Patient

Name:
Date of Birth:
Sex: Female
Case Number: TN22-
Diagnosis: Adenocarcinoma, NOS

Specimen Information

Primary Tumor Site: Splenic flexure of colon
Specimen Site: Colon, NOS
Specimen ID:
Specimen Collected:
Test Report Date:

Ordered By

Results with Therapy Associations

BIOMARKER	METHOD	ANALYTE	RESULT	THERAPY ASSOCIATION		BIOMARKER LEVEL*
KRAS	Seq	DNA-Tumor	Mutation Not Detected	BENEFIT	cetuximab, panitumumab	Level 2
Mismatch Repair Status	IHC	Protein	Deficient	BENEFIT	dostarlimab, nivolumab, nivolumab/ipilimumab combination, pembrolizumab	Level 2
MSI	Seq	DNA-Tumor	High	BENEFIT	nivolumab, nivolumab/ipilimumab combination, pembrolizumab	Level 2
NRAS	Seq	DNA-Tumor	Mutation Not Detected	BENEFIT	cetuximab, panitumumab	Level 2
NTRK1	Seq	RNA-Tumor	Pathogenic Fusion	BENEFIT	entrectinib, larotrectinib	Level 2
TMB	Seq	DNA-Tumor	High, 48 mut/Mb	BENEFIT	pembrolizumab	Level 2
ERBB2 (Her2/Neu)	IHC	Protein	Negative | 0	LACK OF BENEFIT	lapatinib, pertuzumab, trastuzumab	Level 2
BRCA2	Seq	DNA-Tumor	Pathogenic Variant Exon 14 | p.N2460fs		oxaliplatin olaparib A pathogenic or likely pathogenic BRCA2 mutation, and/or deletion, was detected in the tumor for which germline status is negative or unavailable for interpretation of therapy associations. The strongest evidence for DNA-damaging agents like PARP inhibitors or platinum compounds comes from studies that included predominantly germline mutations. Additionally, prescribing information and consensus guidelines (e.g. NCCN) for PARP inhibitors state a requirement for germline mutations. Therefore, the clinical benefit of these therapies in the context of tumor/somatic-only mutations (including deletions) remains to be fully determined.	

* Biomarker reporting classification: Level 1 – Companion diagnostic (CDx); Level 2 – Strong evidence of clinical significance or is endorsed by standard clinical guidelines; Level 3 – Potential clinical significance. Bolded benefit therapies, if present, highlight the most clinically significant findings.

MI FOLFOXai™ **Result:** **DECREASED BENEFIT to FOLFOX + bevacizumab in first-line metastatic CRC**   See Page 3 for important details about clinical data regarding MI FOLFOXai

The selection of any, all, or none of the matched therapies resides solely with the discretion of the treating physician. Decisions on patient care and treatment must be based on the independent medical judgment of the treating physician, taking into consideration all available information concerning the patient's condition, the FDA prescribing information for any therapeutic, and in accordance with the applicable standard of care. Whether or not a particular patient will benefit from a selected therapy is based on many factors and can vary significantly. All trademarks and registered trademarks are the property of their respective owners.

Important Note

A TPM3-NTRK1 gene fusion was detected in this specimen. This fusion has been previously reported in several different cancers (Ardini 2014 Mol Oncol 8:1495; Chiang 2018 Am J Surg Pathol 42:791).

A pathogenic frameshift mutation was detected in BRCA2. Germline pathogenic variants in this gene are causal for hereditary cancers of the breast, ovaries, pancreas, and prostate. Confirmation of the patient's carrier status should be considered.

TMB-High status should only be used to guide pembrolizumab treatment when no satisfactory alternative treatment options are available.

Pembrolizumab monotherapy is FDA-approved for first-line treatment of patients with unresectable or metastatic MSI-H or dMMR colorectal cancer.

Cancer-Type Relevant Biomarkers

Biomarker	Method	Analyte	Result
NTRK2	Seq	RNA-Tumor	Fusion Not Detected
NTRK3	Seq	RNA-Tumor	Fusion Not Detected
BRAF	Seq	RNA-Tumor	Fusion Not Detected
		DNA-Tumor	Variant of Uncertain Significance Exon 4	p.K183N
EGFR	CNA-Seq	DNA-Tumor	Amplification Not Detected
	Seq	DNA-Tumor	Mutation Not Detected
ERBB2 (Her2/Neu)	CNA-Seq	DNA-Tumor	Amplification Not Detected
KRAS	CNA-Seq	DNA-Tumor	Amplification Not Detected

Biomarker	Method	Analyte	Result
NF1	Seq	DNA-Tumor	Variant of Uncertain Significance Exon 50	p.R2452H
		DNA-Tumor	Variant of Uncertain Significance Exon 51	p.P2493S
PIK3CA	Seq	DNA-Tumor	Mutation Not Detected
POLE	CNA-Seq	DNA-Tumor	Deletion Not Detected
	Seq	DNA-Tumor	Variant of Uncertain Significance Exon 24	p.S925P
PTEN	IHC	Protein	Positive	2+, 100%
	CNA-Seq	DNA-Tumor	Deletion Not Detected

Genomic Signatures

Biomarker	Method	Analyte	Result
Microsatellite Instability (MSI)	Seq	DNA-Tumor	High
Tumor Mutational Burden (TMB)	Seq	DNA-Tumor	Result: High 48 Low 10 High
Genomic Loss of Heterozygosity (LOH)	Seq	DNA-Tumor	Low - 3% of tested genomic segments exhibited LOH (assay threshold is ≥ 16%)

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MI FOLFOXai™

Result:

DECREASED BENEFIT to FOLFOX + bevacizumab in first-line metastatic CRC

Intended Use and Result Interpretation:

To determine the sequencing of therapy for patients who are not being considered for FOLFOXIRI:

This patient may achieve improved results by receiving an alternative to FOLFOX, such as FOLFIRI, as their initial regimen.

As an adjustment to frontline FOLFOXIRI following toxicity:

This patient may achieve improved results by removing the oxaliplatin portion of their regimen.

MI FOLFOXai is a molecular signature that predicts relative benefit from FOLFOX + bevacizumab therapy given as the first-line treatment in metastatic colorectal cancer patients. The signature was developed using Caris Molecular Intelligence sequencing data and an artificial intelligence algorithm. The signature was validated using two independent data sets, as reported in Abraham et al., "Clinical validation of a machine-learning derived signature predictive of outcomes from first-line oxaliplatin-based chemotherapy in patients with advanced colorectal cancer". (December 8, 2020), Clinical Cancer Res., 10.1158/1078-0432.CCR-20-3286.

412 manually curated cases with real world evidence (insurance claims, electronic medical records and death registries):

Median Overall Survival difference between the increased benefit arm and the decreased benefit arm: 17.5 months

149 cases analyzed retrospectively from the randomized, prospective Phase III TRIBE2 study:

Median Overall Survival difference between the increased benefit arm and the decreased benefit arm: 6.0 months

All patients in the validation studies above had stage IV CRC and received FOLFOX + bevacizumab.

Any therapeutic decision should be based on the physician's judgement considering all of the patient's clinical conditions. Please see the Appendix of this report for MI FOLFOXai methodology.

Genes Tested with Pathogenic or Likely Pathogenic Alterations

Gene	Method	Analyte	Variant Interpretation	Protein Alteration	Exon	DNA Alteration	Variant Frequency %
ARID1A	Seq	DNA-Tumor	Pathogenic Variant	p.R1593fs	18	c.4777delC	14
	Seq	DNA-Tumor	Pathogenic Variant	p.D1850fs	20	c.5548delG	17
BRCA2	Seq	DNA-Tumor	Pathogenic Variant	p.N2460fs	14	c.7379delA	19
GATA3	Seq	DNA-Tumor	Likely Pathogenic Variant	p.V379fs	6	c.1134delA	17
KMT2A	Seq	DNA-Tumor	Pathogenic Variant	p.K1748*	17	c.5242A>T	15
KMT2C	Seq	DNA-Tumor	Pathogenic Variant	p.P2135fs	36	c.6404delC	15
MLH3	Seq	DNA-Tumor	Pathogenic Variant	p.N674fs	2	c.2021delA	14
MSH3	Seq	DNA-Tumor	Pathogenic Variant	p.K383fs	7	c.1148delA	18
NBN	Seq	DNA-Tumor	Pathogenic Variant	p.R466fs	10	c.1396delA	17
NTRK1	Seq	RNA-Tumor	Pathogenic Fusion	TPM3-NTRK1	10	-	-
PPM1D	Seq	DNA-Tumor	Pathogenic Variant	p.N512fs	6	c.1535dupA	22
SETD2	Seq	DNA-Tumor	Pathogenic Variant	p.R1407fs	3	c.4219delA	18
SMAD2	Seq	DNA-Tumor	Likely Pathogenic Variant	p.L453S	11	c.1358T>C	17
	Seq	DNA-Tumor	Pathogenic Variant	p.R57*	2	c.169C>T	16
SPEN	Seq	DNA-Tumor	Pathogenic Variant	p.A2105fs	11	c.6313delG	22

PATIENT:	TN22-	PHYSICIAN:

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CustomerSupport@carisls.com

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