CARIS MOLECULAR INTELLIGENCE®
ENABLING PRECISION MEDICINE

MI Profile Report

Report Summary – Biomarker Highlights and Drug Associations

The first page provides an overview of disease-relevant biomarkers and associated immunotherapies, targeted therapeutics and/or chemotherapies to inform more personalized treatment decisions.

Patient and Specimen Information

High Impact Results contain important biomarker and associated therapy results with 1) evidence and/or biomarker association included on the drug label (i.e. companion dx); 2) guideline-directed evidence, and/or 3) biomarkers with some clinical evidence or promising clinical trials.

Additional Results contains disease-relevant biomarker information, as well as other altered biomarker results.

MI PROFILE™

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Patient

Name: Patient, Test
Date of Birth: XX/Mon/19XX
Sex: Male
Case Number: TN19-XXXXXX
Diagnosis: Mucinous adenocarcinoma

Specimen Information

Primary Tumor Site: Transverse colon
Specimen Site: Liver
Specimen ID: ABC-1234-XYZ
Specimen Collected: XX-Mon-2019
Completion of Testing: XX-Mon-2019

Ordered By

Ordering Physician, MD
Cancer Center
123 Main Street
Springfield, XY 12345, USA
1 (123) 456-7890

High Impact Results

BIOMARKER	METHOD	RESULT	THERAPY ASSOCIATION		BIOMARKER LEVEL*
Mismatch Repair Status	IHC	Deficient	BENEFIT	nivolumab, nivolumab/ipilimumab combination, pembrolizumab	Level 1
MSI	NGS	High			
BRAF	NGS	Mutated, Pathogenic Exon 15 | p.V600E	BENEFIT	Irinotecan + [cetuximab or panitumumab] + vemurafenib	Level 2
			LACK OF BENEFIT	vemurafenib/dabrafenib monotherapy	Level 3A
ERBB2 (Her2/Neu)	CISH	Amplified	BENEFIT	lapatinib, pertuzumab, trastuzumab	Level 3A

* Biomarker reporting classification: Level 1 - highest level of clinical evidence and/or biomarker association included on the drug label; Level 2 - strong evidence of clinical significance and is endorsed by standard clinical guidelines; Level 3 - potential clinical significance (3A - evidence exists in patient's tumor type, 3B - evidence exists in another tumor type).

Biomarker Levels indicates the strength of evidence as defined by the FDA tiered biomarker reporting classification.

Therapies with Potential Benefit are noted in **green**.

Therapies with Potential Lack of Benefit are noted in **red**.

Important Note

This patient has a potential NCI-MATCH Trial-eligible result. Please see Clinical Trial *see page 6*

Important Note contains significant information about drug/biomarker associations and comments from Caris pathologists and/or molecular geneticists, if applicable.

Additional Results

CANCER TYPE RELEVANT BIOMARKERS		
Biomarker	Method	Result
NTRK1	RNA-Seq	Fusion Not Detected
NTRK2	RNA-Seq	Fusion Not Detected
NTRK3	RNA-Seq	Fusion Not Detected
Tumor Mutational Burden		High | 121 Mutations/Mb
ERBB2 (Her2/Neu)	NGS	Amplified
KRAS	NGS	Mutation Not Detected
NRAS	NGS	Mutation Not Detected
PIK3CA	NGS	Mutation Not Detected

CANCER TYPE RELEVANT BIOMARKERS (cont)		
Biomarker	Method	Result
PTEN	IHC	Positive | 1+, 55%
OTHER FINDINGS (see page 2 for additional results)		
Biomarker	Method	Result
PD-L1	SP142 IHC	Positive | 2+, 5%
FBXW7	NGS	Mutated, Pathogenic
		Exon 10 | p.R479Q
TSC1	NGS	Mutated, Pathogenic
		Exon 12 | p.N891fs
CCNE1	NGS	Amplified

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.

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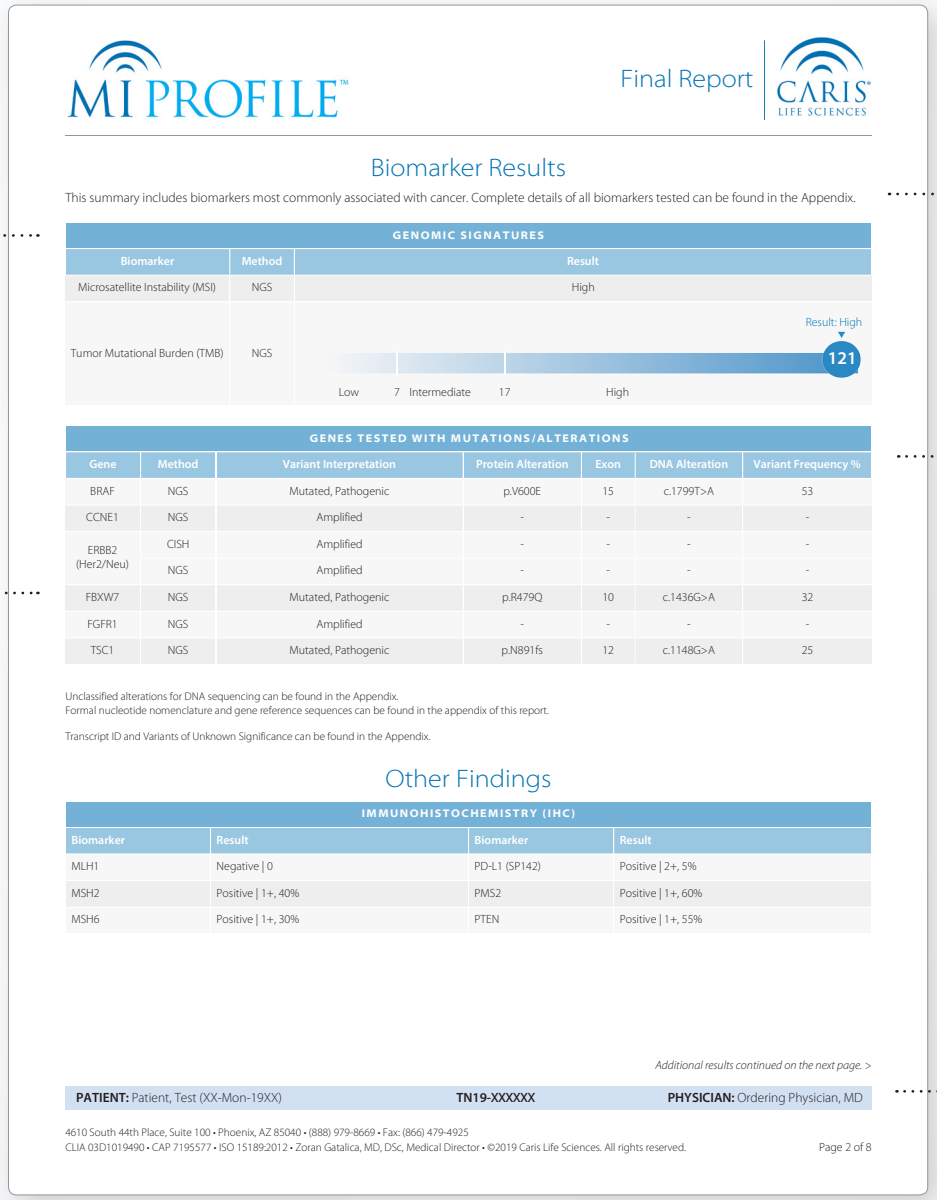
Biomarker Summary of Results

The Biomarker Summary of Results page includes biomarkers most commonly associated with cancer for each of the technologies performed. Complete biomarker details are found in the Appendix.



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Biomarker Results

This summary includes biomarkers most commonly associated with cancer. Complete details of all biomarkers tested can be found in the Appendix.

GENOMIC SIGNATURES

Biomarker	Method	Result
Microsatellite Instability (MSI)	NGS	High
Tumor Mutational Burden (TMB)	NGS	Result: High 121 (Low 7 Intermediate 17 High)

GENES TESTED WITH MUTATIONS/ALTERATIONS

Gene	Method	Variant Interpretation	Protein Alteration	Exon	DNA Alteration	Variant Frequency %
BRAF	NGS	Mutated, Pathogenic	p.V600E	15	c.1799T>A	53
CCNE1	NGS	Amplified	-	-	-	-
ERBB2 (Her2/Neu)	CISH	Amplified	-	-	-	-
	NGS	Amplified	-	-	-	-
FBXW7	NGS	Mutated, Pathogenic	p.R479Q	10	c.1436G>A	32
FGFR1	NGS	Amplified	-	-	-	-
TSC1	NGS	Mutated, Pathogenic	p.N891fs	12	c.1148G>A	25

Unclassified alterations for DNA sequencing can be found in the Appendix.
Formal nucleotide nomenclature and gene reference sequences can be found in the appendix of this report.

Transcript ID and Variants of Unknown Significance can be found in the Appendix.

Other Findings

IMMUNOHISTOCHEMISTRY (IHC)

Biomarker	Result	Biomarker	Result
MLH1	Negative | 0	PD-L1 (SP142)	Positive | 2+, 5%
MSH2	Positive | 1+, 40%	PMS2	Positive | 1+, 60%
MSH6	Positive | 1+, 30%	PTEN	Positive | 1+, 55%

Additional results continued on the next page. >

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Genomic signatures for both Microsatellite Instability (MSI) and Tumor Mutational Burden (TMB) are always reported first, if applicable.

Altered biomarkers are listed in alphabetical order.

Biomarker results are grouped based on their result (gene alterations, protein expression, etc.), thereby avoiding massive duplication and reducing page length.

For complete assay results see the Appendix section (interpretative statements, technical information, etc.).

Gene alteration information is included in the biomarker summary when a gene is mutated or altered.

Patient/case information is included on each page of the report.

Specimen Information

The Specimen Information page provides important sample details, including dates, gross description, pathologic diagnosis and dissection information.

Notes of significance contains additional information relevant to the case, as applicable.

Gross Description and Pathologic Diagnosis are included for additional reference.

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Notes of Significance

SEE APPENDIX FOR DETAILS

Clinical Trials Connector™ opportunities based on biomarker expression: 337 Targeted Therapy Trials. See page 6 for details.

Specimen Information

Specimen ID: ABC-12345-XYZ

Specimen Collected: XX/Mon/2019

Specimen Received: XX/Mon/2019

Testing Initiated: XX/Mon/2019

Gross Description: 1 (A) Paraffin Block - Client ID (ABC-123-XYZ)

Clinical History: Comments will appear here.

Pathologic Diagnosis: Comments will appear here.

Dissection Information: Molecular testing of this specimen was performed after harvesting of targeted tissues with an approved manual microdissection technique. Candidate slides were examined under a microscope and areas containing tumor cells (and separately normal cells, when necessary for testing) were circled. A laboratory technician harvested targeted tissues for extraction from the marked areas using a dissection microscope. The areas marked and extracted were microscopically reexamined on post-microdissected slides and adequacy of microdissection was reviewed by a board certified Pathologist.

Interpretation (Caris Life Sciences Microscopic Diagnosis):
Interpretation comment inserted for testing purposes

Electronic Signature
XX/Mon/2019

By my electronic signature, I as the attending pathologist affirm that I have personally reviewed and examined microscopically the prepared slide(s) and that the above diagnosis has been made or confirmed by me.

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Microdissection for every case (when possible) to increase the proportion of tumor cells for testing.

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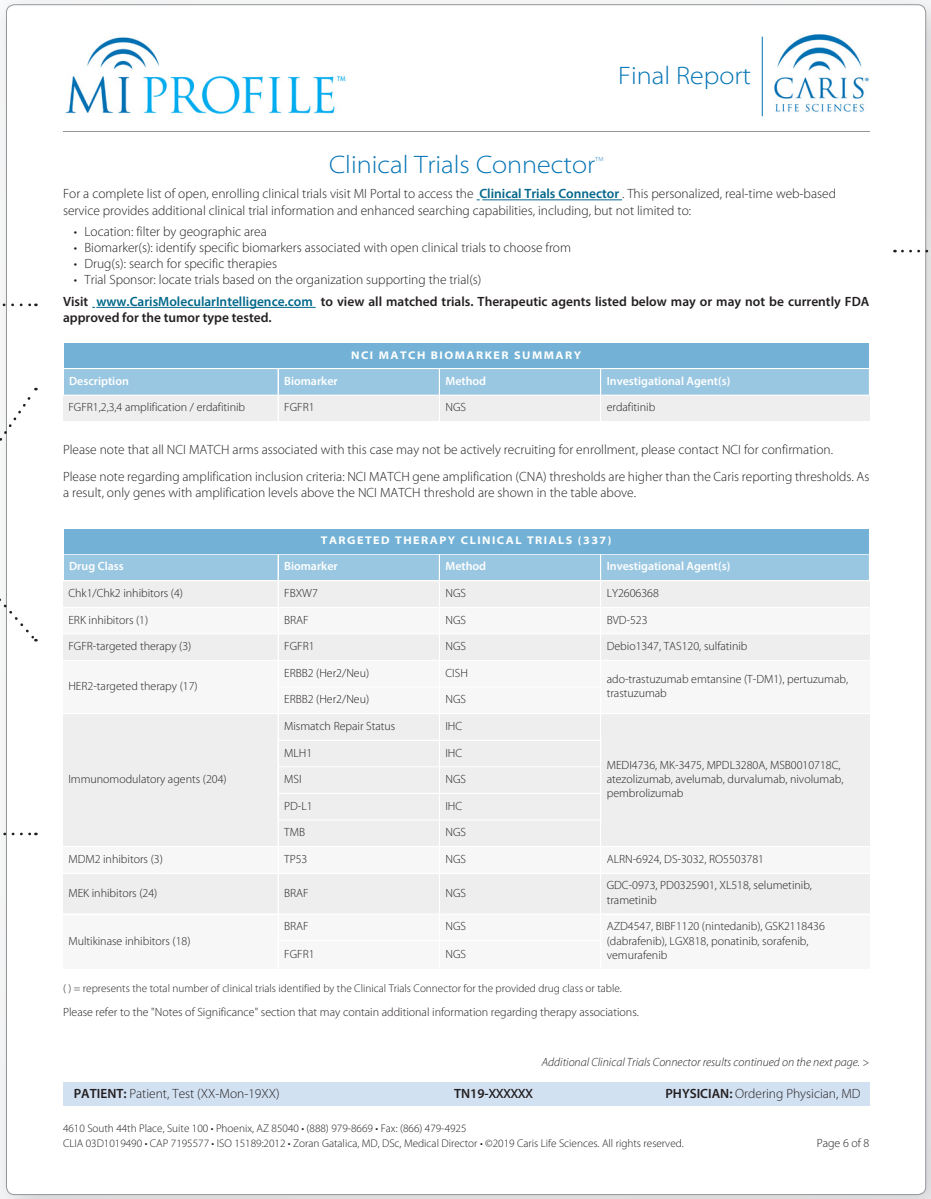
Clinical Trials Connector

The Clinical Trials Connector™ matches each patient's unique biomarker expression profile to open, relevant clinical trials opportunities.

Visit MI Portal to access regularly updated, molecularly matched clinical trial opportunities.

Clinical trials results are broken into different groups with drug class, biomarker, testing method and investigational agent information.

Dynamic results including the total number of clinical trial opportunities.



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Clinical Trials Connector™

For a complete list of open, enrolling clinical trials visit MI Portal to access the Clinical Trials Connector. This personalized, real-time web-based service provides additional clinical trial information and enhanced searching capabilities, including, but not limited to:

- Location: filter by geographic area
- Biomarker(s): identify specific biomarkers associated with open clinical trials to choose from
- Drug(s): search for specific therapies
- Trial Sponsor: locate trials based on the organization supporting the trial(s)

Visit www.CarisMolecularIntelligence.com to view all matched trials. Therapeutic agents listed below may or may not be currently FDA approved for the tumor type tested.

NCI MATCH BIOMARKER SUMMARY

Description	Biomarker	Method	Investigational Agent(s)
FGFR1,2,3,4 amplification / erdafitinib	FGFR1	NGS	erdafitinib

Please note that all NCI MATCH arms associated with this case may not be actively recruiting for enrollment, please contact NCI for confirmation.

Please note regarding amplification inclusion criteria: NCI MATCH gene amplification (CNA) thresholds are higher than the Caris reporting thresholds. As a result, only genes with amplification levels above the NCI MATCH threshold are shown in the table above.

TARGETED THERAPY CLINICAL TRIALS (337)

Drug Class	Biomarker	Method	Investigational Agent(s)
Chk1/Chk2 inhibitors (4)	FBXW7	NGS	LY2606368
ERK inhibitors (1)	BRAF	NGS	BVD-523
FGFR-targeted therapy (3)	FGFR1	NGS	Debio1347, TAS120, sulfatinib
HER2-targeted therapy (17)	ERBB2 (Her2/Neu)	CISH	ado-trastuzumab emtansine (T-DM1), pertuzumab, trastuzumab
	ERBB2 (Her2/Neu)	NGS	
Immunomodulatory agents (204)	Mismatch Repair Status	IHC	MEDI4736, MK-3475, MPDL3280A, MSB0010718C, atezolizumab, avelumab, durvalumab, nivolumab, pembrolizumab
	MLH1	IHC	
	MSI	NGS	
	PD-L1	IHC	
	TMB	NGS	
MDM2 inhibitors (3)	TP53	NGS	ALRN-6924, DS-3032, RO5503781
MEK inhibitors (24)	BRAF	NGS	GDC-0973, PD0325901, XL518, selumetinib, trametinib
Multikinase inhibitors (18)	BRAF	NGS	AZD4547, BIBF1120 (nintedanib), GSK2118436 (dabrafenib), LGX818, ponatinib, sorafenib, vemurafenib
	FGFR1	NGS	

( ) = represents the total number of clinical trials identified by the Clinical Trials Connector for the provided drug class or table.

Please refer to the "Notes of Significance" section that may contain additional information regarding therapy associations.

Additional Clinical Trials Connector results continued on the next page. >

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Detailed clinical trial information available through online Clinical Trials Connector™.

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Appendix

Appendix pages include full assay results, value information and technical details for each biomarker and technology, including appropriate cutoffs, units of measure, etc. .

Biomarker results by technology are listed in alphabetical order on the respective technology page.

Mutational Analysis by Next-Generation Sequencing (NGS)

GENES TESTED WITH ALTERATIONS						
Gene	Variant Interpretation	Protein Alteration	Exon	DNA Alteration	Variant Frequency %	Transcript ID
BRAF	Mutated, Pathogenic	p.V600E	15	c.1799T>A	53	NM_004333

Interpretation: The oncogenic p.V600E mutation was detected in BRAF

BRAF encodes a protein belonging to the raf/mil family of serine/threonine protein kinases. This protein plays a role in regulating the MAP kinase/ERK signaling pathway initiated by EGFR activation, which affects cell division, differentiation, and secretion. BRAF somatic mutations have been found in melanoma (43%), thyroid (39%), biliary tree (14%), colon (12%), and ovarian tumors (12%). BRAF inherited mutations are associated with Noonan/Cardio-Facio-Cutaneous (CFC) syndrome, syndromes associated with short stature, distinct facial features, and potential heart/skeletal abnormalities.

FBXW7	Mutated, Pathogenic	p.R479Q	10	c.1436G>A	32	NM_033632

Interpretation: A pathogenic mutation was detected in FBXW7

FBXW7 or E3 ligase F-box and WD repeat domain containing 7, also known as Cdc4, encodes three protein isoforms which constitute a component of the ubiquitin-proteasome complex. Mutation of FBXW7 occurs in hotspots and disrupts the recognition of and binding with substrates which inhibits the proper targeting of proteins for degradation (e.g. Cyclin E, c-Myc, SREBP1, c-Jun, Notch-1, mTOR and MCL1). Mutation frequencies identified in cholangiocarcinomas, acute T-lymphoblastic leukemia/lymphoma, and carcinomas of endometrium, colon and stomach are 35%, 31%, 9%, 9%, and 6%, respectively. Targeting an oncoprotein downstream of FBXW7, such as mTOR or c-Myc, may provide a novel therapeutic strategy.

TSC1	Mutated, Pathogenic	p.N891fs	12	c.1148G>A	25	NM_000368

Interpretation: A pathogenic mutation was detected in TSC1. Germline mutations in TSC1 are causal for Tuberous Sclerosis Complex.

This gene encodes a growth inhibitory protein thought to play a role in the stabilization of tuberin. Mutations in this gene have been associated with tuberous sclerosis. In complex with TSC2, inhibits the nutrient-mediated or growth factor-stimulated phosphorylation of S6K1 and EIF4EBP1 by negatively regulating mTORC1 signaling. Seems not to be required for TSC2 GAP activity towards RHEB. Implicated as a tumor suppressor. Involved in microtubule-mediated protein transport, but this seems to be due to unregulated mTOR signaling.

Protein Expression by Immunohistochemistry (IHC)

Biomarker	Patient Tumor			Thresholds*
	Staining Intensity (0, 1+, 2+, 3+)	Percent of cells	Result	Conditions for a Positive Result:
MLH1	0	100	Negative	Intensity ≥1+ and ≥1% of cells stained
MSH2	1 +	40	Positive	Intensity ≥1+ and ≥1% of cells stained
MSH6	1 +	30	Positive	Intensity ≥1+ and ≥1% of cells stained
PD-L1 (SP142)	2 +	5	Positive	Intensity ≥2+ and ≥5% of cells stained
PMS2	1 +	60	Positive	Intensity ≥1+ and ≥1% of cells stained
PTEN	1 +	55	Positive	Intensity ≥1+ and ≥1% of cells stained

Clones used: MLH1 (M1), MSH2 (G219-1129), MSH6 (44), PMS2 (EPR3947), PD-L1 (SP142), PTEN (6H2.1).

Electronic Signature
XX/Mon/2019

Full assay results, including descriptions and thresholds, are reported.

Methods for each technology are provided.

IHC Methods

The Laboratory Developed Tests (LDT) immunohistochemistry (IHC) assays were developed and their performance characteristics determined by Caris Life Sciences. These tests have not been cleared or approved by the US Food and Drug Administration. The FDA has determined that such clearance or approval is not currently necessary. Interpretations of all immunohistochemistry (IHC) assays were performed manually by a board certified pathologist.

The following IHC assays were performed using FDA-approved companion diagnostic or FDA-cleared tests consistent with the manufacturer's instructions: ALK (VENTANA ALK (D5F3) CDx Assay, Ventana), ER (CONFIRM anti-Estrogen Receptor (ER) (SP1), Ventana), PR (CONFIRM anti-Progesterone Receptor (PR) (1E2), Ventana), HER2/neu (PATHWAY anti-HER-2/neu (4B5), Ventana), Ventana), PD-L1 22c3 (pharmDx, Dako), PD-L1 SP142 (VENTANA, Ventana in Urothelial Carcinomas), and PD-L1 28-8 (pharmDx, Dako).

HER2 results and interpretation follow the ASCO/CAP scoring criteria.

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References

References pages include full citations for the biomarker and drug associations. More than 120,000 references have been evaluated and only the strongest citations are included.

Full citations of supporting biomarker and drug associations are listed.

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References

#	Drug	Biomarker	Reference
1	vemurafenib/dabrafenib monotherapy	BRAF	Kopetz, S., L. Saltz, et al. (2015). "Phase II Pilot Study of Vemurafenib in Patients with Metastatic BRAF-Mutated Colorectal Cancer." J Clin Oncol 33:1-7. View Citation Online
2	Irinotecan + [cetuximab or panitumumab] + vemurafenib	BRAF	Beson, A.B., D.A. Freedman-Cass et al (2018) "NCCN Guidelines Insights: Colon Cancer, Version 2.2018." J Natl Compr Canc Netw. 16(4):359-369. doi: 10.6004/jnccn.2018.0021 View Citation Online
3	Irinotecan + [cetuximab or panitumumab] + vemurafenib	BRAF	Kopetz 2017 "Randomized trial of irinotecan and cetuximab with or without vemurafenib in BRAF-mutant metastatic colorectal cancer (SWOG S1406)." Journal of Clinical Oncology 35, no. 15_suppl View Citation Online
4	lapatinib, pertuzumab, trastuzumab	ERBB2 (Her2/Neu)	Sartore-Bianchi, A., S. Siena, (2018) "Dual-targeted therapy with trastuzumab and lapatinib in treatment-refractory, KRAS codon 12/13 wild-type, HER2-positive metastatic colorectal cancer (HERACLES): a proof-of-concept, multicentre, open-label, phase 2 trial." Lancet Oncol.17(6):738-746 View Citation Online
5	lapatinib, pertuzumab, trastuzumab	ERBB2 (Her2/Neu)	Hainsworth, J.D., R. Kurzrock, et al (2018) "Targeted Therapy for Advanced Solid Tumors on the Basis of Molecular Profiles: Results From MyPathway, an Open-Label, Phase IIa Multiple Basket Study." J Clin Oncol. 36(6):536-542. View Citation Online
6	nivolumab, nivolumab/ipilimumab combination, pembrolizumab	Mismatch Repair Status, MSI	Le, DT, LA Diaz, et al. (2017). ""Mismatch repair deficiency predicts response of solid tumors to PD-1 blockade"". Science. 357:409-413. View Citation Online
7	nivolumab, nivolumab/ipilimumab combination, pembrolizumab	Mismatch Repair Status, MSI	Le, D.T., L.A. Diaz, et al. (2015). "PD-1 blockade in tumors with mismatch-repair deficiency". N Engl J Med. 372:2509-2520. View Citation Online
8	nivolumab, nivolumab/ipilimumab combination, pembrolizumab	Mismatch Repair Status, MSI	Overman, M.J., T. Andre, et. al. (2018) "Durable Clinical Benefit With Nivolumab Plus Ipilimumab in DNA Mismatch Repair-Deficient/Microsatellite Instability-High Metastatic Colorectal Cancer" J Clin Oncol 36:773-779. View Citation Online
9	nivolumab, nivolumab/ipilimumab combination, pembrolizumab	Mismatch Repair Status, MSI	Overman, M.J., T., Andre, et al. (2016) "Nivolumab ± ipilimumab in treatment (tx) of patients (pts) with metastatic colorectal cancer (mCRC) with and without high microsatellite instability (MSI-H): CheckMate-142 interim results." J Clin Oncol 34, (suppl; abstr 3501). View Citation Online

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References sorted for your convenience by drug and biomaker.

Each reference is hyperlinked to www.PubMed.org for study details.

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