GUIDE

Patient ID	7884-24	**Diagnosis**	brain neoplasm
Case ID	EU032436	**ICD-10 code**	C71.9
Date of birth	23 Sep 2013		

PATIENT

Patient ID	7884-24
Case ID	EU032436
Date of birth	23 Sep 2013
Sex	Male
Country	SK

SAMPLE

Primary tumor site	—
Tissue type	—
Metastatic	unknown
Tumor cellularity	—
Collected	—

ORDER & REPORT

Labtest	VCF Illumina TSO500 (unpaired) Biopticka
Order date	16 May 2024
Signed by	Mgr. Veronika Hajkova
Signed on	16 May 2024
Version	1

SUMMARY OF GENOMIC AND BIOMARKER FINDINGS

Detected biomarkers with therapy implications:

BIOMARKER	VAF (%)	APPROVED TREATMENTS FOR PATIENT DISEASE	BIOMARKER SCORE	TRIALS	OTHER TREATMENTS	DRUG APPROVAL	BIOMARKER SCORE	TRIALS
TMB-L 3.15 mut/Mb	-	*No therapies or clinical trials related to this biomarker*						
MS-stable	-	*No therapies or clinical trials related to this biomarker*						
ST7/MET	-	*No approved therapy identified for the patient disease*			E Crizotinib	Off-label	n/a 5	0
					E Capmatinib	Off-label	III 4	0
					E Cabozantinib	Off-label	n/a 4	2
					E Tepotinib	Off-label	n/a 4	0

E Effective: potentially effective treatments

Biomarker score: AMP/ASCO/CAP category and CVI score. See the glossary for more information.

PATHOGENIC VARIANTS

Identified pathogenic and likely pathogenic variants:

VARIANT	CODING DNA	TYPE AND EFFECT	VAF (%)	CLASSIFICATION
PTEN p.A39V	ENST00000371953.3 c.116C>T	SNV Missense	10.31	Pathogenic
ST7/MET	—	fusion Fusion	—	Likely pathogenic

ADDITIONAL TEST RESULTS

No additional test results were added to the report.

BIOMARKER DETAILS

ST7/MET (Fusion)

[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 hepatocyte growth factor receptor MET is a receptor tyrosine kinase that activates the RAS/MAPK, PI3K/AKT, PLC/PKC, and JAK/STAT signaling pathways to promote cell proliferation, survival, and invasion. The MET fusion gene consists of MET lacking the juxtamembrane regulatory sequence and different N-terminal partners, such as TPR, TRIM4, ZKSCAN1, and CLIP2. In a pre-clinical setting, these proteins are constitutively phosphorylated and induce tumorigenesis. Clinical responses were reported in patients with non-small cell lung cancer (NSCLC) MET fusion-positive treated with crizotinib. A case report described an NSCLC patient with MET fusion who achieved a significant response after crizotinib, cabozantinib, and tepotinib treatment. A patient with KIF5B-MET fusion-positive NSCLC had a durable response to capmatinib after acquired resistance to telisotuzumab. Cell lines overexpression MET fusions showed sensitivity to cabozantinib and crizotinib.

PubMed ID
36033470, 35434049, 32716573, 32654927, 30339198, 30244854, 29527595, 29284707

POTENTIAL IMPACT	TREATMENT	DRUG APPROVAL	BIOMARKER SCORE	BIOMARKER APPROVAL
Effective	Crizotinib	Off-label	AMP n/a · 5 Clinical	—
Effective	Capmatinib	Off-label	AMP Tier III · 4 Clinical	—
Effective	Cabozantinib	Off-label	AMP n/a · 4 Clinical	—
Effective	Tepotinib	Off-label	AMP n/a · 4 Clinical	—

CVI score: see the glossary for more information.

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://trialsearch.who.int (clinical trials from other registries) for more information.

Clinical trials in total: 2 **Disease (MeSH):** Brain Neoplasms **Trial country:** SK, AT, BE, CA, CH, CZ, DE, ES, FI, FR, GB, HU, IT, NL, NO, PL, SE, US

TITLE	PHASE AND ID	INTERVENTION	DISEASE	AGE AND SEX
A Study of Cabozantinib as a Maintenance Agent to Prevent Progression or Recurrence in High-Risk Pediatric Solid Tumors **Status:** Recruiting **Location: US**-4 locations **Matching trial biomarker(s):** none available	Phase 2; NCT05135975	Cabozantinib	Solid tumor	Min age: 18 month(s) Max age: 40 year(s) Sex: Both
Cabozantinib in Combination With 13-cis-Retinoic Acid in Children With Relapsed or Refractory Solid Tumors **Status:** Recruiting **Location: US**-2 locations **Matching trial biomarker(s):** none available	Phase 1; NCT03611595	Cabozantinib	Solid tumor	Min age: 2 year(s) Max age: 26 year(s) Sex: Both

MOLECULAR HEALTH GLOSSARY

The glossary contains terms for all available report sections. Your report may not include all sections.

AMP/ASCO/CAP category:
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 and/or EMA-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 and/or EMA-approved therapies for different cancer types or investigational therapies. Multiple small published studies with some consensus.
- **Tier IID:** Variants of potential clinical significance. Preclinical trials or a few case reports without consensus.
- **Tier III:** Variants of unknown clinical significance.
- **Tier IV:** Benign or likely benign variants.

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

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

Biomarker score and approval:
Displays the AMP score and CVI score of the biomarker. AMP score IA and CVI score 7 indicate biomarker approval by the FDA and/or EMA for the cancer entity. Faded biomarker score icons indicate that the biomarker is not approved by the agency defined for the analysis of this case in MH Guide. N/S displayed next to biomarker score icons mean that the biomarker approval source was not specified by an MH Guide user.

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).
- **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.

Description key:

E Potentially effective treatments. These treatment recommendations are based solely on tumor biology and do not override your oncologist's clinical treatment plan.

I 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.

S 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.

P Biomarkers identified in the patient tumor that have been reported to have a prognostic relevance.

D 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.

Drug approval:
The drug approval status of the treatment for the patient's indication in the selected country.

- **Approved:** This drug is launched for the primary or a secondary patient disease.
- **Approved*:** 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 apply for this patient.
- **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 for the patient disease.
- **Other:** The drug approval status Other is used to indicate the following terms:
  - The drug is the subject of a trial that has been withdrawn
  - The filing for drug approval has been withdrawn or suspended
  - The drug is approved but currently not on the market
  - The drug is approved but patent issues must be resolved
  - No information on the drug approval status is available

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.

Trial status:

- **Recruiting:** The trial is currently recruiting participants.
- **Active, not recruiting:** The trial is ongoing; participants are not currently being recruited or enrolled.
- **Authorised-recruitment may be ongoing or finished:** no further information available from the source.
- **Enrolling by invitation:** The trial is selecting its participants from a predefined population; it is not open to other participants.
- **Not yet recruiting:** The trial has not started recruiting participants.
- **Suspended:** The study has stopped early but may start again.
- **Unknown status:** On ClinicalTrials.gov, this indicates trials whose status has not been verified within the past 2 years.

Variant classification:
The variants listed can either be unclassified or they can be assigned to a classification. Following ACMG (American College of Medical Genetics and Genomics) recommendations, classifications of variants can be Pathogenic, Likely pathogenic, Uncertain significance, Likely benign, or Benign. Source: Richards S., Aziz N., Bale S., Bick D., Das S., Gastier-Foster J., Grody W.W., Hegde M., Lyon E., Spector E., Voelkerding K., Rehm HL.; ACMG Laboratory Quality Assurance Committee "Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology, " Genetics in Medicine, vol. 17, issue 5, pp. 405-24, 2015, doi: 10.1038/gim.2015.30. The final variant classification results from the combination of applied criteria according to the ACMG decision tree.
Classifications of variants can be:

- **Pathogenic:** Variants with sufficient evidence to be classified as pathogenic (capable of causing disease).
- **Likely pathogenic:** Variants with strong evidence in favor of pathogenicity.
- **Uncertain significance:** Variants with limited and/or conflicting evidence regarding pathogenicity.
- **Likely benign:** Variants with strong evidence against pathogenicity.
- **Benign:** Variants with very strong evidence against pathogenicity.

MOLECULAR HEALTH DISCLAIMER

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 or from VCF. 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.

MH Guide covers:

1. Primary identification of genetic alterations from next-generation sequencing (NGS) data, 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, 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 trained user. The trained user is neither a contractor nor an employee of MH. The information provided in the report must be evaluated by the treating physician in conjunction with all other relevant clinical information of the patient before the appropriate course of medication is selected by the treating physician. The selection of any, all, or none of the medications identified in the report is at the sole discretion of the treating physician and not of MH or the MH medical staff.

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

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

The patient disease must be provided in MeSH ontology format for correct interpretation of patient data. Other disease ontologies such as ICD must be converted to the correct MeSH term by the trained user.

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, 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 treatment option in 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 trained user 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 supports annotation, classification, interpretation and reporting for variants detected from FASTQ input, submitted in VCF format, or manually added by the trained user. The quality of the analysis results depends on the quality of the input data submitted to MH Guide by the trained user. For FASTQ data the provision of data that fulfill the quality criteria of the MH Guide sequencing guidelines is at the sole responsibility of the trained user. For VCF data the accuracy, analytic sensitivity and specificity of the variant lists is the sole responsibility of the trained user.

Based on raw NGS data (FASTQ input) 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). The detection methods for indels, fusion genes and copy number alterations from FASTQ 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. The clinical validity of TMB defined by the underlying lab test has not been established. It is the responsibility of the trained user 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.

Based on variant input in VCF format, MH Guide supports processing of single nucleotide variants (SNVs), insertions and deletions (indels), fusion genes (fusions), copy number alterations (CNAs), microsatellite instability (MSI-H) and tumor mutational burden (TMB).

MH Guide also supports the processing of wild-types, methylation, gene expression, protein expression, microsatellite instability, homologous recombination deficiency, and tumor mutational burden data that were manually added by the trained user.

For ethnicity Japanese (JPT), population frequencies from ToMMo (MAF>=1%) are available in the application for display and filtering and used for automated variant pre-classification.

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.

In the European Union, MH Guide is registered as an in vitro diagnostic medical device (IVD). Molecular Health GmbH is the legal manufacturer of MH Guide as a stand-alone software, and the statutory provisions of the German Medical Devices Implementation Act (MPDG) and the European Regulation (EU)2017/246 apply. Molecular Health therefore maintains 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 Guide is a registered trademark of Molecular Health GmbH.

ADDITIONAL ANALYSIS SPECIFICATIONS

Product	MH Guide
Input format	VCF
Reference genome	GRCh37
Organizational unit	Biopticka-Laborator
Software version	6.3.0
General dataset	17-Apr-2024 (171857882393)
CVI dataset	17-Apr-2024 (171857882393)
Patient MeSH term(s)	Main: Brain Neoplasms Additional: —
Defined agency for biomarker approval display	EMA