reported to predict safety issues. Treatment of a patient with any of these reported drugs may lead to serious drug-related toxicities.
- Biomarkers identified in the patient tumor that have been reported to have a prognostic relevance.
- Biomarkers identified in the patient tumor that have been reported to have a diagnostic relevance.
- The report contains conflicting evidence about the potential effect of the treatment.

MOLECULAR HEALTH GLOSSARY

AMP score:
Displays the classification of a biomarker according to the recommendations of the Association for Molecular Pathology (AMP). Source: Marilyn M. Li, Michael Datto, Eric J. Duncavage, Shashikant Kulkarni, Neal I. Lindeman, Somak Roy, Apostolia M. Tsimberidou, Cindy L. Vnencak-Jones, Daynna J. Wolff, Anas Younes, and Marina N. Nikiforova "Standards and Guidelines for the Interpretation and Reporting of Sequence Variants in Cancer," Journal of Molecular Diagnostics, vol. 19, no. 1, pp. 4-23 ,2017, doi: 10.1016/j.jmoldx.2016.10.002.

- Tier IA: Variants of strong clinical significance. FDA-approved therapy or biomarkers included in professional guidelines.
- Tier IB: Variants of strong clinical significance. Well-powered studies with consensus from experts in the field.
- Tier IIC: Variants of potential clinical significance. FDA-approved therapies for different cancer types or investigational therapies. Multiple small published studies with some consensus.
- Tier IID: Variants of potential clinical significance. Preclinical trials or a few case reports without consensus.
- Tier III: Variants of unknown clinical significance.
- Tier IV: Benign or likely benign variants.

Note that in the evidence-based variant categorization context, therapy refers to the combination of variant, drug, and disease.

Biomarker:
In general, a biomarker is any characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathological processes, or pharmacological response to a therapeutic intervention. In the context of MH Guide, reported biomarkers predict a patient's response to therapy and are based on the characterization of the patient/tumor genomic DNA. Depending on the analysis type, such genomic characteristics can include single nucleotide variants (SNVs), insertions and deletions (indels), fusion genes, and copy number alterations (CNAs).

Biomarker score:
Displays the AMP score and the CVI score of the biomarker.

CVI score:
The clinical variant interpretation (CVI) scores 7-1 indicate the reliability of a biomarker to predict a specific patient outcome. This can include predictive treatment effects; in this case, the scores 7-1 apply for biomarkers associated with a single drug or drug combination.
The CVI scores are defined as follows:
7, Clinically approved: The biomarker has been approved by a regulatory agency such as the FDA to predict a specific effect (i.e., response, resistance, or toxicity) in the patient's disease or cancer type.
6, Clinical: Patient's disease: The biomarker has not yet been approved by a regulatory agency for the patient's disease. However, the biomarker has been observed in at least one large cohort study to predict a specific effect of the drug (i.e., to be effective, resistance) in the patient's disease. Other diseases: The biomarker has been approved by a regulatory agency to predict a specific effect of the drug (response, resistance) with other diseases or conditions. This CVI will be available for matching with the less-specific disease Neoplasms in CVIs. Biomarkers predicting toxicity: For all disease matches, this score indicates that there is evidence from a randomized controlled trial or its meta-analysis for biomarkers predicting a drug to be toxic.
5, Clinical: The biomarker has not yet been approved by a regulatory agency for the patient's disease. However, this biomarker has been observed to predict a specific effect of the drug (i.e., response, resistance) on patients with other diseases or conditions. For biomarkers predicting a drug to be effective or resistant, there is evidence from some patients in several cohort studies and additional preclinical evidence. For biomarkers predicting a drug to be toxic, there is evidence from >1 prospective studies or meta-analyses from prospective and/or retrospective studies.
4, Clinical: The biomarker has not yet been approved by a regulatory agency for the patient's disease. However, this biomarker has been observed to predict a specific effect of the drug (i.e., response, resistance) on patients with other diseases or conditions. For biomarkers predicting a drug to be effective or resistant, there is evidence from a few clinical case reports and additional preclinical evidence. For biomarkers predicting a drug to be toxic, there is evidence from a prospective study, >1 retrospective studies, or >1 cohort studies.
3, Preclinical: The biomarker has not yet been observed/tested in patients to predict a specific effect. The biomarker has been observed in preclinical experiments. There is experimental evidence from cell lines or mouse models, for example.
2, Preclinical: The biomarker has not yet been observed/tested in patients or preclinical models to predict a specific effect. However, this effect can be inferred when drug-sensitivity data are available for another variant. This applies only if the two variants have the identical functional impact on the same downstream pathway.
1, Preclinical: The biomarker has not yet been observed/tested in patients or preclinical models to predict a specific effect. However, this effect can be inferred when drug-sensitivity data are available for another variant. This applies only if both variants have the identical functional impact on the protein.

Drug approval:
The development stage of the treatment for the patient's indication in the patient's country.

- **Approved** - This drug is launched for the primary or a secondary patient disease.
- **Off-label** - This drug is launched for a disease other than the primary or secondary patient diseases.
- **Investigational** - This drug is currently under clinical development in the patient disease.
- **Other** - None of the other stages are applicable. The drug is, for example, suspended, discontinued, or withdrawn. Other is also used for the drug approval stage of drug classes.

Drug-drug interactions:
A drug-drug interaction is a situation in which a substance (usually another drug) affects the activity of one or both drugs when both are administered together. In the MH Guide report, drug-drug interactions are reported where a drug is predicted to affect the activity of the agent(s) in the treatment option.

Fold change:
The fold change is a value for copy number variants obtained from the Illumina data of TSO500/TSO500 ctDNA/TST170 panels. It indicates the ratio of the gene coverage for the amplification/deletion to a gene specific base line, calculated by Illumina. For amplifications the fold change is greater than a predefined amplification cutoff. For deletions the fold change is less than a predefined deletion cutoff.

Medications with potential for adverse reaction or ineffectiveness.:
Medications with potential for adverse reaction or ineffectiveness refers to Molecular Health's ability to identify treatments that are predicted to be associated with negative physiological responses to a drug therapy (i.e., drug resistance and toxicity).

Open trials:
Clinical trials that are currently recruiting patients with specific disease indication(s) to assess the clinical efficacy and safety of the listed treatment.

Potential impact:
The specific drug effect predicted by the identified mutation (i.e. response, resistance, or toxicity).

PubMed ID:
A PubMed identifier is a unique number assigned to each PubMed record - also termed PMID. A PMID can be used to retrieve a specific publication from the PubMed database by entering the PMID in the search box on the PubMed site at http://www.ncbi.nlm.nih.gov/pubmed.

Treatment:
The generic name of the therapeutic agent listed on the report.

MOLECULAR HEALTH DISCLAIMER

Molecular Health GmbH (MH) develops and operates software systems for the integrated analysis of clinical and genomic patient data to support physicians in choosing the optimal treatment for individual patients with respect to effectiveness and safety.

Molecular Health Guide (MH Guide) is a bioinformatics software tool to aid clinical decision making by processing genetic variant data from a patient's tumor through a variant detection pipeline. This enables generation of a customizable clinical report with a summary of potentially effective medications, potentially ineffective medications, and medications that may pose a higher risk of adverse reactions.
The MH Guide Variant Detection Pipeline covers:

1. Primary identification of genetic alterations from next-generation sequencing (NGS) data by the MH Guide Variant Detection Pipeline, either from the patient's tumor (targeted panel analysis) or from both the patient's tumor and the control sample (whole exome analysis) (optional).
2. Aggregation, integration, collation, and maintenance of up-to-date biomedical reference information relevant for clinical decision support in clinical oncology.
3. Mapping of the patient's genetic alterations to the biomedical reference information.
4. Integration of the patient's genetic alterations based on the mapping to biomedical reference information.
5. Computational integration of the above information into a summary of potentially effective, ineffective, and toxic medications, for the individual patient. Also, prognostic and diagnostic biomarkers may be detected and shown for the given disease context.
6. Generation of a customizable clinical report by a trained user (MH-certified physician), providing links to the sources of evidence of the information displayed for full traceability.

The information consolidated in the clinical report provided to the patient's treating physician is the result of a comprehensive filter setting based on values defined by the MH-certified physician. The MH-certified physician is neither a contractor nor an employee of MH. The information provided in the report must be evaluated by the treating physician in conjunction with all other relevant clinical information of the patient before the appropriate course of medication is selected by the treating physician. The selection of any, all, or none of the medications identified in the report is at the sole discretion of the treating physician and not of MH or the MH medical staff.

The information provided in this disclaimer may not be applicable when the product is used in other configurations than the MH standard configuration.

MH Guide is designed for processing the molecular data from patients diagnosed with cancer. Diseases beyond this are out of the scope of the application. In particular, the following data cannot be determined using MH Guide: blood groups; infections and infectious diseases; irregular anti-erythrocytic antibodies; the hereditary disease phenylketonuria; the HLA tissue groups DR, A, and B; the tumoral marker PSA, and the risk of trisomy 21.

The patient disease must be provided in MeSH ontology format for correct interpretation of patient data. Other disease ontologies such as ICD must be converted to the correct MeSH term by the certified physician.
Any genetic findings outside of the intended use of treatment decision support in cancer care, e.g., risk factors for potential future diseases of a patient or variants that indicate that the patient is a genetic carrier for hereditary diseases are not annotated and reported, even though corresponding variants or risk factors may be identified as a result of an MH Guide analysis.

The identification of a genomic biomarker does not necessarily imply pharmacological effectiveness or ineffectiveness. The medications identified by the treating physician may or may not be suitable for use on a particular patient. Thus, the clinical report does not guarantee that any particular agent will be effective in the treatment of any particular condition. Also, the absence of a recommendation for a medication by MH Guide does not determine the effectiveness or predict an ineffective or safety-relevant effect of a medication selected by the treating physician.

The contents of the clinical report, a result of mapping patient data against the MH Guide database, and selection of treatment-relevant information by the MH-certified physician are to be used only as an additional aid to the clinical decision by the treating physician. Interpretation of the report contents must occur in consultation with a medical expert. Decisions on patient care and treatment must be based on the independent medical judgment of the treating physician, taking into consideration all applicable information concerning the patient's condition, such as patient and family history, physical examinations, information from other diagnostic tests, and patient preferences, in accordance with the applicable standard of care. Decisions regarding care and treatment should not be based solely on the information contained in this report.

MH Guide can detect single nucleotide variants (SNVs), insertions and deletions (indels), fusion genes (from DNA or RNA data in unpaired analyses or from RNA data in paired analyses), copy number alterations (paired analyses only), microsatellite instability (MSI-H, paired analyses only) and tumor mutational burden (TMB) from NGS data.
The clinical validity of TMB defined by the underlying lab test has not been established.

The detection methods for indels, fusion genes and copy number alterations from FASTQ and BAM were validated using synthetic data only. Therefore, indel, fusion gene, and CNA detection in MH Guide must be validated with an orthogonal method (e.g., Sanger sequencing) before a treatment is recommended. MSI status of unclassified cases or MSS cases should be assessed with orthogonal methods before a treatment decision is made based on the MSI status.

It is the responsibility of the MH-certified physician to assess the pre- and post-alignment QC results within MH Guide and to communicate with the treating physician any data which are of suboptimal quality.

If genetic aberration signals are submitted in the format of a VCF file for processing in MH Guide, the quality of the results from MH Guide depends on the quality of the input data submitted by a lab on behalf of the MH-certified physician. The accuracy, analytic sensitivity and specificity of the variant lists is the sole responsibility of the MH-certified physician.

For ethnicity Japanese (JPT) population frequencies from ToMMo 3.5KJPNv2 (MAF>=1%) are available in the application for display and filtering.

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