cancertrack REPORT

PATIENT AND SPECIMEN DETAILS

PATIENT NAME	:	Ms. A.B.C	TUMOR TYPE	:	Colon carcinoma
AGE	:	51 Years	SPECIMEN TYPE	:	Blood
GENDER	:	Female	DATE OF COLLECTION	:	21.12.2021
ADDRESS	:	--	DATE OF ACCESSION	:	23.12.2021
REFERRED BY	:	Dr. X.Y.Z	DATE OF REPORT	:	30.12.2021

SUMMARY OF RESULTS

DRUGS WITH CLINICAL BENEFIT

GENE	ALTERATION(S)	USFDA APPROVED / STANDARD OF CARE (Colon Cancer)	OFF LABEL THERAPY
BRAF	p.V600E (MAF 0.25% at 48523X)	Encorafenib + (Cetuximab/Panitumumab)	---

MAF: Mutant Allele Frequency

DRUGS WITHOUT CLINICAL BENEFIT / WITH POTENTIAL RESISTANCE

GENE	ALTERATION(S)	USFDA APPROVED / STANDARD OF CARE (Colon Cancer)	OFF LABEL THERAPY
BRAF	p.V600E (MAF 0.25% at 48523X)	Cetuximab Panitumumab	Necitumumab

DATAR CANCER GENETICS
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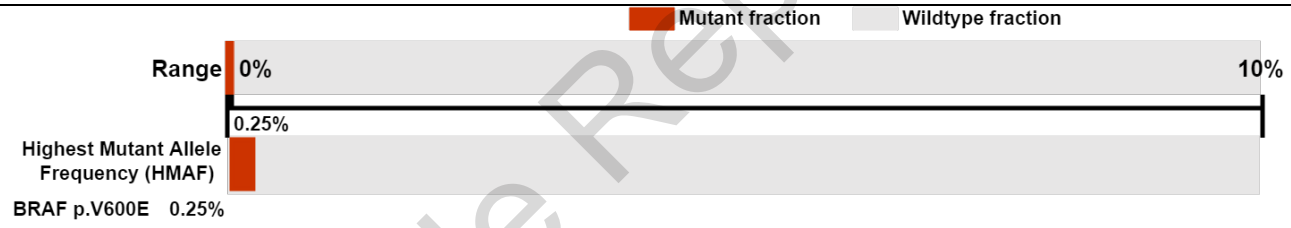
DISEASE RELEVANT FINDINGS

BIOMARKERS	RESULT
KRAS	No mutations detected
NRAS	No mutations detected
HER2/ERBB2	No alterations detected
NTRK1/3	No fusions detected

HIGHEST MUTANT ALLELE FREQUENCY (HMAF) AND CTCs

Highest mutant allele frequency (HMAF)	0.25%
Number of CTCs detected	2 CTCs / ml



HMAF of 0.25% was detected in the cell free nucleic acids isolated from patient's plasma.

SUMMARY OF OTHER GENOMIC ALTERATIONS

Gene	SNV/INDEL	Variant Classification	Therapeutic Significance

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Gene	CNV	Therapeutic Significance
None detected		

Gene	FUSION	Therapeutic Significance
None detected		

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SOMATIC GENOME ALTERATIONS

SINGLE NUCLEOTIDE VARIATIONS/INDELS

Markers (Transcript ID)	Variant	Result	Category
BRAF (NM_004333.6)	c.1799T>A p.V600E; [p.(Val600Glu)]	Detected	Tier I (Level A)

Interpretation: BRAF mutation is reported in 7-10% patients with colorectal cancer (CRC) and associated with tumourigenesis, microsatellite instability and an adverse overall survival (Vandrovcova et al., 2006; Manthravadi et al., 2018; Bond and Whitehall, 2018; Luu and Price, 2019).

Activating BRAF mutants are capable of constitutively activating MAPK, often through C-RAF stimulation (Li et al., 2009; Pakneshan et al., 2013). Therefore, activating BRAF mutations may confer susceptibility to RAF inhibitors Encorafenib, Vemurafenib, Dabrafenib, as well as MEK inhibitors, Trametinib, Binimetinib, Cobimetinib, Selumetinib (Zhang et al., 2014; Richtig et al., 2016; Parmar et al., 2017).

Encorafenib in combination with Cetuximab is USFDA approved for the treatment of BRAF V600E mutation positive colorectal cancer.
Encorafenib along with Binimetinib is USFDA approved for the treatment of patients with unresectable or metastatic melanoma with BRAF V600E mutation.
Encorafenib in combination with Cetuximab/ Panitumumab is a standard of care regimen for the treatment of BRAF V600E positive colon cancer as per NCCN guidelines (NCCN guidelines, 2021).

Binimetinib in combination with Encorafenib is USFDA approved for the treatment of BRAF V600E or V600K positive unresectable or metastatic melanoma.
In an open-label, phase III trial, patients with BRAF V600E mutated metastatic colorectal cancer were randomly assigned in a 1:1:1 ratio to receive Encorafenib, Binimetinib, and Cetuximab (triplet-therapy group) (n=224); Encorafenib and Cetuximab (doublet-therapy group) (n=220); or either Cetuximab and Irinotecan or Cetuximab and FOLFIRI (Folinic acid, Fluorouracil, and Irinotecan) (control group) (n=221). Median overall survival of 9.0 months in the triplet-therapy group, 8.4 months in the doublet-therapy group and 5.4 months in the control group was observed. The confirmed response rates were 26%, 20% and 2% in the triplet-therapy, doublet-therapy and the control groups, respectively (Kopetz et al 2019).

Although data exists for use of Cetuximab/Panitumumab in combination with Vemurafenib and Irinotecan or Dabrafenib plus Trametinib for BRAF V600E positive CRC, in view of superior data and/or lower toxicity of the Encorafenib-doublets, these combinations are not standard of care as per NCCN guidelines (NCCN guidelines, 2021).

Vemurafenib is a USFDA approved for the treatment of patients with unresectable or metastatic melanoma with a BRAF V600E or V600K mutation.
In a randomized phase II trial, Vemurafenib in combination with Irinotecan and Cetuximab in previously treated patients with BRAF p.V600E-mutant metastatic colorectal cancer (n=50) showed objective response rate of 17% and disease control rate of 65% (Kopetz et al., 2021).

Dabrafenib in combination with Trametinib is USFDA approved for the treatment of BRAF V600E positive non small cell lung cancer as well as BRAF V600E or V600K positive unresectable or metastatic melanoma. Trametinib, used alone or with Dabrafenib is USFDA approved for the treatment of BRAF V600E positive anaplastic thyroid and non-small cell lung cancer as well as BRAF V600E or V600K positive unresectable or metastatic melanoma.
In a clinical study, Dabrafenib in combination with Trametinib in BRAF p.V600E mutated colorectal cancer patients (n=43) showed partial response in 5 patients (12%) and 24 patients (56%) achieved stable disease as best confirmed response (Corcoran et al., 2015).

Cobimetinib is a USFDA approved kinase inhibitor indicated for the treatment of patients with unresectable or metastatic melanoma with a BRAF V600E or V600K mutation, in combination with Vemurafenib.
In a TAPUR study, the treatment of Cobimetinib plus Vemurafenib in BRAF V600E-mutated colorectal cancer patients, demonstrated 8 partial response and 8 stable disease (disease control and overall response rate were 57% and 29%, respectively) among 30 evaluable patients (NCT02693535; Klute et al., 2020).

Selumetinib is a kinase inhibitor indicated for the treatment of pediatric patients 2 years of age and older with neurofibromatosis type 1 (NF1) who have symptomatic, inoperable plexiform neurofibromas (PN).
In a phase II trial, Selumetinib in patients with BRAF V600E mutated melanoma showed tumor regression in 3 of 5 patients (Catalanotti et al., 2013).
In a clinical study, treatment of Selumetinib plus Irinotecan as second-line therapy in patients with exon 2 KRAS mutated colorectal cancer, demonstrated partial response in 3 and stable disease in 16 patients for 4 weeks, (including three >1 year) of 31 evaluable patients (Hochster et al., 2015).
However, efficacy of Selumetinib in BRAF V600E mutated colon cancer is not well evaluated.

BRAF mutations are associated with resistance to EGFR-targeted monoclonal antibodies, Cetuximab, Panitumumab, Necitumumab as well as anti-EGFR tyrosine kinase inhibitors (TKIs), Erlotinib, Gefitinib, Afatinib, Dacomitinib and Osimertinib (Pratilas et al., 2008; Mao et al., 2011; Ohashi et al., 2012; Stewart et al., 2015; Lovly et al., 2015; Stover, 2015; Pietrantonio et al., 2015; Shinozaki et al., 2017; Zhong et al., 2017; NCCN guidelines, 2021). Mutations in BRAF gene are also suggestive of lack of response to anti-HER2-directed monotherapies, Trastuzumab, Pertuzumab, Lapatinib, Neratinib and Tucatinib in HER2 positive tumors (de Oliveira et al., 2018; Patra et al., 2017; Chen et al., 2020).

BRAF p.V600E lies within the activation segment of the kinase domain of the BRAF protein (Wan et al., 2004). This variant confers a gain-of-function to the BRAF protein as demonstrated by increased Braf kinase

activity, downstream signaling, and the ability to transform cells in culture (Ng et al., 2018). In silico analysis also predicts BRAF p.V600E to be a gain-of-function mutation. It is reported in tumors of thyroid, skin, large intestine, haematopoietic and lymphoid system.

The BRAF gene provides instructions for making a protein that helps transmit chemical signals from outside the cell to the cell's nucleus. It encodes a protein which is part of a signaling pathway known as the RAS/MAPK pathway, which controls several important cell functions like cell division, differentiation, and secretion. The BRAF gene belongs to a class of genes known as oncogenes and mutations in this gene have been associated with various cancers.

COPY NUMBER VARIATIONS

Markers (Cytoband)	Result	Interpretation	Category
No copy number variations detected			

FUSION ANALYSIS

No fusions detected

CIRCULATING TUMOR CELLS ENUMERATION

Circulating tumor cells (CTCs): **DETECTED**

No. of CTCs: **2 CTCs / ml peripheral blood**

CTCs are defined as CK+, EPCAM+, CD45- cells.

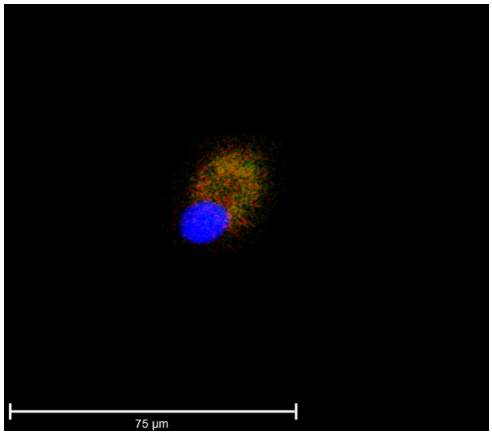

Fig: Fluorescent microscopic image of CTC

INTERPRETATION

2 CTCs/ ml peripheral blood detected in the submitted sample.

RECOMMENDATION

Circulating tumor cell enumeration may be performed every 8 to 12 weeks to monitor disease status in consultation with the treating physician.

VARIANT ALLELE FRACTION AND COVERAGE

Variant (Transcript ID)	Genomic co-ordinates	Allele fraction	Coverage (X)
BRAF (NM_004333.6) c.1799T>A, p.V600E	chr7:140453136A>T	0.25	48523

BIOMARKERS ANALYZED

SNV Genes:

AKT1, ALK, APC, AR, ARAF, BRAF, CHEK2, CTNNB1, DDR2, EGFR, ERBB2, ERBB3, ESR1, FBXW7, FGFR1, FGFR2, FGFR3, FGFR4, FLT3, GNA11, GNAQ, GNAS, HRAS, IDH1, IDH2, KIT, KRAS, MAP2K1, MAP2K2, MET, MTOR, NRAS, NTRK1, NTRK3, PDGFRA, PIK3CA, PTEN, RAF1, RET, ROS1, SF3B1, SMAD4, SMO, TP53

Fusion Genes:

ALK, BRAF, ERG, ETV1, FGFR1, FGFR2, FGFR3, MET, NTRK1, NTRK3, RET, ROS1

CNV Genes:

CCND1, CCND2, CCND3, CDK4, CDK6, EGFR, ERBB2, FGFR1, FGFR2, FGFR3, MET, MYC

CRITERIA FOR CLASSIFICATION OF SOMATIC VARIANTS

The criteria/guidance used in this report is in accordance with the guidelines provided by the American College of Medical Genetics and Genomics (ACMG) for the interpretation and reporting of sequence variants in cancer. Somatic sequence variations are categorized into four tiers based on their clinical significance (Li et al, 2017).

- **Tier I:** Variants/biomarkers with strong clinical significance (therapeutic, prognostic and/or diagnostic)
  - **Level A evidence:** FDA approved therapies or standard guidelines for a specific tumor type.
  - **Level B evidence:** Statistically significant studies with consensus for specific tumor type.
- **Tier II:** Biomarkers with potential clinical significance (therapeutic, prognostic and/or diagnostic)
  - **Level C evidence:** FDA approved therapies or standard guidelines for a different tumor type (off-label use of the drug). An inclusion criteria for clinical trials.
  - **Level D evidence:** No consensus among different studies.
- **Tier III:** Biomarker whose association with cancer is not evident from available literature and is not frequently present in general population.
- **Tier IV:** Biomarker whose association with cancer has not been reported till date and is frequently present

in general population. This category of variants is not included in this report as per guidelines.

ABOUT CTCs

CTC detection is a promising prognostic tool in both primary and metastatic setting.

CTCs are rare cells in a background of 10^6 -10^7 nucleated blood cells.

Evaluation of CTCs at any time during the course of therapy allows assessment of patient prognosis and is predictive of progression-free survival and overall survival. Circulating tumor cells (CTCs) in the blood stream play a critical role in establishing metastasis.

As an adjunct to standard monitoring methods, monitoring patients with the circulating tumor cell test can help to assess patient's status based on real-time prediction. Enumeration of the number of circulating tumor cells (CTCs) before and during treatment helps predicting response to chemotherapy. Throughout therapy, CTC testing can be used to monitor a patient's status to understand response to the given therapy is favorable or unfavorable at any given time.

Circulating tumor cell test results should be used in conjunction with a clinical information derived from other diagnostic tests, physical examination and complete medical history, in consultation with treating oncologist.

METHODS AND LIMITATIONS

Cell free nucleic acids analysis:

Cell free nucleic acids were analyzed for mutation and fusion detection using semiconductor based Next Generation Sequencing technology. Cell free nucleic acids extracted from the plasma of submitted specimen was subjected to target enrichment by multiplex PCR amplification using Oncomine™ Pan-Cancer Cell-Free panel (see gene list in the 'Biomarkers analysed section'). Enriched DNA sequences were ligated with platform specific adaptor molecules and were sequenced on using semiconductor P1 chip. The minimum average depth was 17000x for gene panel analyzed. High quality sequencing data (proportion Q20 bases ≥75%) was analyzed using a customized in-house pipeline DCGL NGS Bioinformatics Pipeline v11.8 designed to accurately detect the rare somatic variants.

Analytical validation of this test has shown sensitivity of 94.72 % and specificity of 97.88 %.

Lower limit of detection of the mutations targeted is 0.1% and variants present below 0.1% may not be detectable with this assay, whereas analytical sensitivity is 97.14% and specificity is 93.75% for SNV, CNV and Fusion. Actionable variant(s) observed below Limit of Detection are confirmed by Droplet Digital PCR.

A negative test result does not exclude the possibility of mutations being present in the test sample probably

due to the reads representing minor allele fraction is below the detectable limit of the assay or other limiting technical / analytical factors. The scope of copy number variations analysis includes copy number gain/amplification of the detected gene(s).

The clinical sensitivity of most assays for detection of mutant cell free nucleic acids is limited as compared with tumor tissue-based testing. This may result from a high ratio of normal to tumor DNA or excess degradation of cell free nucleic acids or may simply reflect the biologic heterogeneity of solid tumors, some of which may shed abundant nucleic acid into the circulation and others that may not. Tumor type, size, disease stage, sites of metastasis, histologic grade, or other features may also affect levels, however, much remains to be elucidated.

CTCs enumeration:

Enriched CTCs from the submitted peripheral blood were labelled with EPCAM, Cytokeratin and CD45 antibodies and analyzed by High content imaging platform. Analytical Validation of this assay shown sensitivity of 99.99% and specificity 99.99%.

This test does not detect variants in gene other than tested. Cancertrack™ is limited in detecting the epigenetic factors, mutations in repetitive or high GC rich regions. Rare and novel mutations may be clinically uncharacterized.

This test was developed, and its performance characteristics determined by Datar Cancer Genetics. It has not been cleared or approved by the U.S. Food and Drug Administration.

This laboratory is certified under the Clinical Laboratory Improvement Amendments (CLIA)-USA as qualified to perform high complexity clinical laboratory testing.

The Patient Analysis raw data may be shared on written request by the individual patient.

DISCLAIMER

The aberrant / absent/ downregulated expression of cell surface or intracellular markers used for CTCs detection can give rise to ambiguous test results. Cells with EPCAM/Cytokeratin down regulation or absent expression will not be detected with this test.

This report documents the genetic alterations detected in the submitted sample material. Information in this report is provided for information purpose only and should only be considered in conjunction with all other relevant information regarding a particular patient before the patient's treating physician recommends a course of treatment.

Decisions on patient care and treatment must be based on the independent medical judgment of the treating physicians, taking into consideration all applicable information concerning the patient's condition, such as

patients and family history, physician's examination, information from other diagnostic test and patient references, in accordance with the standard of care in a given community. A treating physician's decisions should not be based on a single test or on the information contained in this report.

The information in this report does not constitute a treatment recommendation by Datar Cancer Genetics, either to use or not to use any specific therapeutic agent and should not be interpreted as treatment advice. Decisions on patient care and treatment rest solely within the discretion of the patient's treating physician.

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End of Report

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