Patient ID	quality-check-2	Diagnosis	sigmoid adenocarcinoma …
Case ID	EU000421	ICD-10-CM code	—
Date of birth	—	MeSH ID/term	D015179 (Colorectal Neopl…
		Additional MeSH IDs	—

Sex	Male	Primary tumor site	—	Collected	19 Jun 2018	Ordering physician	—
Ethnicity	EUR	Surgical pathology	—	Tumor cellularity	—	Facility	—
Country	RU	Tissue type	—	Barcode	777666	Email	—
Trial ZIP code	—	Metastatic	yes	Sample type	FFPE	Phone	—
		General dataset ID	67377993300	Labtest	MedExome 151 (paired)	Fax	—
		CVI dataset ID	67377993300	Software version	3.0.1	Product	MH Guide
		Organizational unit	DE-GreifswaldGyn-psl			Report	IVD Premium

CLINICAL IMPRESSION

Mutational status of commonly mutated genes in the patient disease.

ALK not identified	APC 1 SNV	EGFR not identified	EPCAM not identified	KRAS not identified	MLH1 not identified	MSH2 not identified	MSH6 1 SNV	MUTYH not identified	NRAS not identified	PIK3CA 1 ins
PMS2 1 SNV	PTEN not identified	SMAD4 not identified	STK11 not identified	TP53 not identified						

SUMMARY

Overview of potential treatment impacts

5 Effective | 2 Ineffective | 6 Toxic

Overview of prognostic and diagnostic findings

1 Prognostic | 3 Diagnostic

Potential impact	Treatment	Drug approval*	Biomarker	VAF	Biomarker score	
Effective	Plx8394	Other	BRAF p.G469A (SNV)	9.09%	AMP Tier II D	3 Preclinical
Effective	Trametinib	Other	BRAF p.G469A (SNV)	9.09%	AMP Tier II D	3 Preclinical
Effective	Pd0325901	Other	BRAF p.G469A (SNV)	9.09%	AMP Tier II D	3 Preclinical
Effective	Beta-catenin inhibitors	Other	APC p.R554* (SNV)	19.38%	AMP n/a	n/a
Effective	PARP inhibitors	Other	CHEK2 p.E8fs (frameshift)	7.41%	AMP n/a	n/a
Toxic	Methotrexate	Other	MTHFR p.A222V (SNV)	35.00%	AMP Tier I B	6 Clinical
Toxic	Trastuzumab	Other	ERBB2 p.P1170A (SNV)	100.00%	AMP Tier II C	4 Clinical

Patient ID	quality-check-2	Diagnosis	sigmoid adenocarcinoma …
Case ID	EU000421	ICD-10-CM code	—
Date of birth	—	MeSH ID/term	D015179 (Colorectal Neopl…
		Additional MeSH IDs	—

Potential impact	Treatment	Drug approval*	Biomarker	VAF	Biomarker score
			ERBB2 p.I655V (SNV)	60.00%	AMP Tier I B · 5 Clinical
Toxic	Cyclophosphamide Rituximab Vincristine Prednisone Doxorubicin	Other Other Other Other Other	FCGR3A p.F176V (SNV)	100.00%	AMP Tier II C · 4 Clinical
Ineffective	Vemurafenib	Other	BRAF p.G469A (SNV)	9.09%	AMP Tier II D · 4 Clinical
Toxic	Temozolomide	Other	MGMT p.I143V (SNV) MGMT p.K178R (SNV)	53.06% 46.75%	AMP Tier II D · 4 Clinical
Toxic	Radiotherapy	Other	ERCC2 p.D312N (SNV)	32.35%	AMP Tier II D · 4 Clinical
			ERCC2 p.K751Q (SNV)	45.83%	AMP Tier II D · 4 Clinical
Ineffective	O(6)-Benzylguanine	Other	MGMT p.I143V (SNV)	53.06%	AMP Tier II D · 3 Preclinical
Toxic	DNA damaging agents	Other	MGMT p.I143V (SNV) MGMT p.K178R (SNV)	53.06% 46.75%	AMP n/a · n/a
Prognostic	—	—	ERBB2 p.P1170A (SNV)	100.00%	AMP Tier II C · 6 Clinical
Diagnostic	—	—	APC p.R554* (SNV)	19.38%	AMP Tier II D · 6 Clinical
Diagnostic	—	—	PMS2 p.G857A (SNV)	69.77%	AMP Tier IV · 3 Preclinical
Diagnostic	—	—	MGMT p.K178R (SNV)	46.75%	AMP Tier IV · 3 Preclinical

VAF = Variant allele frequency; * in the patient's disease

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 AMP and CVI score in the glossary.

Patient ID	quality-check-2	Diagnosis	sigmoid adenocarcinoma …
Case ID	EU000421	ICD-10-CM code	—
Date of birth	—	MeSH ID/term	D015179 (Colorectal Neopl…
		Additional MeSH IDs	—

BIOMARKER DETAILS

BRAF p.G469A (SNV)

[The information provided in this CVI should be carefully reviewed for clinical relevance since no specific match with the patient's disease term was detected.] The serine/threonine-protein kinase BRAF activates the RAS/MAPK signaling pathway to promote cell proliferation and survival. This mutation is located in the P-loop of the protein and confers high kinase activity. A clinical case of lung cancer with this mutation showed tumor progression when treated with vemurafenib. Lung cancer cell lines with this mutation are sensitive to second-generation BRAF inhibitor PLX8394 or MEK inhibitors trametinib or PD0325901. The ERK inhibitor ulixertinib revealed early evidence of clinical activity in solid tumors with BRAF V600X and non-V600 mutation in the presence of oncogenic RAS, including tumors with high p-ERK levels and the BRAF G469A mutation.

PubMed ID
29247021, 20551065, 28783719, 22649091, 27834212, 25706985, 19010912, 26200454

Potential impact	Treatment	Drug approval*	Biomarker score
Effective	Plx8394	Other	AMP Tier II D; 3 Preclinical
Effective	Trametinib	Other	AMP Tier II D; 3 Preclinical
Effective	Pd0325901	Other	AMP Tier II D; 3 Preclinical
Ineffective	Vemurafenib	Other	AMP Tier II D; 4 Clinical

* in the patient's disease

APC p.R554* (SNV)

A nonsense mutation in APC was identified. APC is one of the most frequently mutated genes in colorectal adenocarcinoma, and this mutation may be critical to the mechanism of disease. APC acts as a negative regulator of Wnt signaling by inhibiting beta-catenin; nonsense mutations in APC are expected to activate the Wnt pathway. Preclinical studies have shown that defects in APC may be targeted with investigational drugs inhibiting beta-catenin and tankyrase, although no clinical trials are currently available.

PubMed ID
23258168, 26056595, 26542362, 24702624, 25850553

The adenomatous polyposis coli protein APC is an adhesion molecule which negatively regulates beta-catenin and inactivates the canonical WNT signaling pathway to inhibit cell proliferation and differentiation. Non sense mutations are likely to impair APC function, resulting in activation of the WNT pathway as well as in altered cell migration and reduced chromosome stability by mechanisms independent of canonical WNT signaling. Biallelic mutation of the APC gene occurs in 45-80% of colorectal cancers and is an early step in the development of this cancer. Inactivating germline mutations in APC cause familial adenomatous polyposis (FAP), which is characterized by adenomatous polyps of colon and rectum and a predisposition to cancer, in particular, colorectal carcinomas, but also desmoid tumors and other neoplasms.

PubMed ID
17938238, 29318445

Patient ID	quality-check-2	Diagnosis	sigmoid adenocarcinoma …
Case ID	EU000421	ICD-10-CM code	—
Date of birth	—	MeSH ID/term	D015179 (Colorectal Neopl…
		Additional MeSH IDs	—

Potential impact	Treatment	Drug approval*	Biomarker score
Effective	Icg-001, Pri-724	Other	AMP n/a (n/a)
Diagnostic	—	—	AMP Tier II D (6 Clinical)

* in the patient's disease

CHEK2 p.E8fs (frameshift)

The CHEK2 (checkpoint kinase 2) gene encodes a Ser/Thr kinase that is involved in repair of double-strand DNA breaks and acts as a tumor suppressor. Tumors in which this gene is inactivated have defects in the homologous recombination repair pathway (HRR). The present tumor has a frameshift mutation which would be expected to result in the inactivation of the mutant gene copy, suggesting that the tumor has an HRR defect. Deficiencies in HRR proteins confer sensitivity to PARP inhibitors in several tumor types.

PubMed ID
27447864, 24240112, 16912188, 26510020, 26775620

Potential impact	Treatment	Drug approval*	Biomarker score
Effective	Rucaparib, Niraparib, Veliparib, Talazoparib, Olaparib	Other	AMP n/a (n/a)

* in the patient's disease

MTHFR p.A222V (SNV)

The methylenetetrahydrofolate reductase (MTHFR) gene encodes an enzyme required for processing amino acids, especially the conversion of homocysteine to methionine. The germline mutation (MTHFR p.A222V; or c.C677T) was identified that encodes proteins with lower (~30–40%) enzymatic activity, which causes an increased level of homocysteine and an altered distribution of folate. Patients with this variant have an increased risk for hepatic, gastrointestinal, and skin toxicity associated with methotrexate treatment. Care should be taken when considering these drugs in these patients. Homozygosity for this allele puts patients at a significantly higher risk for toxicity.

PubMed ID
25177243, 26528799, 27142726, 22528943, 27270164

Potential impact	Treatment	Drug approval*	Biomarker score
Toxic	Methotrexate	Other	AMP Tier I B (6 Clinical)

* in the patient's disease

ERBB2 p.P1170A (SNV)

The receptor tyrosine-protein kinase ERBB2 (HER2) activates the RAS/MAPK, PI3K/AKT and JAK/STAT signaling pathways to promote cell proliferation and survival. This polymorphism in ERBB2 (rs1058808) causes a P1170A variant. Contradicting data exist about this well studied polymorphism. Although not previously characterized in this disease type, there is evidence that this polymorphism is clinically relevant. It remains conflicting if in breast cancer patients treated with trastuzumab the presence of a Pro allele might constitute a risk factor for cardiac toxicity. In a small, single-institution study, homozygosity in

this p.P1170A variant (Pro/Pro) was independently correlated with cardiotoxicity, versus either Pro/Ala or Ala/Ala genotypes. However, another recent large study with 1446 breast cancer patients did not find an association between this polymorphism and trastuzumab-induced cardiotoxicity. This SNP might have a prognostic value, as multivariate analysis revealed that at least one Ala allele was an unfavorable factor for distant recurrence-free survival (DRFS) (P=0.029) only in the subgroup of HER2-negative breast cancer patients (n=2,442).

PubMed ID
28529593, 20952131, 25885598, 28763429

Potential impact	Treatment	Drug approval*	Biomarker score
Toxic	Trastuzumab	Other	AMP Tier II C; 4 Clinical
Prognostic	—	—	AMP Tier II C; 6 Clinical

* in the patient's disease

ERBB2 p.I655V (SNV)

The receptor tyrosine-protein kinase ERBB2 (HER2) activates the RAS/MAPK, PI3K/AKT and JAK/STAT signaling pathways to promote cell proliferation and survival. This polymorphism in ERBB2 (rs1136201) causes a I655V variant. Contradicting data exist about this well studied polymorphism. Although not previously characterized in this disease type, there is evidence that this mutation is clinically relevant. It remains conflicting whether the presence of a Val allele predicts increased risk of cardiac toxicity in breast cancer patients treated with trastuzumab. A meta study, including in total more than 340 patients, found a link between Val genotype and cardiotoxicity compared to the homozygous carriers of Ile/Ile. Another recent large study with 1446 breast cancer patients did not find an association between this polymorphism and trastuzumab-induced cardiotoxicity. There was no link found between tumor response and survival with either genotype.

PubMed ID
23780683, 21474413, 26049584, 28763429, 17693647, 23749910

Potential impact	Treatment	Drug approval*	Biomarker score
Toxic	Trastuzumab	Other	AMP Tier I B; 5 Clinical

* in the patient's disease

FCGR3A p.F176V (SNV)

[The information provided in this CVI should be carefully reviewed for clinical relevance since no specific match with the patient's disease term was detected.] The Low affinity immunoglobulin gamma Fc region receptor III-A FCGR3A is involved in the removal of antigen-antibody complexes from the circulation, as well as other antibody-dependent responses. A polymorphism in this gene was detected (rs396991 c.526T>G (p.F176V)) at a position directly interacting with the lower hinge region of IgG1. A meta-analysis of seven studies including 731 cases found no association between this polymorphism and response to CHOP-R treatment (cyclophosphamide/doxorubicin/vincristine/prednisone/rituximab) in diffuse large B-cell lymphoma (DLBCL). An independent study from Australia also showed no significant impact on event free or overall survival, but found a correlation between the homozygous V allele carriers and late onset neutropenia (LON) after CHOP-R treatment for diffuse large B-cell lymphoma. The FCGR3A-176V/V genotype was significantly associated with LON compared with V/F (P = 0.028) and F/F genotypes (P = 0.005). (This SNP is known in the literature by many names, including F158V.)

PubMed ID
25050883, 21883784

Patient ID	quality-check-2	Diagnosis	sigmoid adenocarcinoma …
Case ID	EU000421	ICD-10-CM code	—
Date of birth	—	MeSH ID/term	D015179 (Colorectal Neopl…
		Additional MeSH IDs	—

Potential impact	Treatment	Drug approval*	Biomarker score
Toxic	Cyclophosphamide + Rituximab + Vincristine + Prednisone + Doxorubicin	Other, Other, Other, Other, Other	AMP Tier II C; 4 Clinical

* in the patient's disease

MGMT p.I143V (SNV) + MGMT p.K178R (SNV)

The DNA/protein methyltransferase MGMT is a DNA repair enzyme that removes alkylated guanines from damaged DNA and thus affects the cell cycle and apoptosis. This protein is well known as the main determinant of resistance to alkylating agents. A polymorphism MGMT.K178R (rs2308327) was detected that has been identified to be in complete linkage disequilibrium with MGMT.I143V (rs2308321). In a prospective study with Caucasian cancer patients these variants have shown to be associated with an increased risk of secondary myelodysplastic syndrome (MDS) after chemotherapy treatment (p=0.0383). Another clinical study with 187 glioma patients reported an increased risk of severe myelotoxicity during temozolomide treatment. Patients carrying the variant alleles of MGMT exhibited a 240% increase in risk of severe myelotoxicity.

PubMed ID
20938339, 24238921, 19179423, 28436299

Potential impact	Treatment	Drug approval*	Biomarker score
Toxic	Temozolomide	Other	AMP Tier II D; 4 Clinical
Toxic	Doxorubicin	Other	AMP n/a; n/a

* in the patient's disease

ERCC2 p.D312N (SNV)

The DNA helicase ERCC2 is a component of transcriptional factor TFIIH complex involved in nucleotide excision repair. A polymorphism was identified in ERCC2 (p.D312N, rs1799793). While there is conflicting evidence concerning the effect of the variant, preliminary clinical data from one study shows that in patients with non-small cell lung cancer, this allele is associated with increased risk of radiotherapy-induced pneumonitis.

PubMed ID
25069034

Potential impact	Treatment	Drug approval*	Biomarker score
Toxic	Radiotherapy	Other	AMP Tier II D; 4 Clinical

* in the patient's disease

ERCC2 p.K751Q (SNV)

The DNA helicase ERCC2 is a component of transcriptional factor TFIIH complex involved in nucleotide excision repair. A polymorphism was identified in ERCC2 (p.K751Q, rs13181). While there is conflicting evidence concerning the effect of the variant, preliminary clinical data from one study shows that in patients with non-small cell lung cancer, GG genotype of this polymorphism is associated with increased risk of radiotherapy-induced pneumonitis compared to GT or TT genotype.

Patient ID	quality-check-2	Diagnosis	sigmoid adenocarcinoma …
Case ID	EU000421	ICD-10-CM code	—
Date of birth	—	MeSH ID/term	D015179 (Colorectal Neopl…
		Additional MeSH IDs	—

PubMed ID
25069034

Potential impact	Treatment	Drug approval*	Biomarker score
Toxic	Radiotherapy	Other	AMP Tier II D · 4 Clinical

* in the patient's disease

MGMT p.I143V (SNV)

The DNA/protein methyltransferase MGMT is a DNA repair enzyme that removes alkylated guanines from damaged DNA and thus affects the cell cycle and apoptosis. A germline mutation was identified that causes conformational changes in the active site pocket without affecting the alkyltransferase activity. Based on pre-clinical evidence, this mutation is associated with resistance to the chemotherapeutic alkylating agent sensitizer O6-benzylguanine (O6-BG).

PubMed ID
24947262, 17482892, 19846906, 17996846, 17569599

Potential impact	Treatment	Drug approval*	Biomarker score
Ineffective	O(6)-Benzylguanine	Other	AMP Tier II D · 3 Preclinical

* in the patient's disease

PMS2 p.G857A (SNV)

PMS2 is important for DNA mismatch repair, and mutations in this gene are frequently seen in colon adenocarcinomas. Although mutations in this gene are associated with Lynch syndrome, a majority of tumors harboring these mutations are not the result of genetic predisposition, but acquire these mutations spontaneously. This PMS2 variant is considered to be functionally neutral based on in vitro functional assay. This variant should not be interpreted as evidence of a somatic or germline clinically relevant mutation.

PubMed ID
27435373, 28494185, 24027009, 26028255, 24944470

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

* in the patient's disease

MGMT p.K178R (SNV)

The DNA/protein methyltransferase MGMT is a DNA repair enzyme that removes alkylated guanines from damaged DNA and thus affects the cell cycle and apoptosis. Increased activity of this protein is well known as the main determinant of resistance to DNA alkylating agents. This common polymorphism (population allele frequency around 10%) has shown no change in enzymatic activity compared to wild-type. Based on the pre-clinical evidence, this variant may be considered as neutral/benign in response to the DNA alkylating agent chemosensitizer O6-benzylguanine (O6-BG).

PubMed ID

Patient ID	quality-check-2	Diagnosis	sigmoid adenocarcinoma …
Case ID	EU000421	ICD-10-CM code	—
Date of birth	—	MeSH ID/term	D015179 (Colorectal Neopl…
		Additional MeSH IDs	—

24947262, 19846906, 17996846, 17569599, 18812520

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

* in the patient's disease

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 AMP and CVI score in the glossary.

Patient ID	quality-check-2	Diagnosis	sigmoid adenocarcinoma …
Case ID	EU000421	ICD-10-CM code	—
Date of birth	—	MeSH ID/term	D015179 (Colorectal Neopl…
		Additional MeSH IDs	—

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.

Plx8394 — Drug approval in patient disease: Other

Detected variants supporting this treatment effect:
BRAF p.G469A (SNV)

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

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Trametinib — Drug approval in patient disease: Other

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

Detected variants supporting this treatment effect:
BRAF p.G469A (SNV)

Drug-drug interactions
/ **A**modiaquine / **R**ilpivirine

Pd0325901 — Drug approval in patient disease: Other

Detected variants supporting this treatment effect:
BRAF p.G469A (SNV)

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

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Beta-catenin inhibitors — Drug approval in patient disease: Other

Icg-001, Pri-724

Detected variants supporting this treatment effect:
APC p.R554* (SNV)

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

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PARP inhibitors — Drug approval in patient disease: Other

Rucaparib, Niraparib, Veliparib, Talazoparib, Olaparib

Detected variants supporting this treatment effect:
CHEK2 p.E8fs (frameshift)

Drug-drug interactions

Patient ID	quality-check-2	Diagnosis	sigmoid adenocarcinoma …
Case ID	EU000421	ICD-10-CM code	—
Date of birth	—	MeSH ID/term	D015179 (Colorectal Neopl…
		Additional MeSH IDs	—

There are no drug-drug interactions available for this treatment

Potentially ineffective treatments

Vemurafenib — Drug approval in patient disease: Other

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

Detected variants supporting this treatment effect:
BRAF p.G469A (SNV)

O(6)-Benzylguanine — Drug approval in patient disease: Other

6-O-benzylguanine has been used in trials studying the treatment of HIV Infection, Adult Gliosarcoma, Adult Glioblastoma, Stage I Adult Hodgkin Lymphoma, and Stage II Adult Hodgkin Lymphoma, among others.(DB11919)

Detected variants supporting this treatment effect:
MGMT p.I143V (SNV)

Treatments with potential for adverse reaction

Methotrexate — Drug approval in patient disease: Other

An antineoplastic antimetabolite with immunosuppressant properties. It is an inhibitor of tetrahydrofolate dehydrogenase and prevents the formation of tetrahydrofolate, necessary for synthesis of thymidylate, an essential component of DNA.(DB00563)

Detected variants supporting this treatment effect:
MTHFR p.A222V (SNV)

Trastuzumab — Drug approval in patient disease: Other

A recombinant IgG1 kappa, humanized monoclonal antibody 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. Produced in CHO cell culture.
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.(DB00072)

Detected variants supporting this treatment effect:
ERBB2 p.I655V (SNV), ERBB2 p.P1170A (SNV)

Cyclophosphamide	Drug approval in patient disease: Other
Rituximab	Drug approval in patient disease: Other
Vincristine	Drug approval in patient disease: Other
Prednisone	Drug approval in patient disease: Other
Doxorubicin	Drug approval in patient disease: Other

Precursor of an alkylating nitrogen mustard antineoplastic and immunosuppressive agent that must be activated in the liver to form the active aldophosphamide. It has been used in the treatment of lymphoma and leukemia. Its side effect, alopecia, has been used for defleecing sheep. Cyclophosphamide may also cause sterility, birth defects, mutations, and cancer. [PubChem](DB00531)
Rituxan is a genetically engineered chimeric murine/human monoclonal antibody directed against the CD20 antigen found on the surface of normal and malignant B lymphocytes. The antibody is an IgG1 kappa immunoglobulin containing murine light- and heavy-chain variable region sequences and human constant region sequences. Rituximab is composed of two heavy chains of 451 amino acids and two light chains of 213 amino acids(DB00073)
Vincristine is an antitumor vinca alkaloid isolated from Vinca Rosea. It is marketed under several brand names, many of which have different formulations such as Marqibo (liposomal injection) and Vincasar. Vincristine is indicated for the treatment of acute leukaemia, malignant lymphoma, Hodgkin's disease, acute erythraemia, and acute panmyelosis. vincristine sulfate is often chosen as part of polychemotherapy because of lack of significant bone–marrow suppression (at recommended doses) and of unique clinical toxicity (neuropathy).(DB00541)
It act by the induction of phospholipase A2 inhibitory proteins (lipocortins) which control the biosynthesis of potent mediators inflammation such as prostaglandin and leukotrienes

Patient ID	quality-check-2	Diagnosis	sigmoid adenocarcinoma …
Case ID	EU000421	ICD-10-CM code	—
Date of birth	—	MeSH ID/term	D015179 (Colorectal Neopl…
		Additional MeSH IDs	—

Doxorubicin is a cytotoxic anthracycline antibiotic isolated from cultures of Streptomyces peucetius var. caesius. Doxorubicin binds to nucleic acids, presumably by specific intercalation of the planar anthracycline nucleus with the DNA double helix.(DB00997)

Detected variants supporting this treatment effect:
FCGR3A p.F176V (SNV)

Temozolomide — Drug approval in patient disease: Other

Temozolomide (Temodar and Temodal) is an oral alkylating agent used for the treatment of refractory anaplastic astrocytoma -- a type of cancerous brain tumor. Temozolomide is not active until it is converted at physiologic pH to the active form, 5-(3-methyltriazen-1-yl)imidazole-4-carboxamide (MTIC).(DB00853)

Detected variants supporting this treatment effect:
MGMT p.I143V (SNV) + MGMT p.K178R (SNV)

Radiotherapy — Drug approval in patient disease: Other

Detected variants supporting this treatment effect:
ERCC2 p.D312N (SNV), ERCC2 p.K751Q (SNV)

DNA damaging agents — Drug approval in patient disease: Other

Doxorubicin

Detected variants supporting this treatment effect:
MGMT p.I143V (SNV) + MGMT p.K178R (SNV)

Patient ID	quality-check-2	**Diagnosis**	sigmoid adenocarcinoma …
Case ID	EU000421	**ICD-10-CM code**	—
Date of birth	—	**MeSH ID/term**	D015179 (Colorectal Neopl…
		Additional MeSH IDs	—

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 target region of the assay. CNA genes include all genes that are potentially affected by a copy number alteration.

Variant type	Variant count	Variant count per analyzed megabase
SNV	102	2.18
Indel	108	2.31
Fusion	0	n/a
CNA genes	0	n/a

Patient ID	quality-check-2	Diagnosis	sigmoid adenocarcinoma …
Case ID	EU000421	ICD-10-CM code	—
Date of birth	—	MeSH ID/term	D015179 (Colorectal Neopl…
		Additional MeSH IDs	—

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.

Patient ID	quality-check-2	Diagnosis	sigmoid adenocarcinoma …
Case ID	EU000421	ICD-10-CM code	—
Date of birth	—	MeSH ID/term	D015179 (Colorectal Neopl…
		Additional MeSH IDs	—

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 tumor 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 tumor type.
6, 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. For biomarkers predicting a drug to be effective or resistant, there is evidence from a large cohort study. For biomarkers predicting a drug to be toxic, there is evidence from a randomized controlled trial and its meta-analysis.
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 patients from several case control studies 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

Patient ID	quality-check-2	**Diagnosis**	sigmoid adenocarcinoma …
Case ID	EU000421	**ICD-10-CM code**	—
Date of birth	—	**MeSH ID/term**	D015179 (Colorectal Neopl…
		Additional MeSH IDs	—

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 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.

MH Guide is designed for processing the molecular data from patients diagnosed with solid tumor cancer. Diseases beyond this, including hematological cancers, 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) and fusion genes from NGS data. SNV detection is fully validated. Fusion gene detection is limited to unpaired panel analyses.

The detection methods for indels and fusion genes from FASTQ and BAM were validated using synthetic data only. Therefore, indel and fusion gene detection in MH Guide must be validated with an orthogonal method (e.g., Sanger sequencing) before a treatment is recommended.

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.

MH Guide does not call copy number alterations (CNAs) from capture-based NGS sequencing data. Therefore, annotation of CNAs is only supported when CNA signals are submitted in the format of a VCF or XML file for the variant detection pipeline in MH Guide.

If genetic aberration signals are submitted in the format of a VCF or XML 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.

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, such clearance and approval is not currently required for clinical implementation.
In the European Union, MH Guide is registered as an in vitro diagnostic medical device (IVD).

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.