The HudsonAlpha CLINICAL SERVICES LAB

Patient name	*****	Diagnosis	NSCLC
Patient ID	GBW-029	ICD-10-CM code	—
Case ID	EU005620	MeSH ID/term	D002289 (Carcinoma, Non-Small-Cell Lung)
Date of birth	*****	Additional MeSH IDs	D008175

Sex	Female	Primary tumor site	—	Collected	—	Ordering physician	Dr. Franklin Richards
Ethnicity	HSA	Surgical pathology	—	Tumor cellularity	0%	NPI	—
Country	US	Tissue type	Lung	Barcode	-	Facility	NYU
Trial ZIP code	77381	Metastatic	yes	Sample type	FFPE	Email	—
		General dataset ID	111436917024	Labtest	HA-VCF-TST170	Phone	—
		CVI dataset ID	111436917024	Organizational unit	HudsonAlpha-Valid	Fax	—
		Software version	4.3.7			Product	MH Guide
						Report	MH Guide

INTERPRETATION

Mutational status of commonly mutated genes in the patient disease

ABCB1 not identified	ALK not identified	BRAF not identified	EGFR not identified	ERBB2 not identified	KRAS 1 SNV	MET not identified	NF1 not identified	NRAS not identified	PIK3CA not identified	RET not identified
ROS1 not identified	STK11 1 del	TP53 not identified								

A pathohistological evaluation was performed that confirmed the diagnosis of lung adenocarcinoma. Microdissection was performed, resulting in a tumor cellularity of 50%.

The resultant sample was submitted for a Comprehensive Genomic Profile test, which evaluated the sample for DNA and RNA alterations. A review of the resultant genomic information was performed in conjunction with patient information, including a review of the patient history, diagnosis, and clinical scenario.

Although numerous variants were detected in this tumor, the most relevant to patient management is KRAS G12C. While this confers resistance to most EGFR inhibitors often used in lung adenocarcinomas, and has been notoriously difficult to treat, new therapies have been and are being developed to target this mutation that is frequently observed in these tumors. Sotorasib has now been approved by the FDA to treat NSCLC patients with the KRAS G12C mutation. Adagrasib has also been approved and targets the same mutation. Interestingly, patients with concurrent STK11 mutations (and a lack of KEAP1 mutations) have even greater likelihood of response to these therapies, with an ORR as high as 50%.

While other mutations are present and some are associated with response to therapies, such as the MDM2 copy number alteration, these are investigational or off-label and should not be of further consideration unless more established therapies are exhausted. These are listed within this report.

Other variants not considered to have definitive clinical significance at this time are listed at the end of this report, and should not be considered as clinically impactful.

SUMMARY

Overview of potential treatment impacts

3 Effective | 5 Ineffective | 0 Safety

Overview of prognostic and diagnostic findings

0 Prognostic | 0 Diagnostic

Clinical trials found

3 Trials

Potential impact	Treatment	Drug approval	Biomarker	VAF	Biomarker score		Trials
Effective	Sotorasib	Investigational	KRAS p.G12C (SNV)	13.30%	AMP Tier I A	7 Clinically Approved	1

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Patient ID GBW-029
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Diagnosis NSCLC
ICD-10-CM code —
MeSH ID/term D002289 (Carcinoma, Non-Small-Cell Lung)
Additional MeSH IDs D008175

Potential impact	Treatment	Drug approval	Biomarker	VAF	Biomarker score		Trials
Effective	Idasanutlin	Other	MDM2 Copy number GAIN (CNA)	—	AMP Tier II D	3 Preclinical	1
Effective	Buparlisib Sirolimus	Other Off-label	STK11 p.F255fs (del)	16.15%	AMP n/a	1 Preclinical	2
Ineffective	Gefitinib	Approved*	KRAS p.G12C (SNV)	13.30%	AMP Tier I B	6 Clinical	—
Ineffective	Erlotinib	Approved*	KRAS p.G12C (SNV)	13.30%	AMP Tier I B	6 Clinical	—
Ineffective	Crizotinib	Approved*	KRAS p.G12C (SNV)	13.30%	AMP Tier II D	4 Clinical	—
Ineffective	Afatinib	Approved*	KRAS p.G12C (SNV)	13.30%	AMP Tier II D	3 Preclinical	—
Ineffective	Osimertinib	Approved*	KRAS p.G12C (SNV)	13.30%	AMP Tier II D	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; 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.

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	1	2.46
Synonymous SNVs	0	0.00
Deletions, Insertions, Indels	1	2.46

BIOMARKER DETAILS

KRAS p.G12C (SNV)

The small GTPase KRAS activates the RAS/MAPK signaling pathway to promote cell proliferation and survival. In preclinical studies this variant promotes transformation due to enhanced downstream signaling. KRAS mutations at codon 12 are seen frequently in lung cancer (28%). Clinical studies of patients with lung cancer showed that the tumor with this mutation is resistant to EGFR inhibitors erlotinib and gefitinib. This variant conferred resistance to crizotinib in ALK fusion rearranged lung cancer. The FDA has recently approved sotorasib and adagrasib for use in NSCLC with KRAS G12C mutations. In 51 response-evaluable patients in the KRYSTAL study, 23 (45%) had a partial response and 26 had stable disease. In a sub-population of patients with co-mutations in STK11 (n = 14), the objective response rate (ORR) was 64%, which is considered high for tumors harboring KRAS G12C mutations. In the CodeBreaK 100 clinical trial (NCT03600883), in 124 evaluable patients with locally advanced or metastatic disease progressing after an immune checkpoint inhibitor and/or platinum-based chemotherapy, the objective response rate with sotorasib was 36% (95% CI, 28%-45%) with 56% of patients maintaining a response longer than 6 months. The disease control rate—comprised of patients achieving complete and partial responses or stable disease–was 81% (95% CI, 73%-87%).

PubMed ID
28492898, 28961841, 31331945, 31612108, 31666701, 32955176

The small GTPase KRAS activates the RAS/MAPK signaling pathway to promote cell proliferation and survival. In preclinical studies this variant promotes transformation due to enhanced downstream signaling. KRAS mutations at codon 12 are seen frequently in lung cancer (28%). Sotorasib is indicated for NSCLC with KRAS.G12C by the FDA. Clinical studies of patients with lung cancer showed that the tumor with this mutation is resistant to EGFR inhibitors erlotinib and gefitinib. Patients with such tumors had also no clinical benefit of monotherapy with MEK inhibitors selumetinib or trametinib compared to standard therapy. This variant conferred resistance to crizotinib in ALK fusion rearranged lung cancer. Preclinical models with additional amplified MET and EGFR.T790M mutation showed that this KRAS mutation confers resistance to afatinib, osimertinib, and MET inhibitor capmatinib but retains sensitivity to combination treatment with capmatinib and afatinib. Other preclinical data in lung cancer cells with mutated FGFR2 revealed that this KRAS codon 12 mutation confers resistance to FGFR inhibitor erdafitinib. While MEK inhibitor monotherapy with binimetinib, cobimetinib or refametinib showed only moderate sensitivity in lung cancer cells, the strategy of dual-node inhibition demonstrated pronounced synergistic effects to combination therapy with trametinib and ponatinib, trametinib and afatinib, or selumetinib combined with afatinib, neratinib, or dacomitinib.

PubMed ID
31612108, 28492898, 31331945, 31666701, 28961841

Potential impact	Treatment	Drug approval	Biomarker score	
Effective	Sotorasib	Investigational	AMP Tier I A	7 Clinically Approved
Ineffective	Gefitinib	Approved*	AMP Tier I B	6 Clinical
Ineffective	Erlotinib	Approved*	AMP Tier I B	6 Clinical
Ineffective	Crizotinib	Approved*	AMP Tier II D	4 Clinical
Ineffective	Afatinib	Approved*	AMP Tier II D	3 Preclinical

Potential impact	Treatment	Drug approval	Biomarker score
Ineffective	Osimertinib	Approved*	AMP Tier II D; 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.

MDM2 Copy number GAIN (CNA)

The E3 ubiquitin-protein ligase MDM2 activates the proteasomal degradation of TP53 to inhibit cell cycle arrest and apoptosis. MDM2 amplification with protein overexpression abrogates the tumor-suppressive effects of the TP53 pathway. Preclinical studies in lung cancer cells with MDM2 amplification in the presence of wild-type TP53 protein revealed sensitivity to MDM2 inhibitor idasanutlin.

PubMed ID
26200271, 28351930

Potential impact	Treatment	Drug approval	Biomarker score
Effective	Idasanutlin	Other	AMP Tier II D; 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.

STK11 p.F255fs (del)

STK11 is a serine/threonine-protein kinase that negatively regulates the mTOR pathway. STK11 functions as a tumor suppressor and is mutated in a variety of cancers. Frameshift mutations are likely to be inactivating. In preclinical studies, STK11 deficiency was shown to increase mTOR signaling. However, STK11 inactivation did not sensitize lung cancer cells to treatment with the mTOR inhibitor sirolimus alone, but did sensitize them to the combination of sirolimus and the PI3K inhibitor buparlisib. In independent cohorts of lung adenocarcinoma (LUAC) patients (with or without KRAS mutation), STK11 mutations were associated with inferior clinical outcome with PD-1/PD-L1 blockade. In addition, STK11 deficiency reduced CD8 T-cell infiltration and PD-L1 expression in human lung cancer cells and tumor samples and promoted primary resistance to PD-1/PD-L1 blockade in mouse models of KRAS-mutant LUAC. However, some patients also responded to immunotherapy, so this association requires further investigation and may also depend on co-occurring mutations. Germline mutations in STK11 are associated with Peutz-Jeghers syndrome, which is a cancer predisposition syndrome.

PubMed ID
15231735, 31401029, 30825612, 29773717, 26833127, 26027660

Potential impact	Treatment	Drug approval	Biomarker score
Effective	Buparlisib + Sirolimus	Other, 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.

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.

Sotorasib — Drug approval in patient disease: Investigational

AMG-510 is an acrylamide derived KRAS inhibitor developed by Amgen and is currently undergoing clinical trials for solid tumors with KRAS G12C mutations.[A187547,A187556] This mutation makes up >50% of all KRAS mutations.[A187550] It is the first experimental KRAS inhibitor.[A187547] The drug [MRTX849] is also currently being developed and has the same target.[A187547](DB15569)

Detected variants supporting this treatment effect:
KRAS p.G12C (SNV)

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

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Idasanutlin — Drug approval in patient disease: Other

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)

Detected variants supporting this treatment effect:
MDM2 Copy number GAIN (CNA)

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

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Buparlisib — Drug approval in patient disease: Other
Sirolimus — Drug approval in patient disease: Off-label

Buparlisib has been used in trials studying the treatment and basic science of Lymphoma, Metastases, Lung Cancer, Solid Tumors, and Breast Cancer, among others.(DB11666)
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:
STK11 p.F255fs (del)

Drug-drug interactions
/ **1**67933-07-5 / **2**-Methoxyethanol / **5**-Fluorouracil / **6**-Mercaptopurine / **9**-(N-Methyl-L-Isoleucine)-Cyclosporin A
/ **A**bametapir, Abatacept, Abetimus, Abiraterone, Acalabrutinib, Acetaminophen, Acetazolamide, Acteoside, Actinomycin D, Adalimumab, Adenovirus Type 7 Vaccine Live, Afatinib, Afelimomab, Aldesleukin, Alefacept, Alemtuzumab, Alpelisib, Altretamine, Ambrisentan, Amdray, Aminoglutethimide, Amitriptyline Hydrochloride, Amobarbital, Amprenavir, Amsacrine, Anakinra, Anthrax Vaccine, Anti-Thymocyte Globulin (Equine), Antithymocyte Immunoglobulin (Rabbit), Apixaban, Apomorphine Hydrochloride, Apremilast, Aprepitant, Aprobarbital, Aripiprazole, Aripiprazole Lauroxil, Arsenic Trioxide, Artemether, Astemizole, Asunaprevir, Atazanavir, Avasimibe, Axitinib, Azacitidine, Azathioprine, Azelastine, Azimilide
/ **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 Sodium Phosphate, Bevacizumab, Bexarotene, Bicalutamide, Bifonazole, Biricodar, Black Cohosh, Bleomycin, Blephamide S.O.P., Bleselumab, Blinatumomab, Boceprevir, Bortezomib, Bosentan, Bosutinib, Brentuximab Vedotin, Brequinar, Briakinumab, Brodalumab, Bromocriptine, Buprenophine, Busulfan, Butalbital

/ **C**abazitaxel, Cabergoline, Calcitriol, Canagliflozin, Canakinumab, Cannabidiol, Capecitabine, Capsaicin, Carboplatin, Carfilzomib, Carmustine, Castanospermine, Cepeginterferon Alfa-2b, Cephradine, Cerebyx, Ceritinib, Cerivastatin Sodium, Certolizumab Pegol, Chlorambucil, Chloramphenicol, Chloroquine, Chlorpheniramine Maleate, Chlorpromazine, Ciclesonide, Cilostazol, Cimetidine, Ciprofloxacin, Cisapride, Cisplatin, Citalopram, Cladribine, Clobazam, Clobetasol, Clobetasol Propionate, Clocortolone Acetate, Clofarabine, Clofazimine, Clofibrate, Clonidine, Cnto-1959, Cobicistat, Colchicin, Conivaptan Hydrochloride, Copanlisib, Cortef Acetate, Curcumin Sulfate, Cyclo((4r)-4-(2-Aminoethylcarbamoyloxy)-L-Prolyl-L-Phenylglycyl-D-Tryptophyl-L-Lysyl-4-O-Benzyl-L-Tyrosyl-L-Phenylalanyl-), Cyclophosphamide, Cyclosporine, Cyproterone Acetate, Cytarabine
/ **D**abrafenib, Dacarbazine, Daclatasvir Dihydrochloride, Daclizumab, Dacomitinib, Dalfopristin, Danazol, Danoprevir, Dapoxetine, Dapsone, Darbepoietin, Dasatinib, Daunorubicin, Decitabine, Deferasirox, Delavirdine Mesylate, Deoxyspergualin, Dermotic, Desipramine Hydrochloride, Desvenlafaxine, Deutetrabenazine, Dexamethasone Isonicotinate, Dexloxiglumide, Dexnorgestrel Acetime, Dexrazoxane, Dextromethorphan, Dhea Sulfate, Diazepam, Dicloxacillin Sodium, Diethylstilbestrol, Diflucortolone, Dihydroergocornine, Dihydroergocristine, Dihydroergocryptine, Dihydroergotamine Mesylate, Dimethyl Fumarate, Dimethyl Sulfoxide, Dinutuximab, Dipyrone, Disopyramide, Disulfiram, Ditiocarb, Docetaxel, Domperidone, Doravirine, Dovitinib, Doxifluridine, Doxorubicin, Doxycycline, Duloxetine, Dutasteride
/ **E**chinacea, Eculizumab, Efalizumab, Efavirenz, Elacridar, Elagolix Sodium, Elbasvir, Elexacaftor, Elvitegravir, Emapalumab, Enasidenib, Entrectinib, Enzalutamide, Epinephrine, Epirubicin, Eplerenone, Ergoloid Mesylate, Ergonovine, Ergotamine Tartrate, Eribulin, Erlotinib, Esketamine Hydrochloride, Eslicarbazepine, Eslicarbazepine Acetate, Esomeprazole Magnesium, Estradiol, Estradiol 3-Acetate, Estradiol Benzoate, Estradiol Cypionate, Estradiol Dienanthate, Estramustine, Estrone, Etanercept, Ethinylestradiol, Ethyl Alcohol, Etoposide, Etoricoxib, Etravirine
/ **F**avipiravir, Fedratinib, Felbamate, Fentanyl, Filgrastim, Finasteride, Floxacillin, Floxuridine, Fluclorolone, Fluconazole, Flucytosine, Fludarabine, Fluocortin, Fluocortolona, Fluorometolona, Fluperolone, Fluprednidene, Flutamide, Fluticasone, Fluticasone Furoate, Fluticasone Propionate, Fluvastatin Sodium, Fluvoxamine Maleate, Formestane, Fosnetupitant, Fostamatinib, Fusidic Acid
/ **G**allium Nitrate (Anhydrous), Gefitinib, Gemcitabine, Gemtuzumab Ozogamicin, Genistein, Gestodene, Glasdegib, Glatiramer Acetate, Glecaprevir, Glyburide, Glycerol Phenylbutyrate, Golimumab, Gpi-1485, Griseofulvin, Gusperimus
/ **H**alofantrine Hydrochloride, Human Adenovirus E Serotype 4 Strain Cl-68578 Antigen, Human Interferon Omega-1, Hydralazine, Hydrocortamate, Hydrocortisone Butyrate, Hydrocortisone Cypionate, Hydrocortisone Sodium Phosphate, Hydrocortisone Succinate, Hydroxychloroquine, Hydroxyprogesterone Caproate, Hydroxyurea, Hydroxyzine, Hypericin
/ **I**britumomab Tiuxetan, Ibrutinib, Icotinib, Idarubicin, Idelalisib, Ifosfamide, Iloperidone, Imatinib, Imipramine, Indalpine, Indinavir, Indisulam, Indomethacin, Infliximab, Interferon Alfa-2a, Recombinant, Interferon Alfa-2b, Recombinant, Interferon Alfa-N1, Interferon Alfa-N3, Interferon Alfacon-1, Interferon Beta-1b, Interferon Gamma-1b, Irbesartan, Irinotecan, Isoniazid, Istradefylline, Ivacaftor, Ivosidenib, Ixekizumab
/ **J**uxtapid / **K**etamine, Ketazolam
/ **L**-Phenylalanine, Laniquidar, Lanreotide, Lansoprazole, Lapatinib, Ledipasvir, Lemborexant, Lenalidomide, Lenvatinib, Lesinurad, Lestaurtinib, Letermovir, Levacetylmethadol, Levamlodipine, Levothyroxine Sodium, Lidex-E, Lidocaine, Linagliptin, Linezolid, Lisuride, Lomustine, Lonafarnib, Lorlatinib, Losartan, Lovastatin, Loxapine, Lumefantrine, Lysergide
/ **M**echlorethamine, Medical Cannabis, Medroxyprogesterone Acetate, Melengestrol Acetate, Melphalan, Mepolizumab, Mequitazine, Metergoline, Methadone, Methimazole, Methotrexate, Methylene Blue, Methylergonovine, Methylphenobarbital, Methylprednisolone Succinate, Methysergide, Metronidazole, Metyrapone, Miconazole, Midostaurin, Mifepristone, Milnacipran, Mirabegron, Mirtazapine, Mitomycin C, Mitotane, Mitoxantrone, Mizoribine, Mometasone, Mometasone Furoate, Monomethyl Fumarate, Muromonab, Mycobutin, Mycophenolate Mofetil, Mycophenolic Acid
/ **N**abiximols, Nafcillin Sodium, Naloxone, Nateglinide, Nefazodone Hydrochloride, Nelarabine, Nelfinavir, Neratinib, Netupitant, Nevirapine, Niacin, Nicergoline, Nilotinib, Nitrogen Monoxide, Nk-012, Norethindrone, Norfloxacin, Norgestrel, Noscapine
/ **O**binutuzumab, Ocrelizumab, Olaparib, Ondansetron, Ont-093, Oritavancin Diphosphate, Orlistat, Orphenadrine, Osilodrostat Phosphate, Osimertinib, Oxaliplatin, Oxcarbazepine, Oxethazaine, Oxybutynin, Oxycodone, Oxymetholone, Ozanimod Hydrochloride
/ **P**aclitaxel, Palbociclib, Paliperidone, Panobinostat, Paritaprevir, Paroxetine Mesylate, Pazopanib, Peficitinib, Pegaspargase, Peginterferon Alfa-2a, Peginterferon Beta-1a, Pegvisomant, Pemetrexed, Penicillamine, Pentamidine, Pentobarbital, Pentostatin, Peppermint Oil, Perampanel, Pergolide Mesylate, Phenelzine Sulfate, Phenobarbital, Phenylbutazone, Phenytoin, Pibrentasvir, Pilocarpine, Pimecrolimus, Pimozide, Piperaquine, Pirarubicin, Pirfenidone, Plavix, Pomalidomide, Ponatinib, Posaconazole, Pralatrexate, Pralsetinib, Praziquantel, Prednisolone Hemisuccinate, Prednisolone Phosphate, Prednisone Acetate, Primaquine, Primidone, Probenecid, Procarbazine, Progesterone, Propafenone, Propofol, Propoxyphene Hydrochloride, Propranolol, Propylthiouracil
/ **Q**uetiapine, Quinacrine, Quinidine, Quinine Sulfate, Quinupristin
/ **R**abeprazole, Raloxifene, Raltitrexed, Ravulizumab, Regorafenib, Relugolix, Remacemide, Remdesivir, Reserpine, Resveratrol, Revefenacin, Ribociclib, Rifampicin, Rifamycin Sodium, Rifapentin, Rifaximin, Rilonacept, Rilpivirine, Ripretinib, Risankizumab, Risperidone, Rituximab, Rivaroxaban, Rofecoxib, Rolapitant, Romidepsin, Rosuvastatin, Roxithromycin, Rozanolixizumab, Rubella Virus Vaccine, Rucaparib, Rufinamide, Rutin, Ruxolitinib
/ **S**afinamide Mesylate, Salmeterol, Saquinavir, Saracatinib, Sarilumab, Saxagliptin, Schembl44295, Schembl6195972, Secobarbital Sodium, Secukinumab, Selumetinib, Seproxetine, Seratrodast, Sildenafil, Siltuximab, Simeprevir, Simvastatin, Sirukumab, Sitaxentan, Somatostatin, Sorafenib, St. John'S Wort, Stepronin, Stiripentol, Streptozocin, Sulfasalazine, Sulfinpyrazone, Sunitinib, Suvorexant
/ **T**acrolimus, Tadalafil, Tamoxifen, Tariquidar, Tegafur, Temozolomide, Teniposidum, Tepoxalin, Terbinafine, Terfenadine, Terguride, Teriflunomide, Tesmilifene, Testosterone, Testosterone Heptanoate, Testosterone Undecanoate, Tetracycline, Thalidomide, Thiamylal Sodium, Thioguanine, Thiotepa, Ticagrelor, Tipranavir, Tixocortol, Tocilizumab, Topicort, Topiroxostat, Toremifene, Tositumomab, Trabectedin, Trastuzumab Emtansine, Trazodone, Tretinoin, Triclabendazole, Trifluridine, Triptolide, Trofosfamide, Troglitazone, Trokendi Xr, Typhoid Vaccine Live
/ **U**denafil
/ **V**albenazine, Valproic Acid, Vandetanib, Vapreotide Acetate, Vardenafil, Varicella Zoster Vaccine (Live/Attenuated), Vedolizumab, Velpatasvir, Venetoclax, Vibrio Cholerae Cvd 103-Hgr Strain Live Antigen, Vicriviroc, Vilanterol, Vinblastine, Vincristine, Vindesine, Vinorelbine, Vitamin E, Voclosporin, Voriconazole, Vorinostat, Vortioxetine, Voxelotor, Voxilaprevir, Vx-661

/ **W**artmannin, Wc-3035 / **Y**ellow Fever Vaccine / **Z**afirlukast, Zaleplon, Zidovudine, Zimelidine, Ziprasidone, Zontivity, Zosuquidar

Potentially ineffective treatments

Gefitinib

Drug approval in patient disease: Approved*

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:
KRAS p.G12C (SNV)

Erlotinib

Drug approval in patient disease: Approved*

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:
KRAS p.G12C (SNV)

Crizotinib

Drug approval in patient disease: Approved*

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:
KRAS p.G12C (SNV)

Afatinib

Drug approval in patient disease: Approved*

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:
KRAS p.G12C (SNV)

Osimertinib

Drug approval in patient disease: Approved*

Osimertinib is an oral, third-generation epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor (TKI) drug developed by AstraZeneca Pharmaceuticals. Its use is indicated for the treatment of metastatic non-small cell lung cancer (NSCLC) in cases where tumour EGFR expression is positive for the T790M mutation as detected by FDA-approved testing and which has progressed following therapy with a first-generation EGFR tyrosine kinase inhibitor. Approximately 10% of patients with NSCLC have a rapid and clinically effective response to EGFR-TKIs due to the presence of specific activating EGFR mutations within the tumour cells. More specifically, deletions around the LREA motif in exon 19 and exon 21 L858R point mutations are correlated with response to therapy.
Development of third-generation EGFR-TKIs, such as osimertinib, has been in response to altered tumour resistance patterns following treatment and toxic side effects that impact patient quality of life. Treatment with first-generation EGFR-TKIs (gefitinib and erlotinib) has been associated with the development of resistance through activating mutations in the EGFR gene. Second-generation EGFR-TKIs (afatinib and dacomitinib) were then developed to be more potent inhibitors, although their use is associated with increased toxicity through nonspecific targeting of wild-type EGFR. In contrast, third-generation inhibitors are specific for the gate-keeper T790M mutations which increases ATP binding activity to EGFR and result in poor prognosis for late-stage disease. Furthermore, osimertinib has been shown to spare wild-type EGFR during therapy, thereby reducing non-specific binding and limiting toxicity.(DB09330)

Detected variants supporting this treatment effect:
KRAS p.G12C (SNV)

Treatments with potential for adverse reaction

No treatments with potential for adverse reaction reported

DETECTED VARIANTS

This section provides details on all detected variants matching the filter criteria. VAF = variant allele frequency; PF = population frequency.

Protein	Coding DNA	Genomic	Type	Total reads	VAF	PF	AMP score
—	—	MSS	MSI	—	—	—	—
ERBB4 p.G668V	ENST00000342788.4 c.2003G>T	chr2 g.212495263C>A	SNV	1598	37.80%	—	—
KRAS p.G12C	ENST00000256078.4 c.34G>T	chr12 g.25398285C>A	SNV	1850	13.30%	—	Tier IA
MDM2 Copy number GAIN	—	chr12 Chr12:69201956_69239214gain	CNA	—	—	—	Tier IID
PTCH1 p.G1163S	ENST00000331920.6 c.3487G>A	chr9 g.98212185C>T	SNV	5170	46.96%	0.05%	—
STK11 p.F255fs	ENST00000326873.7 c.762del	chr19 g.1221239del	del	5914	16.15%	—	—

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
Sotorasib Activity in Subjects With Advanced Solid Tumors With KRAS p.G12C Mutation (CodeBreak 101) Eligibility criteria: **Inclusion:**KRAS SNV: p.G12C	NCT04185883	Sirolimus; Sotorasib	Neoplasms; Solid tumor	Houston, Texas (30 miles)	Age: 18, Gender: Both
Tumor-Agnostic Precision Immuno-Oncology and Somatic Targeting Rational for You (TAPISTRY) Platform Study	NCT04589845	Idasanutlin	Neoplasms; Solid tumor	Houston, Texas (30 miles)	
Serial Measurements of Molecular and Architectural Responses to Therapy (SMMART) PRIME Trial Eligibility criteria: **Stratification:**ERBB2 protein expression, BCR fusion gene: ABL1	NCT03878524	Sirolimus	Neoplasms	Portland, Oregon (1809 miles)	Age: 21, Gender: Both

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 3 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) Safety is available and if it fulfills one of the following criteria: Population frequency (general) greater than 0.10, Population frequency (ethnicity) greater than 0.10, or Population frequency (max. ethnicity) greater than 0.10.
An indel variant is identified as a potentially benign polymorphism and filtered out if no matching CVI of impact(s) Safety is available and if it fulfills one of the following criteria: Population frequency (general) greater than 0.10, Population frequency (ethnicity) greater than 0.10, or Population frequency (max. ethnicity) greater than 0.10.

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	13.00	100.00	100.00
Indels	10.00	12.00	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	8.00	95.00	95.00
Indels	5.00	8.00	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, 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" also denotes 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 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 bioinformatics pipeline. It assists clinical laboratories, board-certified Molecular Pathologists, or Molecular Geneticists in the preparation of a patient's clinical report.
MH Guide includes:

1. Primary identification of genetic alterations from next-generation sequencing (NGS) data by the variant detection pipeline, either from a 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.
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 the biomedical reference information.
5. Computational integration of the above information into a clinical report which includes a summary of potentially effective medications, potentially ineffective medications, and medications that may pose a higher risk of adverse reactions for the individual patient. In addition, MH Guide provides information on reportable variants that may be predictive of an increased risk for cancer progression. Also, prognostic and diagnostic biomarkers may be detected and shown in the context of the disease given.
6. Generation of a customizable clinical report by a trained user with information on clinical validity of the evidence shown, as well as links to the sources of evidence of the information displayed for full traceability.

MH Guide is designed for processing molecular data from patients diagnosed with cancer. Diseases beyond this are out of the scope of the application. 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 prior to submission to MH Guide for analysis.

The identification of a genomic biomarker does not necessarily imply pharmacologic effectiveness or ineffectiveness. The medications identified by the users may or may not be suitable for use on a particular patient. Thus, the clinical report does not guarantee that any particular medication will be effective in the treatment of any particular condition. Also, the absence of a known biomarker does not imply effectiveness, ineffectiveness, or concerns regarding a medication selected by the treating physician.
Any genetic findings beyond the intended use of MH Guide are not annotated and reported, even though the corresponding variant's risk factors may be identified by the bioinformatics pipeline in MH Guide.

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.

If genetic aberrations are submitted in the format of a VCF file to MH Guide, the quality of the results from MH Guide depends on the quality of the input data submitted. The accuracy, analytic sensitivity, and specificity of the variant lists is the sole responsibility of the trained users.

MH Guide uses different analysis types based on the input formats. The analysis type is provided in the header section of the report and is important for the final decision on the results for the clinical reports.

The design and the content of a clinical report are at the discretion of the users. A clinical report contains the results analyzed and interpreted by the trained users, such as the Molecular Pathologist or Geneticist. The trained user is neither a contractor nor an employee of Molecular Health.

Variants are prioritized using the filter settings in MH Guide, defined by the trained user. The information provided in the report must be evaluated by the ordering/treating physician in conjunction with all other relevant clinical information of the patient, such as patient and family history, physical examinations, information from other diagnostic tests, and patient preferences, before the appropriate course of medication is selected. 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 Molecular Health or the Molecular Health 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.

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

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. Molecular Health uses reasonable efforts to ensure that this information is as accurate as possible in a tightly controlled curation process. However, Molecular Health cannot guarantee that data from third parties are accurate, comprehensive, and complete. As a result, MH Guide may not contain all relevant or up-to-date information. Information from third-party databases or other

sources may only be updated from time to time.

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.

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