Molecular Characterization Laboratory
Frederick National Laboratory for Cancer Research
Leidos Biomedical Research, Inc.
459 Miller Drive, Frederick, MD 21701
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OCAv3 Next-Generation Sequencing Assay Results

NCI Protocol #10323
Report Date: 8/28/2019

INVESTIGATIONAL USE ONLY

The OCAv3 next-generation sequencing (NGS) assay identifies more than 3000 annotated mutations of interest (MOIs) broadly categorized into 5 mutation types: single nucleotide variants (SNV), small insertions/deletions (Indels), large (>3 bases) insertions/deletions (Large Indels), copy number variants (CNV), and gene fusions. This report summarizes annotated mutations identified in the tumor specimen identified below.

Patient Name: James Johnson	**Patient ID:** MD123-0001	**Specimen ID:** 10323-SK78WG02-1	**MoCha Sample ID:** OCA-15002
Referring Physician: Robert Smith		**Telephone:** 202-555-1234	**Fax:** 202-555-4321
Biopsy Site: Skin	**Date Collected:** Aug 07 2019	**Primary Diagnosis:** Melanoma	**Tumor Content (%)[1,2]:** 75

MOIs (Mutations of Interest) Detected

Single Nucleotide Variants (SNVs) & Small/Large Indels[3,4,5]:

Gene	ID Code	VAF[3]	Variant Class[4]	Function	HGVS[5]	Transcript ID	Protein Change
NRAS	COSM566	37.63%	Hotspot	missense	c.35G>T	NM_002524.4	p.(G12V)
BRAF	COSM476	68.14%	Hotspot	missense	c.1799T>A	NM_004333.4	p.(V600E)
TP53		6.07%	Hotspot	missense	c.557A>G	NM_000546.5	p.(D186G)

Copy Number Variants (CNVs)[6]:

Gene	Chromosome:Position	Copy Number
CDK4	chr12:58141846	8.58
BCL9	chr1:147022100	5.14

Gene Fusions: None identified

Driver Gene	Partner Gene	Annotation (Exon Junction)

[1] *Assessment performed by Nationwide Children's Hospital, 700 Children's Drive, Columbus, OH 43205*

[2] *Reported assay characteristics cannot be guaranteed for specimens that present a tumor content below 20%*

[3] *Reporting thresholds established at ≥ 0.05 Variant Allele Frequency (VAF) for variants annotated as MOIs and at ≥ 0.10 VAF for nonsense SNV and frame-shift indels in tumor suppressor genes*

[4] *Oncomine Variant Classes: Hotspot, Deleterious, Amplification, Fusion (see Key to Variant Classes)*

[5] *Human Genome Variation Society nomenclature (current version)*

[6] *Reporting threshold established at ≥ 7 copies*

Comments:

SIGNATURE APPROVAL:

The signature below attests that the signee has reviewed the data and results reported and concurs with the stated conclusions.

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The OCAv3 NGS Assay

Methodology, Scope, and Application: *The assay utilizes the Thermo Fisher Scientific Oncomine® Comprehensive Assay v3.0 (OCAv3), a next-generation sequencing (NGS) assay that utilizes a multiplex polymerase chain reaction (PCR) with DNA and RNA extracted from formalin-fixed tissue for sequencing on the Ion S5 XL platform and analyzed by Torrent Suite Software v5.12 and Ion Reporter v5.12. The OCAv3 NGS Assay currently can reliably identify the presence or absence of >3000 known mutations and polymorphisms in the 161 unique genes compared to the Human Reference Genome hg19, including the genes listed below. The OCAv3 assay is a laboratory developed test designed to find gene mutations within tumors (somatic mutations).*

Analytical Sensitivity and Specificity: *The OCAv3 NGS Assay has been determined to be suitably analytically sensitive and specific for the various types of abnormalities within its reportable range, demonstrating 97.18% sensitivity compared with orthogonal assay results and 100% specificity for the 5 mutation types reported. 99.99% or greater reproducibility has been demonstrated. All quality measures for this assay were within defined assay parameters.*

Hereditary and Germline Mutations: *This assay examines tumor tissue only and does not examine normal (non-tumor) tissue. Mutations detected by the assay may be present only in the tumor, or in every cell of the body (including non-tumor cells). This test also cannot tell whether a potential germline mutation causes or will cause a hereditary cancer syndrome. If the patient's history includes any one or combination of features suggestive of a possible hereditary cancer predisposition (such as, cancer arising at a young age, especially a cancer of a type unusual in younger patients; a personal history of multiple different types of cancers; or a significant cancer history among blood relatives, especially but not exclusively of the same type as the patient's) it is recommended that the physician arrange for the patient to meet with a genetic counselor and, if warranted, undergo the appropriate genetic test on normal (i.e. non-tumor) tissue (blood or cells brushed from the oral surface of the cheek) to check for a germline abnormality, regardless of the results of this research study.*

Mutations in genes that are tested for by the OCAv3 NGS Assay and that, when present in normal tissue, may be associated with hereditary cancer conditions are indicated (*) in the table below. Listed genes were identified based on currently available published data about known associations with certain health issues. Results demonstrating a mutation in one of these genes may or may not be compatible with a germline mutation. Please refer to the publication "Recommendations for reporting of secondary findings in clinical exome and genome sequencing, 2016 update (ACMG SF v2.0): a policy statement of the American College of Medical Genetics and Genomics" [Kalia SS et al. Genetics in Medicine volume 19, pages 249–255 (2017)] for further information.

Genes Identified by the OCAv3 NGS Assay

Hotspot Genes (n=87)				Tumor Suppressor Genes with Deleterious Mutations (n=48)			Amplified Genes (n=47)			Fusion Driver Genes (n=51, 762 assays)		
AKT1	*ESR1*	*KIT **	*PDGFRB*	*ARID1A*	*NF1 **	*STK11 **	*AKT1*	*FGFR2*	*TERT*	*AKT2*	*KRAS*	*RB1 **
AKT2	*EZH2*	*KNSTRN*	*PIK3CA*	*ATM **	*NF2 **	*TP53 **	*AKT2*	*FGFR3*	*TSC1 **	*ALK*	*MDM4*	*RELA*
AKT3	*FGFR1*	*KRAS*	*PIK3CB*	*ATR*	*NOTCH1*	*TSC1 **	*AKT3*	*FGFR4*	*TSC2 **	*AR*	*MET*	*RET **
ALK	*FGFR2*	*MAGOH*	*PPP2R1A*	*ATRX*	*NOTCH2*	*TSC2 **	*ALK*	*FLT3*		*AXL*	*MYB*	*ROS1*
AR	*FGFR3*	*MAP2K1*	*PTPN11*	*BAP1 **	*NOTCH3*		*AR*	*IGF1R*		*BRAF*	*MYBL1*	*RSPO2*
ARAF	*FGFR4*	*MAP2K2*	*RAC1*	*BRCA1 **	*PALB2*		*AXL*	*KIT **		*BRCA1 **	*NF1 **	*RSPO3*
AXL	*FLT3*	*MAP2K4*	*RAF1*	*BRCA2 **	*PIK3R1*		*BRAF*	*KRAS*		*BRCA2 **	*NOTCH1*	*TERT*
BRAF	*FOXL2*	*MAPK1*	*RET **	*CDK12*	*PMS2 **		*CCND1*	*MDM2*		*CDKN2A **	*NOTCH4*	
BTK	*GATA2 **	*MAX **	*RHEB*	*CDKN1B*	*POLE1*		*CCND2*	*MDM4*		*EGFR **	*NRG1*	
CBL	*GNA11*	*MDM4*	*RHOA*	*CDKN2A **	*PTCH1 **		*CCND3*	*MET*		*ERBB2*	*NTRK1*	
CCND1	*GNAQ*	*MED12*	*ROS1*	*CDKN2B*	*PTEN **		*CCNE1*	*MYC*		*ERBB4*	*NTRK2*	
*CDK4 **	*GNAS*	*MET*	*SF3B1*	*CHEK1*	*RAD50*		*CDK2*	*MYCL*		*ERG*	*NTRK3*	
CDK6	*H3F3A*	*MTOR*	*SMAD4 **	*CREBBP*	*RAD51*		*CDK4 **	*MYCN*		*ESR1*	*NUTM1*	
*CHEK2 **	*HIST1H3B*	*MYC*	*SMO*	*FANCA*	*RAD51B*		*CDK6*	*NTRK1*		*ETV1*	*PDGFRA **	
CSF1R	*HNF1A*	*MYCN*	*SPOP*	*FANCD2*	*RAD51C*		*CDKN2A **	*NTRK2*		*ETV4*	*PDGFRB*	
CTNNB1	*HRAS*	*MYD88*	*SRC*	*FANCI*	*RAD51D*		*CDKN2B*	*NTRK3*		*ETV5*	*PIK3CA*	
DDR2	*IDH1*	*NFE2L2*	*STAT3*	*FBXW7*	*RB1 **		*EGFR **	*PDGFRA **		*FGFR1*	*PPARG*	
*EGFR **	*IDH2*	*NRAS **	*TERT*	*MLH1*	*RNF43*		*ERBB2*	*PDGFRB*		*FGFR2*	*PRKACA*	
ERBB2	*JAK1*	*NTRK1*	*TOP1*	*MRE11A*	*SETD2*		*ESR1*	*PIK3CA*		*FGFR3*	*PRKACB*	
ERBB3	*JAK2 **	*NTRK2*	*U2AF1*	*MSH2 **	*SLX4*		*FGF19*	*PIK3CB*		*FGR*	*PTEN **	
ERBB4	*JAK3*	*NTRK3*	*XPO1*	*MSH6 **	*SMARCA4*		*FGF3*	*PPARG*		*FLT3*	*RAD51B*	
ERCC2	*KDR*	*PDGFRA **		*NBN*	*SMARCB1 **		*FGFR1*	*RICTOR*		*JAK2 **	*RAF1*	

Key to Variant Classes:

Hotspot:	Recurrent missense or in-frame mutation in one of the 87 identified hotspot genes or one of the 48 tumor suppressor genes
Deleterious:	Nonsense or frameshift mutation in one of the 48 tumor suppressor genes
Amplification:	Increased copy number in one of the 47 identified genes or one of the 48 tumor suppressor genes
Fusion:	Gene fusion Involving one of the 762 targeted assays

APPENDIX 1: Appended to this report is an annotated summary of variant details and clinically significant biomarkers, as well as references to potentially relevant therapies and clinical trials. The annotated summary is the result of curated published data sources generated by the Ion Torrent Bioinformatics Data Analysis pipeline via the Oncomine Knowledgebase Reporter (OKR). The summary is not exhaustive and may not include all variants reported by this clinical report. This information is provided for reference purposes only and is not intended to direct or otherwise support assignment of specific therapies and/or clinical trials for this patient.

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Relevant Melanoma Findings

Gene	Finding
BRAF	***BRAF p.(V600E) c.1799T>A***
KIT	Not detected
NTRK1	Not detected
NTRK2	Not detected
NTRK3	Not detected

Clinically Significant Biomarkers

Indicated Contraindicated

Genomic Alteration	Relevant Therapies (In this cancer type)	Relevant Therapies (In other cancer type)	Clinical Trials
BRAF p.(V600E) c.1799T>A B-Raf proto-oncogene, serine/threonine kinase Tier: IA Allele Frequency: 68.14%	dabrafenib + trametinib [1] dabrafenib [1] trametinib [1] binimetinib + encorafenib [1] cobimetinib + vemurafenib [1] vemurafenib [1]	dabrafenib + trametinib [1] dabrafenib [1] trametinib [1] cetuximab + vemurafenib + chemotherapy panitumumab + vemurafenib + chemotherapy vemurafenib	25
NRAS p.(G12V) c.35G>T NRAS proto-oncogene, GTPase Tier: IIC Allele Frequency: 37.63%	None	cetuximab [1] panitumumab [1]	11
CDK4 amplification cyclin dependent kinase 4 Tier: IIC	None	None	4
TP53 p.(D186G) c.557A>G tumor protein p53 Tier: IIC Allele Frequency: 6.07%	None	None	1

Sources included in relevant therapies: FDA[1], NCCN

Prevalent cancer biomarkers without clinical significance based on included data sources
BCL9 amplification

Variant Details

DNA Sequence Variants

Gene	Amino Acid Change	Coding	Variant ID	Locus	Allele Frequency	Transcript	Variant Effect
NRAS	p.(G12V)	c.35G>T	COSM566	chr1:115258747	37.63%	NM_002524.4	missense
BRAF	p.(V600E)	c.1799T>A	COSM476	chr7:140453136	68.14%	NM_004333.4	missense
TP53	p.(D186G)	c.557A>G	.	chr17:7578373	6.07%	NM_000546.5	missense

Copy Number Variations

Gene	Locus	Copy Number
BCL9	chr1:147022100	5.14
CDK4	chr12:58141846	8.58

Biomarker Descriptions

BRAF (B-Raf proto-oncogene, serine/threonine kinase)

Background: The BRAF gene encodes the B-Raf proto-oncogene serine/threonine kinase, a member of the RAF family of serine/threonine protein kinases which also includes ARAF and RAF1 (CRAF). BRAF is among the most commonly mutated kinases in cancer[1]. Activation of the MAPK pathway occurs through BRAF mutations and leads to an increase in cell division, differentiation, and survival[2].

Alterations and prevalence: Recurrent somatic mutations in BRAF are observed in 40-60% of melanoma and thyroid cancer, approximately 10% of colorectal cancer, and about 2% of non-small cell lung cancer (NSCLC)[3,4,5,6,7]. The most recurrent somatic BRAF mutation across diverse cancer types is V600E in exon 15, which results in constitutive kinase activity by relieving negative regulatory inhibition[8]. BRAF V600E is universally present in hairy cell leukemia, mature B-cell cancer and prevalent in histiocytic neoplasms[9,10,11]. Other recurrent BRAF somatic mutations cluster in the glycine-rich phosphate-binding loop at codons 464-469 in exon 11 as well as additional codons flanking V600 in the activation loop[8]. In primary cancers, BRAF amplification is observed in 8% of ovarian cancer and about 1% of breast cancer[4,7]. Chromosomal translocations generating BRAF fusions with a range of partner genes are uncommon (about 0.5%) but have been described in melanoma that lack V600 mutations, thyroid cancer, pilocytic astrocytoma, NSCLC, and several other cancer types[12,13,14,15,16]. BRAF fusions retain the kinase domain but lack the autoinhibitory N-terminal domain of BRAF[12,14].

Potential clinical relevance: Vemurafenib[17] (2011) was the first targeted therapy approved for the treatment of patients with unresectable or metastatic melanoma with BRAF V600E mutation. Subsequently, BRAF kinase inhibitors including dabrafenib[18] (2013) and encorafenib[19] (2018) were approved for the treatment of patients with unresectable or metastatic melanoma with BRAF V600E/K mutations. Due to the tight coupling of RAF and MEK, several MEK inhibitors have been approved for patients harboring BRAF alterations. Trametinib[20] (2013) and binimetinib[21] (2018) were approved for the treatment of metastatic melanoma with BRAF V600E/K mutations. Combination therapies of BRAF plus MEK inhibitors have been approved in melanoma and NSCLC. The combinations of dabrafenib and trametinib (2015) and vemurafenib and cobimetinib[22] (2015) were approved for the treatment of patients with unresectable or metastatic melanoma with a BRAF V600E mutation. Subsequently, the combination of dabrafenib and trametinib was

Biomarker Descriptions (continued)

approved for metastatic NSCLC (2017) with a BRAF V600E mutation. BRAF amplification, alternative splice transcripts, and BRAF fusions are suggested mechanisms of resistance to BRAF targeted therapy in melanoma[23,24,25,26]. Other mechanisms of resistance include activating mutations in KRAS, NRAS, and MAP2K1/2 (MEK1/2) as well as activation of PI3K signaling[25,27,28,29,30]. Clinical responses to sorafenib and trametinib in limited case studies of patients with BRAF fusions have been reported[16].

CDK4 (cyclin dependent kinase 4)

Background: The CDK4 gene encodes the cyclin-dependent kinase-4 protein, a homologue of CDK6. Both proteins are serine/threonine protein kinases that are involved in the regulation of the G1/S phase transition of the mitotic cell cycle[31,32]. CDK4 kinase is activated by complex formation with D-type cyclins (e.g., CCND1, CCND2, or CCND3), which leads to the phosphorylation of retinoblastoma protein (RB), followed by E2F activation, DNA replication, and cell-cycle progression[33]. Germline mutations in CDK4 are associated with familial melanoma[34,35,36].

Alterations and prevalence: Recurrent somatic mutations of CDK4 codon K22 and R24 are observed in melanoma (1-2%) and lung cancer (approximately 0.1%). Codons K22 and R24 are necessary for binding and inhibition by p16/CDKN2A[37,38,39]. CDK4 is recurrently amplified in several cancer types, most notably in sarcomas (15-20%), glioma (10-15%), adrenocortical carcinoma (5%), lung adenocarcinoma (5%), and melanoma (3%)[4,6,7,40].

Potential clinical relevance: Currently, no therapies are approved for CDK4 aberrations. Small molecule inhibitors targeting CDK4/6--including palbociclib (2015), abemaciclib (2017), and ribociclib (2017)-- are FDA approved in combination with an aromatase inhibitor or fulvestrant for the treatment of hormone receptor-positive, HER2-negative advanced or metastatic breast cancer.

NRAS (NRAS proto-oncogene, GTPase)

Background: The NRAS proto-oncogene encodes a GTPase that functions in signal transduction and is a member of the RAS superfamily which also includes KRAS and HRAS. RAS proteins mediate the transmission of growth signals from the cell surface to the nucleus via the PI3K/AKT/MTOR and RAS/RAF/MEK/ERK pathways, which regulate cell division, differentiation, and survival[41,42,43].

Alterations and prevalence: Recurrent mutations in RAS oncogenes cause constitutive activation and are found in 20-30% of cancers. NRAS mutations are particularly common in melanomas (up to 25%) and are observed at frequencies of 5-10% in acute myeloid leukemia, colorectal, and thyroid cancers[7,44]. The majority of NRAS mutations consist of point mutations at G12, G13, and Q61[7,45]. Mutations at A59, K117, and A146 have also been observed but are less frequent[4,46].

Potential clinical relevance: Currently, no therapies are approved for NRAS aberrations. The EGFR antagonists, cetuximab and panitumumab, are contraindicated for treatment of colorectal cancer patients with NRAS mutations in exon 2 (codons 12 and 13), exon 3 (codons 59 and 61), and exon 4 (codons 117 and 146)[46,47,48]. NRAS mutations are associated with poor prognosis in patients with low-risk myelodysplastic syndrome[49] as well as melanoma[50]. In a phase III clinical trial in patients with advanced NRAS-mutant melanoma, binimetinib improved progression free survival (PFS) relative to dacarbazine with median PFS of 2.8 and 1.5 months, respectively[51].

TP53 (tumor protein p53)

Background: The TP53 gene encodes the p53 tumor suppressor protein that binds to DNA and activates transcription in response to diverse cellular stresses to induce cell cycle arrest, apoptosis, or DNA repair. In unstressed cells, TP53 is kept inactive by targeted degradation via MDM2, a substrate recognition factor for ubiquitin-dependent proteolysis. Alterations in TP53 is required for oncogenesis as they result in loss of protein function and gain of transforming potential[52]. Germline mutations in TP53 are the underlying cause of Li-Fraumeni syndrome, a complex hereditary cancer predisposition disorder associated with early-onset cancers[53,54].

Alterations and prevalence: TP53 is the most frequently mutated gene in the cancer genome with approximately half of all cancers experiencing TP53 mutations. Ovarian, head and neck, esophageal, and lung squamous cancers have particularly high TP53 mutation rates (60-90%)[4,7,55,56,57,58]. Approximately two-thirds of TP53 mutations are missense mutations and several recurrent missense

Biomarker Descriptions (continued)

mutations are common including substitutions at codons R158, R175, R248, R273, and R282[4,7]. Invariably, recurrent missense mutations in TP53 inactivate its ability to bind DNA and activate transcription of target genes[59,60,61,62].

Potential clinical relevance: Currently, no targeted therapies are approved for TP53 aberrations. TP53 mutations confer poor prognosis in acute myeloid leukemias, as well as myelodysplastic syndromes and myeloproliferative neoplasms[49,63,64]. Several investigational therapies including drugs aimed at restoring wild type p53 activity, affecting downstream targets, or compounds that induce synthetic lethality are under clinical evaluation[65,66].

Relevant Therapy Summary

● In this cancer type ○ In other cancer type ◑ In this cancer type and other cancer types ⊘ Contraindicated ⚠ Both for use and contraindicated ✖ No evidence

BRAF p.(V600E) c.1799T>A

Relevant Therapy	FDA	NCCN	Clinical Trials*
dabrafenib	◑	◑	✖
dabrafenib + trametinib	◑	◑	✖
trametinib	◑	✖	✖
vemurafenib	●	◑	✖
cobimetinib + vemurafenib	●	●	● (II)
binimetinib + encorafenib	●	●	✖
cetuximab + vemurafenib + irinotecan	✖	○	✖
panitumumab + vemurafenib + irinotecan	✖	○	✖
dabrafenib + spartalizumab + trametinib, dabrafenib + trametinib + placebo	✖	✖	● (III)
dabrafenib + trametinib, ipilimumab + nivolumab, nivolumab	✖	✖	● (III)
atezolizumab + cobimetinib + surgical intervention, atezolizumab + cobimetinib + vemurafenib + surgical intervention	✖	✖	● (II)
dabrafenib + nivolumab + trametinib	✖	✖	● (II)
dabrafenib + pembrolizumab + trametinib	✖	✖	● (II)
dabrafenib + trametinib + surgical intervention	✖	✖	● (II)
ipilimumab + pembrolizumab	✖	✖	● (II)

* Most advanced phase (IV, III, II/III, II, I/II, I) is shown and multiple clinical trials may be available.

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Relevant Therapy Summary (continued)

● In this cancer type ○ In other cancer type ◑ In this cancer type and other cancer types ⊘ Contraindicated ⚠ Both for use and contraindicated ✖ No evidence

BRAF p.(V600E) c.1799T>A (continued)

Relevant Therapy	FDA	NCCN	Clinical Trials*
ASTX029	✖	✖	● (I/II)
bempegaldesleukin + nivolumab	✖	✖	● (I/II)
cobimetinib	✖	✖	● (I/II)
cobimetinib + IMC-CS4 + vemurafenib	✖	✖	● (I/II)
cobimetinib + pembrolizumab + vemurafenib	✖	✖	● (I/II)
CX-072 + vemurafenib	✖	✖	● (I/II)
dabrafenib + lacnotuzumab + trametinib	✖	✖	● (I/II)
pembrolizumab + SX-682, SX-682	✖	✖	● (I/II)
vemurafenib + metformin hydrochloride	✖	✖	● (I/II)
abemaciclib + LY3214996 , LY3214996 , LY3214996 + chemotherapy, LY3214996 + midazolam	✖	✖	● (I)
ASN007	✖	✖	● (I)
E6201	✖	✖	● (I)
KO-947	✖	✖	● (I)
LXH254 , LXH254 + spartalizumab	✖	✖	● (I)
RMC-4630	✖	✖	● (I)
TP-0903	✖	✖	● (I)

NRAS p.(G12V) c.35G>T

Relevant Therapy	FDA	NCCN	Clinical Trials*
cetuximab	⊘	⊘	✖
panitumumab	⊘	⊘	✖
aldesleukin + anti-KRAS G12V mTCR + chemotherapy	✖	✖	● (I/II)

* Most advanced phase (IV, III, II/III, II, I/II, I) is shown and multiple clinical trials may be available.

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Relevant Therapy Summary (continued)

● In this cancer type ○ In other cancer type ◑ In this cancer type and other cancer types ⊘ Contraindicated ⚠ Both for use and contraindicated ✖ No evidence

NRAS p.(G12V) c.35G>T (continued)

Relevant Therapy	FDA	NCCN	Clinical Trials*
ASTX029	✖	✖	● (I/II)
avelumab + binimetinib, avelumab + binimetinib + talazoparib	✖	✖	● (I/II)
cobimetinib	✖	✖	● (I/II)
navitoclax + trametinib	✖	✖	● (I/II)
abemaciclib + LY3214996 , LY3214996 , LY3214996 + chemotherapy, LY3214996 + midazolam	✖	✖	● (I)
ASN007	✖	✖	● (I)
KO-947	✖	✖	● (I)
LTT-462 + LXH254 , LXH254 + trametinib	✖	✖	● (I)
LXH254 + spartalizumab	✖	✖	● (I)
RMC-4630	✖	✖	● (I)

CDK4 amplification

Relevant Therapy	FDA	NCCN	Clinical Trials*
abemaciclib	✖	✖	● (II)
palbociclib	✖	✖	● (II)

TP53 p.(D186G) c.557A>G

Relevant Therapy	FDA	NCCN	Clinical Trials*
adavosertib + olaparib	✖	✖	● (II)

* Most advanced phase (IV, III, II/III, II, I/II, I) is shown and multiple clinical trials may be available.

Clinical Trials Summary

BRAF p.(V600E) c.1799T>A

NCT ID	Title	Phase
NCT02967692	A Randomized, Double-blind, Placebo-controlled, Phase III Study Comparing the Combination of PDR001, Dabrafenib and Trametinib Versus Placebo, Dabrafenib and Trametinib in Previously Untreated Patients With Unresectable or Metastatic BRAF V600 Mutant Melanoma	III
NCT02224781	DREAMseq (Doublet, Randomized Evaluation in Advanced Melanoma Sequencing) a Phase III Trial	III
NCT02231775	Neoadjuvant and Adjuvant Dabrafenib and Trametinib in Patients With Clinical Stage III Melanoma (Combi-Neo)	II
NCT03149029	A Phase II Trial of Abbreviated MAPK Targeted Therapy Plus Pembrolizumab in Patients With Unresectable or Metastatic Melanoma	II
NCT03554083	Neoadjuvant Therapy for Patients With High Risk Stage III Melanoma: A Pilot Clinical Trial	II
NCT02910700	A Phase II Study of the TRIplet Combination of Dabrafenib, Nivolumab, and Trametinib in Patients With Metastatic Melanoma (TRIDeNT)	II
NCT02743819	Phase II Study of Pembrolizumab and Ipilimumab Following Initial Anti-PD1/L1 Antibody	II
NCT03101254	A Phase I/II Study of LY3022855 With BRAF/MEK Inhibition in Patients With Melanoma	I/II
NCT02818023	Dose-seeking Study of Pembrolizumab Plus Vemurafenib and Cobimetinib for Therapy of Advanced Melanoma	I/II
NCT03013491	An Open-Label, Dose-Finding and Proof of Concept Study of the PD-L1 Probody Therapeutic , CX-072, as Monotherapy and in Combination With Yervoy (Ipilimumab) or With Zelboraf (Vemurafenib) in Subjects With Advanced or Recurrent Solid Tumors or Lymphomas PROCLAIM-CX-072: PRObody CLinical Assessment In Man CX-072 clinical trial Probody Clinical Assessment In Man (PROCLAIM-072)	I/II
NCT03455764	A Phase I/II Study of MCS110 With BRAF/MEK Inhibition in Patients With Melanoma After Progression on BRAF/MEK Inhibition	I/II
NCT01638676	A Phase I/II Trial of Vemurafenib and Metformin to Unresectable Stage IIIC and Stage IV BRAF.V600E+ Melanoma Patients	I/II
NCT03161431	A Phase I, Open-Label, Dose-Escalation With Expansion Study of SX-682 in Subjects With Metastatic Melanoma Concurrently Treated With Pembrolizumab	I/II
NCT02983045	A Phase I/II, Open-label, Multicenter Study of the Combination of NKTR-214 and Nivolumab or the Combination of NKTR-214, Nivolumab, and Ipilimumab in Patients With Select Locally Advanced or Metastatic Solid Tumor Malignancies	I/II
NCT02639546	A Phase I/II, Multicenter, Open-Label, Dose-Escalation Study of The Safety And Pharmacokinetics of Cobimetinib In Pediatric And Young Adult Patients With Previously Treated Solid Tumors	I/II
NCT03415126	An Open-Label, Dose-Finding Phase I Study to Evaluate the Safety, Tolerability and Preliminary Efficacy of ASN007 in Advanced Solid Cancer Patients with BRAFV600, KRAS, HRAS or NRAS mutations	I

Clinical Trials Summary (continued)

BRAF p.(V600E) c.1799T>A (continued)

NCT ID	Title	Phase
NCT03543969	Pilot Study of Adaptive BRAF-MEK Inhibitor Therapy for Advanced BRAF Mutant Melanoma	I
NCT03332589	A Phase I Study Of E6201 For The Treatment Of Central Nervous System Metastases (CNS) From BRAF Or MEK-Mutated Metastatic Melanoma	I
NCT02729298	A Phase Ia / Ib, First-in-human, Open-label, Dose-escalation, Safety, Pharmacokinetic, and Pharmacodynamic Study of Oral TP-0903 Administered Daily for 21 Days to Patients With Advanced Solid Tumors	I
NCT02693535	Targeted Agent and Profiling Utilization Registry (TAPUR) Study	II
NCT03520075	A Phase I/II Study of the Safety, Pharmacokinetics, and Activity of ASTX029 in Subjects With Advanced Solid Tumors	I/II
NCT03051035	A Phase I First-in-Human Study of KO-947 in Locally Advanced Unresectable or Metastatic, Relapsed and/or Refractory Non-Hematological Malignancies	I
NCT03634982	A Phase I, Open-Label, Multicenter, Dose-Escalation Study of RMC-4630 Monotherapy in Adult Participants with Relapsed/Refractory Solid Tumors	I
NCT02857270	A Phase I Study of an ERK1/2 Inhibitor (LY3214996) Administered Alone or in Combination With Other Agents in Advanced Cancer	I
NCT02607813	A Phase I Dose Finding Study of Oral LXH254 in Adult Patients With Advanced Solid Tumors Harboring MAPK Pathway Alterations	I

NRAS p.(G12V) c.35G>T

NCT ID	Title	Phase
NCT02639546	A Phase I/II, Multicenter, Open-Label, Dose-Escalation Study of The Safety And Pharmacokinetics of Cobimetinib In Pediatric And Young Adult Patients With Previously Treated Solid Tumors	I/II
NCT02857270	A Phase I Study of an ERK1/2 Inhibitor (LY3214996) Administered Alone or in Combination With Other Agents in Advanced Cancer	I
NCT02974725	A Phase Ib, Open-label, Multicenter Study of Oral LXH254 in Combination With Oral LTT462 in Adult Patients With Advanced or Metastatic KRAS or BRAF Mutant Non-Small Cell Lung Cancer	I
NCT02607813	A Phase I Dose Finding Study of Oral LXH254 in Adult Patients With Advanced Solid Tumors Harboring MAPK Pathway Alterations	I
NCT03190941	Phase I/II Study Administering Peripheral Blood Lymphocytes Transduced With a Murine T-Cell Receptor Recognizing the G12V Variant of Mutated RAS in HLA-A 1101 Patients	I/II

Clinical Trials Summary (continued)

NRAS p.(G12V) c.35G>T (continued)

NCT ID	Title	Phase
NCT02079740	An Open Label, Two-Part, Phase Ib/II Study to Investigate the Safety, Pharmacokinetics, Pharmacodynamics, and Clinical Activity of the MEK Inhibitor Trametinib and the BCL2-Family Inhibitor Navitoclax (ABT-263) in Combination in Subjects With KRAS or NRAS Mutation-Positive Advanced Solid Tumors	I/II
NCT03637491	A Phase 1b/2 Study To Evaluate Safety And Clinical Activity Of Avelumab In Combination With Binimetinib With Or Without Talazoparib In Patients With Locally Advanced Or Metastatic Ras-mutant Solid Tumors	I/II
NCT03520075	A Phase I/II Study of the Safety, Pharmacokinetics, and Activity of ASTX029 in Subjects With Advanced Solid Tumors	I/II
NCT03415126	An Open-Label, Dose-Finding Phase I Study to Evaluate the Safety, Tolerability and Preliminary Efficacy of ASN007 in Advanced Solid Cancer Patients with BRAFV600, KRAS, HRAS or NRAS mutations	I
NCT03051035	A Phase I First-in-Human Study of KO-947 in Locally Advanced Unresectable or Metastatic, Relapsed and/or Refractory Non-Hematological Malignancies	I
NCT03634982	A Phase I, Open-Label, Multicenter, Dose-Escalation Study of RMC-4630 Monotherapy in Adult Participants with Relapsed/Refractory Solid Tumors	I

CDK4 amplification

NCT ID	Title	Phase
NCT01037790	Phase II Trial of the Cyclin-Dependent Kinase Inhibitor PD 0332991 in Patients With Cancer	II
NCT03310879	A Phase II Study of the CDK4/6 Inhibitor Abemaciclib in Patients With Solid Tumors Harboring Genetic Alterations in Genes Encoding D-type Cyclins or Amplification of CDK4 or CDK6	II
NCT02693535	Targeted Agent and Profiling Utilization Registry (TAPUR) Study	II
NCT02896335	A Phase II Study of Palbociclib in Progressive Brain Metastases Harboring Alterations in the CDK Pathway	II

TP53 p.(D186G) c.557A>G

NCT ID	Title	Phase
NCT02576444	A Phase II Study of the PARP Inhibitor Olaparib (AZD2281) Alone and in Combination With AZD1775, AZD5363, or AZD6738 in Advanced Solid Tumors	II

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Thermo Fisher Scientific's Ion Torrent Oncomine Reporter software was used in generation of this report. Software was developed and designed internally by Thermo Fisher Scientific. The analysis was based on Oncomine Reporter (4.3.3 data version 2019.06(005)). The data presented here is a result of the curation of published data sources, but may not be exhaustive. FDA information was sourced from www.fda.gov and is current as of 2019-05-29. NCCN information was sourced from www.nccn.org and is current as of 2019-02-14. Clinical Trials information is current as of 2019-03-01. For the most up-to-date information regarding a particular trial, search www.clinicaltrials.gov by NCT ID or search local clinical trials authority website by local identifier listed in 'Other identifiers.' Variants are reported according to HGVS nomenclature and classified following AMP/ASCO/CAP guidelines (Li et al. 2017). Based on the data sources selected, variants, therapies, and trials listed in this report are listed in order of potential clinical significance but not for predicted efficacy of the therapies.

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