First name
Nathan
Last name
Taylor Davies

Ordering Physician
Dr. Evans

Specimen selected by
Laboratory Clinic Rochester, 123 Main Street Springfield XY123456, USA

Date of Birth
4 NOV 1965

Sex
Male

Patient ID
01-153-19

Pathology
Colorectal cancer

Specimen ID: 01-153-19
Specimen Type: Excisional Biopsy
Preservation method: FFPE
Specimen Collected: -
Specimen Received: -

// Conclusion

Given the actionable biomarkers identified in the patient, a suggested therapy can be combination of Cetuximab and Encorafenib, Ipilimumab and Nivolumab, and Pembrolizumab. Additional systemic therapy to be considered. Patient needs to be re-assessed for clinical progression.

// Overview

Result
Actionability identified

Tumor cell %	MSI status	TMB (all)	TMB (non-synonymous)
40%	High	46.2 mut/Mb	36.2 mut/Mb

3 Actionable biomarkers

3 Therapies with potential benefit **in tumor**

0 Therapies with potential benefit **in different tumor**

0 Therapies with lack of potential benefit

// Summary

SOPHiA GENETICS application: TruSight Oncology 500

About the test: -

Referral reason: Colorectal cancer

Actionable biomarkers	Therapies with potential benefit **in tumor**	Therapies with potential benefit **in different tumor**	Therapies with lack of potential benefit
BRAF V600E	Cetuximab + Encorafenib	-	-
MSI high	Ipilimumab + Nivolumab, Pembrolizumab	-	-
TMB high	Pembrolizumab	-	-

0 Prognostic biomarkers

0 Diagnostic biomarkers

0 Biomarkers with potential clinical significance

// Patient clinical history

Nathan is a 56 years old male with metastatic colorectal cancer. This patient presented with a 2-month history of bloating and abdominal discomfort. His last colonoscopy was about 2 years ago and was negative, and he also had some unintentional weight loss. With regard to his past medical history, it's significant only because of high blood pressure, which is controlled with lisinopril.

// Reported variants

Actionable variants in patient's tumor type

BRAF NM_004333.5:c.1799T>A, p.(Val600Glu) — BRAF V600E

Variant fraction	Coding consequence	Genomic position	Classification	Association type
16.5%	**missense**	**GRCh37/hg19**	**Pathogenic**	**Therapeutic**
Exon	Depth	**Chr7:140453136**	ClinVar	AMP/ASCO/CAP Classification
15	**2208**		**Drug response**	**IA**
			rs1219913440	

Actionable variants in different tumor type

None reported

Other variants with potential clinical significance

None reported

// Other reported variants

None reported

// Reported therapies

Patient's tumor type

Cetuximab (IMC-C225)
+ Encorafenib (LGX818)

EGFR Antibody
BRAF Inhibitor

Approval status	Molecular profile	Disease	Reference
FDA approved - On Companion Diagnostic	**BRAF V600E**	**Colorectal cancer** sensitive	**PMID: 31566309**

Ipilimumab (BMS-734016)
+ Nivolumab (MDX-1106, BMS-936558)

CTLA4 Antibody, Immune Checkpoint Inhibitor
Immune Checkpoint Inhibitor, PD-L1/PD-1 antibody

Approval status	Molecular profile	Disease	Reference
FDA approved	**MSI high**	**Colorectal cancer** sensitive	**PMID: 29355075**

Pembrolizumab (MK-3475)

Immune Checkpoint Inhibitor, PD-L1/PD-1 antibody

Approval status	Molecular profile	Disease	Reference
FDA approved	**MSI high**	**Colorectal cancer** sensitive	**PMID: 33264544**
FDA approved - On Companion Diagnostic	**TMB high**	**Advanced Solid Tumor** sensitive	**PMID: 30787022**

Vemurafenib (RO5185426|PLX4032)

RAF Inhibitor (Pan)

Approval status	Molecular profile	Disease	Reference
Phase II	**BRAF V600E**	**Colorectal cancer** no benefit	**PMID: 20179705**

Different tumor type

None reported

// Interpretation

BRAF V600E

Tier IA

Clinical Associations

Cetuximab + Encorafenib

In a Phase III (BEACON CRC) trial that supported FDA approval, Braftovi (encorafenib) and Erbitux (cetuximab) combination treatment (n=113) resulted in improved median overall survival (8.4 vs 5.4 months, HR=0.60, p<0.001), confirmed response rate (20% vs 2%, p<0.001), and median progression-free survival (4.2 vs 1.5 months, HR=0.40, p<0.001) compared to control (n=107) in patients with metastatic colorectal cancer harboring BRAF V600E (PMID: 31566309; NCT02928224).

Vemurafenib

In a Phase II trial (MyPathway), Zelboraf (vemurafenib) treatment resulted in an objective response of 46% (12/26, 2 complete response, 10 partial response) in patients with advanced solid tumors harboring BRAF V600E, but only 4% (1/23, 1 partial response) in patients harboring non-V600 BRAF mutations (PMID: 29320312; NCT02091141).

Biomarker Description(s)

BRAF V600E (previously reported as V599E) lies within the activation segment of the kinase domain of the Braf protein (PMID: 15035987). V600E 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 (PMID: 15035987, PMID: 29533785).
BRAF NM_004333.5:c.1799T>A, p.(Val600Glu)

MSI high

Tier IA

Clinical Associations

Ipilimumab + Nivolumab

In a Phase II (CheckMate 142) trial that supported FDA approval, Opdivo (nivolumab) and Yervoy (ipilimumab) combination treatment resulted in an objective response rate of 54.6% (65/119), 4 complete response, 61 partial response, and disease control for more than 12 weeks in 80% of patients with DNA mismatch repair-deficient (dMMR), microsatellite instability-high (MSI-H) metastatic colorectal cancer, regardless of BRAF and KRAS mutational status (PMID: 29355075; NCT02060188).

Pembrolizumab

In a Phase II (KEYNOTE-164) trial that supported FDA approval, Keytruda (pembrolizumab) treatment resulted in an objective response rate of 32% (20/63, 2 complete responses, 18 partial responses), a median progression-free survival of 4.1 months in patients with advanced microsatellite instability-high (MSI-H) colorectal cancer whose disease progressed after more than 1 line of therapy (Annals of Oncology, Volume 29, Issue suppl_5; NCT02460198).

Biomarker Description(s)

MSI high indicates a high level of microsatellite instability.
MSI high

TMB high

Tier IA

Clinical Associations

Pembrolizumab

In a retrospective analysis of a Phase II trial (KEYNOTE-158) that supported FDA approval, Keytruda (pembrolizumab) treatment resulted in superior objective response rate (28.3% vs 6.5%) in adult and pediatric patients with TMB high (TMB >= 10 mut/Mb, n=120) advanced solid tumors compared to patients with TMB low (TMB < 10 mut/Mb, n=635) tumors (Ann Oncol, 30 (Suppl 5), Oct 2019, v477-v478; NCT02628067).

Biomarker Description(s)

TMB high indicates a high tumor mutational burden.
-

Gene description(s)

BRAF

BRAF, serine/threonine-protein kinase B-raf, is a member of the Raf family of serine/threonine protein kinases, which signals through the MAP kinase pathway to regulate cell proliferation and cell growth (PMID: 24737949, PMID: 29540830). BRAF mutations and fusions have been identified in a variety of cancers, including, colorectal (PMID: 30122982), lung (PMID: 29729495), thyroid (PMID: 12970315), and melanoma (PMID: 24737949), and a number of mutations have also been demonstrated to confer drug resistance (PMID: 27478040).

// Methodology

SOPHiA GENETICS application
TSO500
SOPHiA DDM version
5.10.4--b131-b74ec54
Pipeline ID/Revision number/Splitting ID
LL1XG1G2_CNV_exome_1 / v5.5.34 / GEN1GN1FSQ2

Reference genome
GRCh37/hg19
Sequencer
Illumina NextSeq 2000

Run date
15.11.2021
Run name
Oncology Application
Analysis ID
200240322
MID
S21

Somatic gene variant annotations and related content have been powered by, without limitation, The Jackson Laboratory Clinical Knowledgebase (JAX-CKB™).

Variant classifications present in the report are the responsibility of the report author and approver.

Signature

Analyzed by **Dr. Smith**

Date 15.11.2021

Signature