DR. SENCKENBERGISCHES INSTITUT FÜR PATHOLOGIE
Wildlab

Patient name	*****	**Diagnosis**	Mammakarzinom
Patient ID	Test1234	**ICD-10-CM code**	—
Case ID	EU001930	**MeSH ID/term**	D001943 (Breast Neoplasms)
Date of birth	*****	**Additional MeSH IDs**	—

Sex	Female	**Sample type**	FFPE	**Labtest**	VCF-complete import (paired)	**General dataset ID**	105685598965
Ethnicity	EUR	**Tumor cellularity**	100%	**Organizational unit**	SIPV2TEST	**CVI dataset ID**	105685598965
Country	DE					**Software version**	4.3.3

Mutational status of commonly mutated genes in the patient disease

ATM not identified	**BRCA1** not identified	**BRCA2** not identified	**CDK4** not identified	**CDKN2A** not identified	**CHEK2** not identified	**EGFR** not identified	**ERBB2** not identified	**ESR1** not identified	**PALB2** not identified	**PIK3CA** 1 SNV
PTEN not identified	**TP53** not identified									

SUMMARY

Overview of potential treatment impacts

3 Effective **1 Ineffective** **0 Safety**

Overview of prognostic and diagnostic findings

0 Prognostic **0 Diagnostic**

Clinical trials found

6 Trials

Potential impact	Treatment	Drug approval	Biomarker	VAF/Copy Number	Biomarker score		Trials
Effective	Alpelisib Fulvestrant	Approved Approved	PIK3CA p.E545A (SNV)	66.67%	AMP Tier I A	7 Clinically Approved	4
Effective	Everolimus	Approved*	PIK3CA p.E545A (SNV)	66.67%	AMP n/a	2 Preclinical	2
Effective	Sirolimus	Other	PIK3CA p.E545A (SNV)	66.67%	AMP n/a	2 Preclinical	0
Ineffective	Trastuzumab	Approved*	PIK3CA p.E545A (SNV)	66.67%	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; VAF = Variant allele frequency

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

PIK3CA p.E545A (SNV)

PIK3CA is the catalytic subunit of the lipid phosphoinositide-3-kinase (PI3K) that activates the PI3K/AKT signaling pathway to promote cell proliferation and survival. This variant strongly activates the downstream pathway in preclinical settings. Alpelisib plus fulvestrant is indicated for this variant for the treatment of hormone receptor-positive, HER2-negative advanced breast cancer. The HER2-positive tumor of a patient with this variant was resistance to trastuzumab. Although not specifically tested for this mutation, preclinical models with activating variants are sensitive to the mTOR inhibitors everolimus and sirolimus and have reduced sensitivity to trastuzumab. A larger study showed that HER2-positive patients with an activating PIK3CA mutation had improved progression-free survival with the addition of everolimus to trastuzumab treatment.

PubMed ID
21358673, 28382169, 27091708, 31091374, 23092874

Potential impact	Treatment	Drug approval	Biomarker score	
Effective	Alpelisib + Fulvestrant	Approved, Approved	AMP Tier I A	7 Clinically Approved
Effective	Everolimus	Approved*	AMP n/a	2 Preclinical
Effective	Sirolimus	Other	AMP n/a	2 Preclinical
Ineffective	Trastuzumab	Approved*	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.
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.

Alpelisib	Drug approval in patient disease: Approved
Fulvestrant	Drug approval in patient disease: Approved

Alpelisib is a phosphatidylinositol 3-kinase (PI3K) inhibitor with potent antitumor activity. It works by selectively inhibiting class I PI3K p110**α** [A179203], which is the catalytic subunit of PI3K, a lipid kinase that plays a role in various biological processes, including proliferation, survival, differentiation, and metabolism. Alpelisib was designed to target this enzyme that appears to be mutated at a rate of nearly 30% in human cancers, leading to hyperactivation.[A179209]
There are several isoform-specific PI3K inhibitors that are under clinical development or currently approved, such as [idelalisib] used for chronic lymphocytic leukemia (CLL).[A179209] Approved by the FDA in May 2019, alpelisib is the first approved PI3K inhibitor indicated for the treatment of hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative, PIK3CA-mutated, advanced or metastatic breast cancer in combination with [fulvestrant] for postmenopausal women and male patients. To initiate alpelisib therapy, it is required that the presence of a PIK3CA mutation in the tissue and/or liquid biopsy sample collection should be confirmed via FDA-approved diagnostic tests. Alpelisib is marketed under the trade name Piqray and is available as oral tablets. Studies evaluating the therapeutic effectiveness of alpelisib in other cancers, such as ovarian cancer [A179200] and colorectal cancer [A179203], are under ongoing investigations.
Alpelisib was granted FDA approval on 24 May 2019.[L6652](DB12015)
Fulvestrant is a drug treatment of hormone receptor (HR)-positive metastatic breast cancer in post-menopausal women with disease progression following anti-estrogen therapy. It is an estrogen receptor antagonist with no agonist effects, which works both by down-regulating and by degrading the estrogen receptor. While it is used as monotherapy for the treatment of breast cancers, it is also used in combination with [alpelisib] for the treatment of HR-positive, human epidermal growth factor receptor 2 (HER2)-negative, PIK3CA-mutated, advanced or metastatic breast cancer(DB00947)

Detected variants supporting this treatment effect:
PIK3CA p.E545A (SNV)

Drug-drug interactions
/ 4-Hydroxycoumarin **/ A**lfentanil, Alprazolam, Aprepitant, Astemizole, Avanafil
/ Baf-312, Boceprevir, Bromocriptine Mesylate, Budesonide, Buspirone Hydrochloride, Busulfan
/ Cisapride, Clarithromycin, Clindamycin Hydrochloride, Clomipramine Hydrochloride, Clonidine, Clorindione, Conivaptan Hydrochloride, Curcumin, Cyclobenzaprine Hydrochloride
/ Danoprevir, Darifenacin, Darunavir, Delavirdine Mesylate, Desipramine Hydrochloride, Digitoxin, Dihydroergotamine Mesylate, Diphenadione, Ditiocarb, Dofetilide, Dothiepin, Dronedarone
/ Ebastine, Efavirenz, Eliglustat Tartrate, Elvitegravir, Eplerenone, Ergotamine Tartrate, Ethosuximide, Ethyl Biscoumacetate
/ Felodipine, Fentanyl, Fosaprepitant Dimeglumine **/ H**ydrocodone Bitartrate **/ I**delalisib, Indinavir Sulfate, Itraconazole **/ K**etoconazole
/ Latuda, Levacetylmethadol, Levothyroxine Sodium, Lofepramine Hydrochloride, Loperamide, Lopinavir, Lumateperone
/ Maraviroc, Melitracen, Meperidine Hydrochloride, Methimazole, Methysergide
/ Naloxone, Nefazodone Hydrochloride, Nisoldipine, Nortriptyline Hydrochloride **/ O**spemifene **/ P**aclitaxel, Pimozide, Posaconazole
/ Ranolazine, Ribociclib, Rivaroxaban **/ S**imvastatin, Sirolimus, Stiripentol
/ Tadalafil, Telaprevir, Telithromycin, Temsirolimus, Terfenadine, Theophylline, Thiopental Sodium, Tianeptine, Ticagrelor, Tipranavir, Tofranil, Tolvaptan, Triazolam, Troleandomycin

Everolimus	Drug approval in patient disease: Approved*

Everolimus is a derivative of Rapamycin (sirolimus), and works similarly to Rapamycin as an mTOR (mammalian target of rapamycin) inhibitor. It is currently used as an immunosuppressant to prevent rejection of organ transplants. In a similar fashion to other mTOR inhibitors Everolimus' effect is solely on the mTORC1 protein and not on the mTORC2 protein.(DB01590)

Detected variants supporting this treatment effect:
PIK3CA p.E545A (SNV)

Drug-drug interactions
/ 2-Methoxyethanol **/ 3**05841-29-6 **/ 5**-Fluorouracil **/ 6**-Deoxyerythronolide B, 6-Mercaptopurine **/ 9**-(N-Methyl-L-Isoleucine)-Cyclosporin A

/ **A**batacept, Abetimus, Acalabrutinib, Acetazolamide, Acteoside, Adalimumab, Adenovirus Type 7 Vaccine Live, Afelimomab, Aldesleukin, Aldosterone, Alefacept, Alemtuzumab, Alprazolam, Altretamine, Aminoglutethimide, Amobarbital, Amphotericin B, Amprenavir, Anakinra, Anthrax Vaccine, Antilymphocyte Immunoglobulin (Horse), Antithymocyte Immunoglobulin (Rabbit), Apremilast, Aprobarbital, Arsenic Trioxide, Avasimibe, Ave9633, 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, Barbexaclone, Barbital, Baricitinib, Basiliximab, Beclomethasone Dipropionate, Begelomab, Belatacept, Belimumab, Belinostat, Bendamustine, Betamethasone, Betamethasone Sodium Phosphate, Bevacizumab, Bexarotene, Bifonazole, Black Cohosh, Bleomycin, Bleselumab, Blinatumomab, Bortezomib, Bosentan, Brequinar, Briakinumab, Brigatinib, Brodalumab, Bryostatin 1, Budesonide, Busulfan, Butalbital
/ **C**abergoline, Calcitriol, Canakinumab, Candicidin, Capecitabine, Capsaicin, Carbomycin, Carboplatin, Carfilzomib, Carmustine, Castanospermine, Cepeginterferon Alfa-2b, Cephradine, Ceritinib, Cerivastatin Sodium, Certolizumab Pegol, Chlorambucil, Chloramphenicol, Ciclesonide, Cimetidine, Cisapride, Cisplatin, Cladribine, Clevidipine, Clobazam, Clobetasol, Clocortolone Acetate, Clofarabine, Clofibrate, Clonidine, Cloprednol, Coltuximab Ravtansine, Corticotropin, Cortisone, Cortisone Acetate, Cortivazol, Curcumin Sulfate, Cyclophosphamide, Cyproterone Acetate, Cytarabine
/ **D**abrafenib, Dacarbazine, Daclizumab, Dalfopristin, Danoprevir, Dapoxetine, Decitabine, Deferasirox, Deflazacort, Delavirdine Mesylate, Deoxyspergualin, Dexamethasone Isonicotinate, Dexrazoxane, Diazepam, Dicloxacillin Sodium, Diethylstilbestrol, Digitoxin, Dihydroergocornine, Dihydroergocristine, Dihydroergocryptine, Dimethyl Fumarate, Dimethyl Sulfoxide, Dinutuximab, Dipyrone, Dirithromycin, Disopyramide Phosphate, Ditiocarb, Docetaxel, Doramectin, Dothiepin, Doxepin Hydrochloride, Doxifluridine, Doxycycline
/ **E**chinacea, Eculizumab, Edetate Calcium Disodium, Efalizumab, Efonidipine, Elbasvir, Eliglustat Tartrate, Elvitegravir, Emapalumab, Epinephrine, Epirubicin, Epofolate, Epothilone B, Epothilone D, Eprinomectin [Usan:Usp:Inn], Ergoloid Mesylates, Eribulin, Esketamine Hydrochloride, Eslicarbazepine, Eslicarbazepine Acetate, Estradiol Benzoate, Estradiol Cypionate, Estradiol Dienanthate, Estradiol Valerate, Etanercept, Ethotoin, Ethyl Alcohol, Etoricoxib, Etravirine
/ **F**elbamate, Femring, Fentanyl, Flecainide Acetate, Floxacillin, Floxuridine, Fluclorolone, Flucytosine, Fludarabine, Fludrocortisone, Flunisolide, Fluocinolone Acetonide, Fluocortin, Fluocortolone, Fluperolone, Fluprednidene, Fluprednidene Acetate, Fluprednisolone, Flurithromycin, Fluticasone, Fluticasone Furoate, Fluticasone Propionate, Fluvastatin Sodium, Formestane, Formocortal, Fosaprepitant Dimeglumine, Fostamatinib
/ **G**allium Nitrate (Anhydrous), Gemcitabine, Gemtuzumab Ozogamicin, Glatiramer Acetate, Glycerol Phenylbutyrate, Golimumab, Gpi-1485, Griseofulvin, Guselkumab, Gusperimus
/ **H**alometasone, Human Adenovirus E Serotype 4 Strain Cl-68578 Antigen, Hydralazine Hydrochloride, Hydrocodone Bitartrate, Hydrocortisone, Hydrocortisone Aceponate, Hydrocortisone Acetate, Hydrocortisone Succinate, Hydroxyurea, Hypericin
/ **I**britumomab Tiuxetan, Idarubicin, Ifosfamide, Indisulam, 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, Ixabepilone, Ixekizumab
/ **K**etamine Hydrochloride, Ketazolam, Kitasamycin, Kos-1584
/ **L**anreotide, Lenalidomide, Lenvatinib, Lesinurad, Lestaurtinib, Linezolid, Lipegfilgrastim, Lisuride, Lomustine, Lorvotuzumab Mertansine, Lumefantrine, Lysergide
/ **M**agnacort, Manidipine, Matromycin, Mechlorethamine Hydrochloride, Medical Cannabis, Melengestrol, Melengestrol Acetate, Melphalan, Mepartricin, Mephenytoin, Mepolizumab, Meprednisone, Mequitazine, Metergoline, Methimazole, Methohexital Sodium, Methotrexate, Methylergonovine, Methylphenobarbital, Methylprednisolone Sodium Succinate, Methysergide, Metyrapone, Midecamycin, Miocamycin, Mirtazapine, Mirvetuximab Soravtansine, Mitemcinal, Mitomycin C, Mizoribine, Mometasone, Mometasone Furoate, Monomethyl Fumarate, Muromonab, Mycophenolate Mofetil, Mycophenolic Acid
/ **N**afcillin Sodium, Naloxone, Nelarabine, Niacin, Nicergoline, Nitric Oxide, Nk-012, Norfloxacin, Norgestimate, Noscapine
/ **O**binutuzumab, Ocrelizumab, Octreotide Acetate, Olaparib, Omega Interferon, Opipramol, Oritavancin, Orlistat, Orphenadrine, Osimertinib, Oxaliplatin, Oxcarbazepine, Oxethazaine, Oxybutynin, Oxymetholone, Ozanimod
/ **P**anobinostat, Paramethasone, Pasireotide, Peficitinib, Pegaspargase, Peginterferon Alfa-2a, Peginterferon Beta-1a, Pegvisomant, Pemetrexed, Penicillamine, Pentostatin, Peppermint Oil, Perampanel, Pergolide Mesylate, Phenelzine Sulfate, Phenylalanine, Phenylbutazone, Pilocarpine, Pimecrolimus, Piperaquine, Pirarubicin, Pirfenidone, Pomalidomide, Pralatrexate, Prednisolone, Prednisolone Hemisuccinate, Prednisolone Sodium Phosphate, Prednisone Acetate, Prednylidene, Probenecid, Procainamide Hydrochloride, Procarbazine, Propoxyphene Hydrochloride, Propylthiouracil
/ **Q**uinupristin
/ **R**abeprazole, Raloxifene, Raltitrexed, Ravulizumab, Remacemide, Resveratrol, Revefenacin, Ribociclib, Ridaforolimus, Rifabutin, Rifapentine, Rilonacept, Risankizumab, Rituximab, Rofecoxib, Rokitamycin, Roxithromycin, Rozanolixizumab, Rubella Virus Vaccine, Rufinamide, Rutin, Ruxolitinib
/ **S**aracatinib, Sarilumab, Secobarbital Sodium, Secukinumab, Selamectin, Seratrodast, Siltuximab, Sirukumab, Sitaxentan, Solithromycin, Somatostatin, Sotalol Hydrochloride, Stepronin, Stiripentol, Streptozocin, Sulfasalazine, Sulfinpyrazone
/ **T**edizolid Phosphate, Telithromycin, Temozolomide, Teniposide, Tepoxalin, Terbinafine, Terfenadine, Terguride, Teriflunomide, Tetracycline, Thalidomide, Theophylline, Thiamylal Sodium, Thioguanine, Thiopental Sodium, Thiotepa, Tildipirosin, Tilmicosin, Tixocortol, Tocilizumab, Tofisopam, Tofranil, Topiramate, Topiroxostat, Tositumomab, Trabectedin, Trametinib, Tranylcypromine Sulfate, Trastuzumab Emtansine, Tretinoin, Triclabendazole, Trifluridine, Trilostane, Trimipramine Maleate, Triptolide, Trofosfamide, Troglitazone, Tylosin, Tylvalosin, Typhoid Vaccine Live
/ **U**nii-J0086219x6
/ **V**alproic Acid, Vapreotide, Varicella Zoster Vaccine (Live/Attenuated), Vedolizumab, Vibrio Cholerae Cvd 103-Hgr Strain Live Antigen, Vilanterol, Vindesine, Vinorelbine, Vitamin E, Voclosporin, Vorinostat, Voxelotor
/ **W**artmannin, Win 55212-2 / **Y**ellow Fever Vaccine / **Z**afirlukast, Zidovudine

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:

PIK3CA p.E545A (SNV)

Drug-drug interactions

/ 167354-41-8 **/ 2**-Methoxyethanol **/ 5**-Fluorouracil **/ 6**-Mercaptopurine **/ 9**-(N-Methyl-L-Isoleucine)-Cyclosporin A
/ Abatacept, 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
/ Bacillus 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
/ Cabazitaxel, 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
/ Dabigatran 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
/ Echinacea, 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
/ Fedratinib, 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
/ Gallium 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
/ Halofantrine 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
/ Ibritumomab 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
/ Juxtapid **/ K**etamine Hydrochloride, Ketazolam
/ Laniquidar, 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
/ Magnacort, Mechlorethamine Hydrochloride, 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
/ Nabiximols, 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
/ Obinutuzumab, 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

Potentially ineffective treatments

Trastuzumab — Drug approval in patient disease: Approved*

Produced in CHO cell cultures, trastuzumab is a recombinant IgG1 kappa, humanized monoclonal antibody [A40276] that selectively binds with high affinity in a cell-based assay (Kd = 5 nM) to the extracellular domain of the human epidermal growth factor receptor protein (HER2) [FDA label]. It is used as a treatment of human epidermal growth factor receptor (HER)-2+ metastatic breast cancer, where there is a proven amplification of the HER-2 oncogene or over-expression of the HER-2 protein in tumours. It is suggested that the overexpression or gene amplification of HER2 has been found in about 20–30% of breast cancers and elevated activation of HER2 triggers multiple downstream pathways leading to abnormal proliferation of cancer cells [A121]. Trastuzumab binds to HER2 and suppresses cancer cells growth, proliferation, and survival directly and indirectly [A121].
In December 2017, FDA approved Ogivri (trastuzumab-dkst) as a biosimilar to Herceptin (trastuzumab) for the treatment of patients with breast or metastatic stomach cancer (gastric or gastroesophageal junction adenocarcinoma) whose tumors overexpress the HER2 gene (HER2+). It displays biosimilar properties as Herceptin according to clinical data. While Ogivri is the first biosimilar approved in the U.S. for the treatment of breast cancer or stomach cancer, it is the second biosimilar approved in the U.S. for the treatment of cancer. Herzuma (trastuzumab-pkrb) is a biosimilar drug approved in December 2018 for the treatment of HER2-overexpressing breast cancer. KANJINTI (trastuzumab-anns) is another biosimilar approved by the FDA in June 2019.[L6715](DB00072)

Detected variants supporting this treatment effect:
PIK3CA p.E545A (SNV)

Treatments with potential for adverse reaction

No treatments with potential for adverse reaction 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
Impact of eHealth-support on Quality of Life in Metastatic Breast Cancer Patients Treated With Palbociclib and Endocrine Therapy (PRECYCLE)	Phase 4; NCT03220178	Fulvestrant	Breast Neoplasms	Mainz	Age: 18, Gender: Female
Eligibility criteria: **Inclusion:**ERBB2 protein expression: no expression, PGR protein expression, ESR1 protein expression					
Study Assessing the Efficacy and Safety of Alpelisib + Nab-paclitaxel in Subjects With Advanced TNBC Who Carry Either a PIK3CA Mutation or Have PTEN Loss Without PIK3CA Mutation (EPIK-B3)	Phase 3; NCT04251533	Alpelisib	Breast Neoplasms	Erlangen, Leipzig, Muenchen, Bavaria, ...	Age: 18, Gender: Both
Eligibility criteria: **Inclusion:**ERBB2 protein expression: no expression, ESR1 protein expression: no expression, PGR protein expression: no expression **Stratification:**PTEN SCNA: loss, PIK3CA mutation					
A Study Evaluating the Efficacy and Safety of GDC-0077 + Palbociclib + Fulvestrant vs Placebo + Palbociclib + Fulvestrant in Patients With PIK3CA-Mutant, Hormone Receptor-Positive, Her2-Negative, Locally Advanced or Metastatic Breast Cancer	Phase 2/ Phase 3; NCT04191499	Fulvestrant	Breast Neoplasms	Berlin, Bonn, Dresden, ...	Age: 18, Gender: Both
Eligibility criteria: **Inclusion:**PIK3CA mutation, ERBB2 protein expression: no expression, ESR1 protein expression, PGR protein expression					
Study Assessing the Efficacy and Safety of Alpelisib Plus Fulvestrant or Letrozole, Based on Prior Endocrine Therapy, in Patients With PIK3CA Mutation With Advanced Breast Cancer Who Have Progressed on or After Prior Treatments (BYLieve)	Phase 2; NCT03056755	Alpelisib; Fulvestrant	Breast Neoplasms	Augsburg, Berlin, Dresden, ...	Age: 18, Gender: Both
Eligibility criteria: **Inclusion:**PGR protein expression, ESR1 protein expression, ERBB2 protein expression: no expression, PIK3CA mutation					
The XENERA™ 1 Study Tests Xentuzumab in Combination With Everolimus and Exemestane in Women With Hormone Receptor Positive and HER2-negative Breast Cancer That Has Spread	Phase 2; NCT03659136	Everolimus	Breast Neoplasms	Erlangen, Heidelberg, Karlsruhe, ...	Age: 18, Gender: Female
Eligibility criteria: **Inclusion:**PGR protein expression, ESR1 protein expression, ERBB2 protein expression: no expression					
Dose EScalation Induction of EvERolimus (Desiree)	Phase 2; NCT02387099	Everolimus	Breast Neoplasms	Bielefeld, Dresden, Sachsen, Erlangen, ...	Age: 18, Gender: Female
Eligibility criteria: **Inclusion:**PGR protein expression, ERBB2 protein expression, ESR1 protein expression					

REFERENCES

The following references were cited in this report:

André F et al. Alpelisib for PIK3CA-Mutated, Hormone Receptor-Positive Advanced Breast Cancer. The New England journal of medicine. 2019 05; 380(20) (PubMed ID: 31091374)

Xu YC et al. Integration of Receptor Tyrosine Kinases Determines Sensitivity to PI3Kα-selective Inhibitors in Breast Cancer. Theranostics. 20177(4) (PubMed ID: 28382169)

André F et al. Molecular Alterations and Everolimus Efficacy in Human Epidermal Growth Factor Receptor 2-Overexpressing Metastatic Breast Cancers: Combined Exploratory Biomarker Analysis From BOLERO-1 and BOLERO-3. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2016 06; 34(18) (PubMed ID: 27091708)

Chandarlapaty S et al. Frequent mutational activation of the PI3K-AKT pathway in trastuzumab-resistant breast cancer. Clinical cancer research : an official journal of the American Association for Cancer Research. 2012 Dec; 18(24) (PubMed ID: 23092874)

Weigelt B et al. PIK3CA mutation, but not PTEN loss of function, determines the sensitivity of breast cancer cells to mTOR inhibitory drugs. Oncogene. 2011 Jul; 30(29) (PubMed ID: 21358673)

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.

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.

MH Guide uses and contains data and information obtained from third-party sources. MH uses reasonable efforts to ensure that this information is as accurate as possible in a tightly controlled curation process. However, MH cannot guarantee that data from any third party are accurate, comprehensive, and complete. Thus, MH Guide may not contain all relevant or all up-to-date information. Third-party databases or other sources in MH Guide may only be updated from time to time with new or revised information.

MH Guide has not been cleared or approved by the U.S. Food and Drug Administration (FDA). However, MH Guide using VCF as input is offered as a bioinformatics service under CLIA.
In the European Union, Molecular Health Guide (MH Guide) is registered as an in vitro diagnostic medical device (IVD). The reports MH Guide and MH Guide Premium are covered by the IVD registration. MH Guide Onco Report, MH Guide Onco Report+ and MH Guide Onco Report Premium are for non-clinical use.

MH is the legal manufacturer of MH Guide as a stand-alone software, and the statutory provisions of the German Medical Devices Act (MPG) and the European Directive 98/79/EC apply to MH. We therefore maintain a quality management system according to EN ISO 13485 for the scope of “Design, Development and Manufacture of software systems for the integrated analysis of clinical and genomic patient data to support treatment decisions and provision of related services”. MH has also received CLIA certification and CAP accreditation for the provision of MH Guide as a dry lab service to clinical laboratories in the US.

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