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Patient Name:	**James Johnson**	Patient DOB:	**7/4/69**
Date Collected:	**8/7/19**	Referring Physician:	**Robert Smith**
Biopsy Site:	**Skin**	Primary Diagnosis:	**Melanoma**
Sample ID:	**10323-SK78WG02-1**	MoCha ID:	**OCA-15002**
Telephone:	**202-555-1234**	Fax:	**202-555-4321**
Tumor Content (%):	**75**		

Tumor content assessment performed by Van Andel Research Institute; Grand Rapids; MI 49503

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Report Highlights

4 Relevant Biomarkers
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Relevant Melanoma Findings

Gene	Finding
BRAF	***BRAF V600E***
KIT	Not detected
NTRK1	Not detected
NTRK2	Not detected
NTRK3	Not detected

Relevant Biomarkers

Tier	Genomic Alteration	Relevant Therapies (In this cancer type)	Relevant Therapies (In other cancer type)	Clinical Trials
IA	*BRAF V600E*	**atezolizumab + cobimetinib + vemurafenib** [1] **binimetinib + encorafenib** [1] **cetuximab + encorafenib** [1] **cobimetinib + vemurafenib** [1] **dabrafenib** [1] **dabrafenib + trametinib** [1] **trametinib** [1] **vemurafenib** [1]	**binimetinib + encorafenib** [1] **cetuximab + encorafenib** [1] **dabrafenib** [1] **dabrafenib + trametinib** [1] **trametinib** [1] encorafenib + panitumumab vemurafenib	59
IA	*NRAS G12V*	binimetinib	None	20
IIC	*CDK4 amplification*	None	None	10

Public data sources included in relevant therapies: FDA[1], NCCN
Tier Reference: Li et al. *Standards and Guidelines for the Interpretation and Reporting of Sequence Variants in Cancer: A Joint Consensus Recommendation of the Association for Molecular Pathology, American Society of Clinical Oncology, and College of American Pathologists.* J Mol Diagn. 2017 Jan;19(1):4-23.

Shahanawaz Jiwani, MD, PhD, Laboratory Director | CLIA ID 21D2097127

Relevant Biomarkers (continued)

Tier	Genomic Alteration	Relevant Therapies (In this cancer type)	Relevant Therapies (In other cancer type)	Clinical Trials
IIC	*TP53 D186G*	None	None	7

Public data sources included in relevant therapies: FDA[1], NCCN
Tier Reference: Li et al. *Standards and Guidelines for the Interpretation and Reporting of Sequence Variants in Cancer: A Joint Consensus Recommendation of the Association for Molecular Pathology, American Society of Clinical Oncology, and College of American Pathologists.* J Mol Diagn. 2017 Jan;19(1):4-23.

Prevalent cancer biomarkers without relevant evidence 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

Comments:
N/A

Signed By: _____

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. Activation of the MAPK pathway occurs through BRAF mutations and leads to an increase in cell division, dedifferentiation, and survival[1,2]. BRAF mutations are categorized into three distinct functional classes namely, class 1, 2, and 3, and are defined by the dependency on the RAS pathway. Class 1 and 2 BRAF mutants are RAS-independent in that they signal as active monomers (Class 1) or dimers (Class 2) and become uncoupled from RAS GTPase signaling, resulting in constitutive activation of BRAF[3]. Class 3 mutants are RAS dependent as the kinase domain function is impaired or dead[3,4,5].

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)[6,7,8,9,10]. Mutations at V600 belong to class 1 and include V600E, the most recurrent somatic BRAF mutation across diverse cancer types[4,11]. Class 2 mutations include K601E/N/T, L597Q/V, G469A/V/R/, G464V/E/, and BRAF fusions[4]. Class 3 mutations include D287H, V459L, G466V/E/A, S467L, G469E, and N581S/I[4]. BRAF V600E is universally present in hairy cell leukemia, mature B-cell cancer, and prevalent in histiocytic neoplasms[12,13,14]. 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[11]. In primary cancers, BRAF amplification is observed in 8% of ovarian cancer and about 1% of breast cancer[7,10]. BRAF fusions are mutually exclusive to BRAF V600 mutations and have been described in melanoma, thyroid cancer, pilocytic astrocytoma, NSCLC, and several other cancer types[15,16,17,18,19]. Part of the oncogenic mechanism of BRAF gene fusions is the removal of the N-terminal auto-inhibitory domain leading to constitutive kinase activation[5,15,17].

Potential relevance: Vemurafenib[20] (2011) was the first targeted therapy approved for the treatment of patients with unresectable or metastatic melanoma with a BRAF V600E mutation. BRAF class 1 mutations, including V600E, are sensitive to vemurafenib, whereas class 2 and 3 mutations are insensitive[4]. BRAF kinase inhibitors including dabrafenib[21] (2013) and encorafenib[22] (2018) are also approved for the treatment of patients with unresectable or metastatic melanoma with BRAF V600E/K mutations. Encorafenib[22] is approved in combination with cetuximab (2020) for the treatment of BRAF V600E mutated colorectal cancer. Due to the tight coupling of RAF and MEK signaling, several MEK inhibitors have been approved for patients harboring BRAF alterations[4]. Trametinib[23] (2013) and binimetinib[24] (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/trametinib (2015) and vemurafenib/cobimetinib[25] (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 approved for metastatic NSCLC (2017) with a BRAF V600E mutation. The pan-RAF kinase inhibitor DAY-101 was granted breakthrough therapy designation (2020) by the FDA for pediatric patients with advanced low-grade glioma harboring activating RAF alterations[26]. The ERK inhibitor ulixertinib[27] was also granted a fast track designation in 2020 for the treatment of patients with non-colorectal solid tumors harboring BRAF mutations G469A/V, L485W, or L597Q. BRAF fusion is a suggested mechanism of resistance to BRAF targeted therapy in melanoma[28]. Additional mechanisms of resistance to BRAF targeted therapy include BRAF amplification and alternative splice transcripts as well as activation of PI3K signaling and activating mutations in KRAS, NRAS, and MAP2K1/2 (MEK1/2)[29,30,31,32,33,34,35]. Clinical responses to sorafenib and trametinib in limited case studies of patients with BRAF fusions have been reported[19].

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[36,37]. 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[38]. Germline mutations in CDK4 are associated with familial melanoma[39,40,41].

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[42,43,44]. 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%)[7,9,10,45].

Potential 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.

Biomarker Descriptions (continued)

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[46,47,48].

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[10,49]. The majority of NRAS mutations consist of point mutations at G12, G13, and Q61[10,50]. Mutations at A59, K117, and A146 have also been observed but are less frequent[7,51].

Potential relevance: Currently, no therapies are approved for NRAS aberrations. The EGFR antagonists, cetuximab[52] and panitumumab[53], 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)[51]. NRAS mutations are associated with poor prognosis in patients with low-risk myelodysplastic syndrome[54] as well as melanoma[55]. 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[56].

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[57]. Germline mutations in TP53 are the underlying cause of Li-Fraumeni syndrome, a complex hereditary cancer predisposition disorder associated with early-onset cancers[58,59].

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%)[7,10,60,61,62,63]. Approximately two-thirds of TP53 mutations are missense mutations and several recurrent missense mutations are common including substitutions at codons R158, R175, Y220, R248, R273, and R282[7,10]. Invariably, recurrent missense mutations in TP53 inactivate its ability to bind DNA and activate transcription of target genes[64,65,66,67].

Potential relevance: The small molecule p53 reactivator, PC14586, received a fast track designation (2020) by the FDA for advanced tumors harboring a TP53 Y220C mutation[68]. The FDA has granted fast track designation (2019) to the p53 reactivator, APR-246 alone,[69] and breakthrough designation[70] (2020) in combination with azacitidine for myelodysplastic syndrome (MDS) and acute myeloid leukemia patients (AML) harboring a TP53 mutation. In addition to investigational therapies aimed at restoring wild-type TP53 activity, compounds that induce synthetic lethality are also under clinical evaluation[71,72]. TP53 mutations confer poor prognosis in multiple blood cancers including AML, MDS, myeloproliferative neoplasms (MPN), chronic lymphocytic leukemia (CLL),[54,73,74,75]. In mantle cell lymphoma, TP53 mutations are associated with poor prognosis when treated with conventional therapy including hematopoietic cell transplant[76]. Mono- and bi-allelic mutations in TP53 confer unique characteristics in MDS, with multi-hit patients also experiencing associations with complex karyotype, few co-occuring mutations, and high-risk disease presentation as well as predicted death and leukemic transformation independent of the IPSS-R staging system[77].

Relevant Therapy Summary

● In this cancer type ○ In other cancer type ◑ In this cancer type and other cancer types ✖ No evidence

BRAF V600E

Relevant Therapy	FDA	NCCN	Clinical Trials*
dabrafenib	◑	◑	✖
dabrafenib + trametinib	◑	◑	✖
binimetinib + encorafenib	◑	●	✖
cetuximab + encorafenib	◑	○	✖
trametinib	◑	✖	✖
vemurafenib	●	◑	● (II)
cobimetinib + vemurafenib	●	●	● (II)
atezolizumab + cobimetinib + vemurafenib	●	✖	✖
encorafenib + panitumumab	✖	○	✖
bempegaldesleukin, nivolumab	✖	✖	● (III)
dabrafenib, trametinib, ipilimumab, nivolumab	✖	✖	● (III)
relatlimab, nivolumab	✖	✖	● (II/III)
sargramostim, nivolumab, ipilimumab	✖	✖	● (II/III)
abemaciclib + LY3214996	✖	✖	● (II)
atezolizumab, cobimetinib, vemurafenib	✖	✖	● (II)
binimetinib, encorafenib	✖	✖	● (II)
buparlisib	✖	✖	● (II)
cobimetinib, atezolizumab, vemurafenib	✖	✖	● (II)
cobimetinib, vemurafenib	✖	✖	● (II)
dabrafenib + pembrolizumab + trametinib	✖	✖	● (II)
dabrafenib, nivolumab, trametinib	✖	✖	● (II)
dabrafenib, pembrolizumab, trametinib	✖	✖	● (II)
dabrafenib, trametinib	✖	✖	● (II)
dabrafenib, trametinib, spartalizumab	✖	✖	● (II)
encorafenib, binimetinib, nivolumab, ipilimumab	✖	✖	● (II)
IMM-101, nivolumab, ipilimumab	✖	✖	● (II)

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

Relevant Therapy Summary (continued)

● In this cancer type ○ In other cancer type ◑ In this cancer type and other cancer types ✖ No evidence

BRAF V600E (continued)

Relevant Therapy	FDA	NCCN	Clinical Trials*
immunostimulant, pembrolizumab	✖	✖	● (II)
ipilimumab, binimetinib, nivolumab, encorafenib	✖	✖	● (II)
ipilimumab, nivolumab, encorafenib, binimetinib, dabrafenib, trametinib	✖	✖	● (II)
LXH254 , LTT-462, trametinib, ribociclib	✖	✖	● (II)
nivolumab, ipilimumab, radiation therapy	✖	✖	● (II)
ulixertinib	✖	✖	● (II)
vemurafenib, cobimetinib	✖	✖	● (II)
vemurafenib, cobimetinib, atezolizumab	✖	✖	● (II)
vemurafenib, cobimetinib, ipilimumab, nivolumab	✖	✖	● (II)
vemurafenib, cobimetinib, surgical intervention, radiation therapy	✖	✖	● (II)
vemurafenib, dabrafenib	✖	✖	● (II)
ASTX029	✖	✖	● (I/II)
bemcentinib, dabrafenib, pembrolizumab, trametinib	✖	✖	● (I/II)
dabrafenib, trametinib, antimalarial	✖	✖	● (I/II)
HH-2710	✖	✖	● (I/II)
lacnotuzumab, trametinib, dabrafenib	✖	✖	● (I/II)
mirdametinib, lifirafenib	✖	✖	● (I/II)
vorinostat	✖	✖	● (I/II)
ABM-1310	✖	✖	● (I)
AZD-0364	✖	✖	● (I)
BGB-3245	✖	✖	● (I)
CART-GD2, vemurafenib	✖	✖	● (I)
cobimetinib, belvarafenib	✖	✖	● (I)
DAY-101	✖	✖	● (I)
E6201	✖	✖	● (I)
HL-085, vemurafenib	✖	✖	● (I)

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

Relevant Therapy Summary (continued)

● In this cancer type ○ In other cancer type ◑ In this cancer type and other cancer types ✖ No evidence

BRAF V600E (continued)

Relevant Therapy	FDA	NCCN	Clinical Trials*
JAB-3312	✖	✖	● (I)
JSI-1187, dabrafenib	✖	✖	● (I)
LY3214996, midazolam, abemaciclib, chemotherapy, encorafenib, cetuximab	✖	✖	● (I)
RG-7461, pembrolizumab	✖	✖	● (I)
RMC-4630	✖	✖	● (I)
RO-5126766, everolimus	✖	✖	● (I)
RX208	✖	✖	● (I)
TQ-B3233	✖	✖	● (I)

NRAS G12V

Relevant Therapy	FDA	NCCN	Clinical Trials*
binimetinib	✖	●	✖
LXH254 , LTT-462, trametinib, ribociclib	✖	✖	● (II)
ulixertinib	✖	✖	● (II)
anti-KRAS G12V mTCR	✖	✖	● (I/II)
ASTX029	✖	✖	● (I/II)
avelumab, binimetinib, talazoparib	✖	✖	● (I/II)
HH-2710	✖	✖	● (I/II)
mirdametinib, lifirafenib	✖	✖	● (I/II)
navitoclax, trametinib	✖	✖	● (I/II)
neratinib, valproic acid	✖	✖	● (I/II)
AZD-0364	✖	✖	● (I)
BGB-3245	✖	✖	● (I)
cobimetinib, belvarafenib	✖	✖	● (I)
DAY-101	✖	✖	● (I)
FCN-159	✖	✖	● (I)

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

Relevant Therapy Summary (continued)

● In this cancer type ○ In other cancer type ◑ In this cancer type and other cancer types ✖ No evidence

NRAS G12V (continued)

Relevant Therapy	FDA	NCCN	Clinical Trials*
IN10018, cobimetinib	✖	✖	● (I)
JSI-1187	✖	✖	● (I)
LY3214996, midazolam, abemaciclib, chemotherapy, encorafenib, cetuximab	✖	✖	● (I)
RMC-4630	✖	✖	● (I)
RO-5126766, everolimus	✖	✖	● (I)

CDK4 amplification

Relevant Therapy	FDA	NCCN	Clinical Trials*
abemaciclib	✖	✖	● (II)
palbociclib	✖	✖	● (II)
palbociclib, abemaciclib	✖	✖	● (II)
SY-5609	✖	✖	● (I)

TP53 D186G

Relevant Therapy	FDA	NCCN	Clinical Trials*
berzosertib	✖	✖	● (II)
niraparib	✖	✖	● (II)
olaparib	✖	✖	● (II)
talazoparib	✖	✖	● (II)
eprenetapopt, pembrolizumab	✖	✖	● (I/II)
HWH-340	✖	✖	● (I)

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

Clinical Trials Summary

BRAF V600E

NCT ID	Title	Phase
NCT03898908	Phase II, Multicentre Clinical Trial to Evaluate the Activity of Encorafenib and Binimetinib Administered Before Local Treatment in Patients With BRAF Mutant Melanoma Metastatic to the Brain.	II
NCT02858921	A Phase II, Randomised, Open Label Study of Neoadjuvant Dabrafenib, Trametinib and / or Pembrolizumab in BRAF V600 Mutant Resectable Stage IIIB/C Melanoma	II
NCT02231775	Neoadjuvant and Adjuvant Dabrafenib and Trametinib in Patients With Clinical Stage III Melanoma (Combi-Neo)	II
NCT04310397	Altering Adjuvant Therapy Based on Pathologic Response to Neoadjuvant Dabrafenib and Trametinib (ALTER-PATH NeoDT)	II
NCT03235245	Combination of Targeted Therapy (Encorafenib and Binimetinib) Followed by Combination of Immunotherapy (Ipilimumab and Nivolumab) vs Immediate Combination of Immunotherapy in Patients With Unresectable or Metastatic Melanoma With BRAF V600 Mutation : an EORTC Randomized Phase II Study (EBIN)	II
NCT02968303	Phase II Study With COmbination of Vemurafenib With Cobimetinib in B-RAF V600E/K Mutated Melanoma Patients to Normalize LDH and Optimize Nivolumab and Ipilimumab therapy	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
NCT02836548	HDAC Inhibitor Vorinostat in Resistant BRAF V600 Mutated Advanced Melanoma	I/II
NCT04190628	A Phase I, First-In-Human, Multicenter, Open-Label Study of ABM-1310, Administered Orally in Adult Patients With Advanced Solid Tumors	I
No NCT ID	Phase I Study of Safety and Immune Effects of an Escalating Dose of Autologous GD2 Chimeric Antigen Receptor-Expressing Peripheral Blood T cells in Patients with Metastatic Melanoma	I
NCT02224781	DREAMseq (Doublet, Randomized Evaluation in Advanced Melanoma Sequencing) a Phase III Trial	III
NCT03554083	Neoadjuvant Therapy for Patients With High Risk Stage III Melanoma: A Pilot Clinical Trial	II
NCT03911869	A Phase II, Open-Label, Randomized, Multicenter Trial of Encorafenib + Binimetinib Evaluating a Standard-dose and a High-dose Regimen in Patients With BRAFV600-mutant Melanoma Brain Metastasis	II
NCT02452294	An Open-label, Uncontrolled, Single Arm Phase II Trial of Buparlisib in Patients With Metastatic Melanoma With Brain Metastases Not Eligible for Surgery or Radiosurgery	II
NCT02036086	A Pilot Study of the Neo-adjuvant Use of Vemurafenib Plus Cobimetinib (GDC-0973) in Patients With BRAF Mutant Melanoma With Palpable Lymph Node Metastases	II
NCT03625141	A Phase II Two Cohort Study Evaluating the Safety and Efficacy of Cobimetinib Plus Atezolizumab in BRAFV600 Wild-type Melanoma With Central Nervous System Metastases and Cobimetinib Plus Atezolizumab and Vemurafenib in BRAFV600 Mutation-positive Melanoma With Central Nervous System Metastases.	II
NCT03430947	An Open-Label Phase II Multicenter Study Of Vemurafenib (Zelboraf) Plus Cobimetinib (Cotellic) After Radiosurgery In Patients With Active BRAF-V600-Mutant Melanoma Brain Metastases	II

Clinical Trials Summary (continued)

BRAF V600E (continued)

NCT ID	Title	Phase
NCT03149029	A Phase II Trial of Abbreviated MAPK Targeted Therapy Plus Pembrolizumab in Patients With Unresectable or Metastatic Melanoma	II
No NCT ID	A Non-Intervention MultiCenter Study of the Combination Tafinlar (Dabrafenib) and Mekinist (Trametinib) in the Treatment of Malignant Melanoma	II
NCT04511013	A Randomized Phase II Trial of Encorafenib + Binimetinib + Nivolumab vs Ipilimumab + Nivolumab in BRAF-V600 Mutant Melanoma With Brain Metastases	II
NCT04417621	A Randomized, Open-label, Multi-arm, Two-part, Phase II Study to Assess Efficacy and Safety of Multiple LXH254 Combinations in Patients With Previously Treated Unresectable or Metastatic BRAFV600 or NRAS Mutant Melanoma	II
NCT03224208	VECODUE A Phase II Trial of Vemurafenib Plus Cobimetinib in Patients Treated With Prior First-line Systemic Immunotherapy for Inoperable Locally Advanced or Metastatic Melanoma	II
NCT02303951	Neoadjuvant Treatment With the Combination of Vemurafenib, Cobimetinib and Atezolizumab in Limited Metastasis of Malignant Melanoma (AJCC Stage IIIC/IV) and Integrated Biomarker Study: a Single Armed, Two Cohort, Phase II EADO Trial NEO-VC	II
NCT03514901	An Evaluation of the Efficacy Beyond Progression of Vemurafenib Combined With Cobimetinib Associated With Local Treatment Compared to Second-line Treatment in Patients With BRAFV600 Mutation-positive Metastatic Melanoma in Focal Progression With First-line Combined Vemurafenib and Cobimetinib.	II
NCT03754179	A lead-in Phase I Followed by a Phase II Clinical Trial on the Combination of Dabrafenib, Trametinib and the Autophagy Inhibitor Hydroxychloroquine in BRAF/MEK Inhibitor-pretreated Patients With Advanced BRAF V600 Mutant Melanoma	I/II
NCT04249843	A First-in-Human, Phase Ia/Ib, Open Label, Dose-Escalation and Expansion Study to Investigate the Safety, Pharmacokinetics, and Antitumor Activity of the RAF Dimer Inhibitor BGB-3245 in Patients With Advanced or Refractory Tumors	I
NCT03284502	A Phase Ib, Open-label, Multicenter, Dose Escalation Study of the Safety, Tolerability, and Pharmacokinetics of Cobimetinib and HM95573 in Patients With Locally Advanced or Metastatic Solid Tumors	I
NCT04418167	A Phase I Study of ERK1/2 Inhibitor JSI-1187 Administered as Monotherapy and in Combination With Dabrafenib for the Treatment of Advanced Solid Tumors With MAPK Pathway Mutations	I
NCT03635983	A Phase III, Randomized, Open-label Study of NKTR-214 Combined With Nivolumab Versus Nivolumab in Participants With Previously Untreated Unresectable or Metastatic Melanoma.	III
NCT03470922	A Randomized, Double-Blind Phase II/III Study of Relatlimab Combined With Nivolumab Versus Nivolumab in Participants With Previously Untreated Metastatic or Unresectable Melanoma	II/III
NCT03711188	A Study of the Safety and Efficacy of IMM-101 in Combination With Checkpoint Inhibitor Therapy in Patients With Advanced Melanoma	II
NCT02339571	Randomized Phase II/III Study of Nivolumab Plus Ipilimumab Plus Sargramostim Versus Nivolumab Plus Ipilimumab in Patients With Unresectable Stage III or Stage IV Melanoma	II/III
NCT02910700	A Phase II Study of the TRIplet Combination of Dabrafenib, Nivolumab, and Trametinib in Patients With Metastatic Melanoma (TRIDeNT)	II

Clinical Trials Summary (continued)

BRAF V600E (continued)

NCT ID	Title	Phase
NCT03563729	Efficacy Of Immunotherapy In Melanoma Patients With Brain Metastases Treated With Steroids	II
NCT02872259	A Phase Ib/II Randomised Open Label Study of BGB324 in Combination With Pembrolizumab or Dabrafenib/Trametinib Compared to Pembrolizumab or Dabrafenib/Trametinib Alone, in Patients With Advanced Non-resectable (Stage IIIc) or Metastatic (Stage IV) Melanoma.	I/II
NCT03332589	A Phase I Study Of E6201 For The Treatment Of Central Nervous System Metastases (CNS) From BRAF Or MEK-Mutated Metastatic Melanoma	I
NCT03453034	To Study the Pharmacokinetic Characteristics of TQ-B233 in the Human Body, Recommend a Reasonable Regimen for Subsequent Research	I
NCT04079166	A Phase II Combination Study of SCIB1 with Pembrolizumab in Patients with Stage III or Stage IV Metastatic Melanoma	II
NCT03340129	A Phase II, Open Label, Single Arm Study of Ipilimumab and Nivolumab With Salvage Radiotherapy in Patients With Melanoma Brain Metastases	II
NCT03875079	An Open-Label, Multicenter, Phase Ib Study To Evaluate Safety And Therapeutic Activity Of RO6874281, An Immunocytokine, Consisting Of Interleukin-2 Variant (IL-2v) Targeting Fibroblast Activation Protein-? (FAP), In Combination With Pembrolizumab (Anti-PD-1), In Participants With Advanced Or Metastatic Melanoma	I
NCT03905148	A Phase Ib, Open-Label, Dose-escalation and Expansion Study to Investigate the Safety, Pharmacokinetics and Antitumor Activities of a RAF Dimer Inhibitor BGB-283 in Combination With MEK Inhibitor PD-0325901 in Patients With Advanced or Refractory Solid Tumors	I/II
NCT02693535	Targeted Agent and Profiling Utilization Registry (TAPUR) Study	II
NCT04591431	The Rome Trial From Histology to Target: the Road to Personalize Target Therapy and Immunotherapy	II
No NCT ID	Phase I study of the safety, tolerability, pharmacokinetics and preliminary efficacy of RX208 in patients with advanced malignant solid tumors	I
NCT03297606	Canadian Profiling and Targeted Agent Utilization Trial (CAPTUR): A Phase II Basket Trial	II
NCT03155620	NCI-COG Pediatric MATCH (Molecular Analysis for Therapy Choice) Screening Protocol	II
NCT03220035	NCI-COG Pediatric MATCH (Molecular Analysis for Therapy Choice)- Phase II Subprotocol of Vemurafenib in Patients With Tumors Harboring Braf V600 Mutations	II
NCT03781219	A Phase I, Single Arm, Dose Escalation Study to Evaluate Safety, Pharmacokinetics and Preliminary Efficacy of HL-085 Plus Vemurafenib in Patients With BRAF V600 Mutant Advanced Solid Tumor	I
NCT04534283	A Phase II Basket Trial of an ERK1/2 Inhibitor (LY3214996) in Combination With Abemaciclib for Patients Whose Tumors Harbor Pathogenic Alterations in BRAF, RAF1, MEK1/2, ERK1/2, and NF1	II
NCT03239015	Efficacy and Safety of Targeted Precision Therapy in Refractory Tumor With Druggable Molecular Event	II
NCT04045496	A Phase I, Multi-Center, Open-Label Study to Evaluate the Safety, Tolerability, Pharmacokinetics, and Preliminary Evidence of Antitumor Activity of JAB-3312 in Adult Patients With Advanced Solid Tumors	I
NCT02407509	A Phase I Trial of RO5126766 (a Dual RAF/MEK Inhibitor) Exploring Intermittent, Oral Dosing Regimens in Patients With Solid Tumours or Multiple Myeloma, With an Expansion to Explore Intermittent Dosing in Combination With Everolimus	I

Clinical Trials Summary (continued)

BRAF V600E (continued)

NCT ID	Title	Phase
NCT04488003	A Two-Part, Phase II, Multi-center Study of the ERK Inhibitor Ulixertinib (BVD-523) for Patients With Advanced Malignancies Harboring MEK or Atypical BRAF Alterations	II
NCT04198818	A First-in-Human, Open Label, Phase I/II Study to Evaluate the Safety, Tolerability and Pharmacokinetics of HH2710 in Patients With Advanced Tumors	I/II
NCT03429803	A Phase I Study of TAK-580 (MLN2480) for Children With Low-Grade Gliomas and Other RAS/RAF/MEK/ERK Pathway Activated Tumors	I
NCT03634982	A Phase I, Open-Label, Multicenter, Dose-Escalation Study of RMC-4630 Monotherapy in Adult Participants with Relapsed/Refractory Solid Tumors	I
NCT03520075	A Phase I/II Study of the Safety, Pharmacokinetics, and Activity of ASTX029 in Subjects With Advanced Solid Tumors	I/II
NCT04305249	A Phase I, Open-Label, Multi-Center Dose Finding Study to Investigate the Safety, Pharmacokinetics, and Preliminary Efficacy of ATG-017 Monotherapy in Patients With Advanced Solid Tumors and Hematological Malignancies	I
NCT02857270	A Phase I Study of an ERK1/2 Inhibitor (LY3214996) Administered Alone or in Combination With Other Agents in Advanced Cancer	I

NRAS G12V

NCT ID	Title	Phase
NCT04417621	A Randomized, Open-label, Multi-arm, Two-part, Phase II Study to Assess Efficacy and Safety of Multiple LXH254 Combinations in Patients With Previously Treated Unresectable or Metastatic BRAFV600 or NRAS Mutant Melanoma	II
NCT03284502	A Phase Ib, Open-label, Multicenter, Dose Escalation Study of the Safety, Tolerability, and Pharmacokinetics of Cobimetinib and HM95573 in Patients With Locally Advanced or Metastatic Solid Tumors	I
NCT03932253	A Phase Ia/Ib Clinical Study to Evaluate the Safety, Pharmacokinetics (PK) and Preliminary Anti-tumor Activity of FCN-159 in Patients With Advanced Melanoma Harboring NRAS-aberrant (Ia) and NRAS-mutant (Ib)	I
NCT04109456	A Phase Ib, Open-label Clinical Study to Evaluate the Safety, Tolerability, Pharmacokinetics and Antitumor Activities of IN10018 as Monotherapy and Combination Therapy in Subjects With Metastatic Melanoma	I
NCT02974725	A Phase Ib, Open-label, Multicenter Study of Oral LXH254-centric Combinations in Adult Patients With Advanced or Metastatic KRAS or BRAF Mutant Non-Small Cell Lung Cancer or NRAS Mutant Melanoma	I
NCT02857270	A Phase I Study of an ERK1/2 Inhibitor (LY3214996) Administered Alone or in Combination With Other Agents in Advanced Cancer	I
NCT03905148	A Phase Ib, Open-Label, Dose-escalation and Expansion Study to Investigate the Safety, Pharmacokinetics and Antitumor Activities of a RAF Dimer Inhibitor BGB-283 in Combination With MEK Inhibitor PD-0325901 in Patients With Advanced or Refractory Solid Tumors	I/II

Clinical Trials Summary (continued)

NRAS G12V (continued)

NCT ID	Title	Phase
NCT03190941	A 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*11:01 Patients	I/II
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 Ib/II Study To Evaluate Safety And Clinical Activity Of Combinations Of Avelumab, Binimetinib And Talazoparib In Patients With Locally Advanced Or Metastatic Ras-Mutant Solid Tumors	I/II
NCT03919292	Phase 1/2 Study of Neratinib and Divalproex Sodium (Valproate) in Advanced Solid Tumors, With an Expansion Cohort in Ras-Mutated Cancers	I/II
NCT04249843	A First-in-Human, Phase Ia/Ib, Open Label, Dose-Escalation and Expansion Study to Investigate the Safety, Pharmacokinetics, and Antitumor Activity of the RAF Dimer Inhibitor BGB-3245 in Patients With Advanced or Refractory Tumors	I
NCT04418167	A Phase I Study of ERK1/2 Inhibitor JSI-1187 Administered as Monotherapy and in Combination With Dabrafenib for the Treatment of Advanced Solid Tumors With MAPK Pathway Mutations	I
NCT02407509	A Phase I Trial of RO5126766 (a Dual RAF/MEK Inhibitor) Exploring Intermittent, Oral Dosing Regimens in Patients With Solid Tumours or Multiple Myeloma, With an Expansion to Explore Intermittent Dosing in Combination With Everolimus	I
NCT03155620	NCI-COG Pediatric MATCH (Molecular Analysis for Therapy Choice) Screening Protocol	II
NCT04198818	A First-in-Human, Open Label, Phase I/II Study to Evaluate the Safety, Tolerability and Pharmacokinetics of HH2710 in Patients With Advanced Tumors	I/II
NCT03429803	A Phase I Study of TAK-580 (MLN2480) for Children With Low-Grade Gliomas and Other RAS/RAF/MEK/ERK Pathway Activated Tumors	I
NCT03634982	A Phase I, Open-Label, Multicenter, Dose-Escalation Study of RMC-4630 Monotherapy in Adult Participants with Relapsed/Refractory Solid Tumors	I
NCT03520075	A Phase I/II Study of the Safety, Pharmacokinetics, and Activity of ASTX029 in Subjects With Advanced Solid Tumors	I/II
NCT04305249	A Phase I, Open-Label, Multi-Center Dose Finding Study to Investigate the Safety, Pharmacokinetics, and Preliminary Efficacy of ATG-017 Monotherapy in Patients With Advanced Solid Tumors and Hematological Malignancies	I

CDK4 amplification

NCT ID	Title	Phase
NCT03994796	Genomically-Guided Treatment Trial in Brain Metastases	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

Clinical Trials Summary (continued)

CDK4 amplification (continued)

NCT ID	Title	Phase
NCT02465060	Molecular Analysis for Therapy Choice (MATCH).	II
NCT03239015	Efficacy and Safety of Targeted Precision Therapy in Refractory Tumor With Druggable Molecular Event	II
NCT02693535	Targeted Agent and Profiling Utilization Registry (TAPUR) Study	II
NCT03297606	Canadian Profiling and Targeted Agent Utilization Trial (CAPTUR): A Phase II Basket Trial	II
NCT04591431	The Rome Trial From Histology to Target: the Road to Personalize Target Therapy and Immunotherapy	II
NCT03155620	NCI-COG Pediatric MATCH (Molecular Analysis for Therapy Choice) Screening Protocol	II
NCT03526250	NCI-COG Pediatric MATCH (Molecular Analysis for Therapy Choice) - Phase 2 Subprotocol of Palbociclib in Patients With Tumors Harboring Activating Alterations in Cell Cycle Genes	II
NCT04247126	A Phase I Study of SY 5609, an Oral, Selective CDK7 Inhibitor, in Adult Patients With Select Advanced Solid Tumors	I

TP53 D186G

NCT ID	Title	Phase
NCT03925350	A Phase II Study of Niraparib in Patients With Advanced Melanoma With Genetic Homologous Recombination (HR) Mutation / Alteration	II
NCT04383938	Study of APR-246 in Combination With Pembrolizumab in Subjects With Solid Tumor Malignancies	I/II
NCT03718091	A Phase II Study of M6620 (VX-970) in Selected Solid Tumors	II
NCT02029001	A Two-period, Multicenter, Randomized, Open-label, Phase II Study Evaluating the Clinical Benefit of a Maintenance Treatment Targeting Tumor Molecular Alterations in Patients With Progressive Locally-advanced or Metastatic Solid Tumors MOST: My own specific treatment	II
NCT03297606	Canadian Profiling and Targeted Agent Utilization Trial (CAPTUR): A Phase II Basket Trial	II
NCT02401347	A Phase II Clinical Trial of the PARP Inhibitor Talazoparib in BRCA1 and BRCA2 Wild Type Patients With Advanced Triple Negative Breast Cancer and Homologous Recombination Deficiency or Advanced HER2 Negative Breast Cancer or Other Solid Tumors With a Mutation in Homologous Recombination Pathway Genes Talazoparib Beyond BRCA (TBB) Trial	II
NCT03415659	A Phase I, Open-label, Single-center, Single/Multiple-dose, Dose-escalation/Dose-expansion Clinical Study on Tolerance and Pharmacokinetics of HWH340 Tablet in Patients With Advanced Solid Tumors	I

Assay Information

Methodology, Scope, and Application: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 (SNVs), small insertions/deletions (Indels), large (>3 bases) insertions/deletions (Large Indels), copy number variants (CNVs), and gene fusions. 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 the current version of Torrent Suite Software and Ion Reporter. 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.

Report Content:Thermo Fisher Scientific's Ion Torrent Oncomine Reporter software was used in the generation of this report. Software was developed and designed internally by Thermo Fisher Scientific. The analysis was based on the current version of Oncomine Reporter. The data presented here is from a curated knowledgebase of publicly available information, but may not be exhaustive. FDA information was sourced from www.fda.gov and is current as of this version. NCCN information was sourced from www.nccn.org and reflects its current version. Clinical Trials information reflects the current version. For the most up-to-date information regarding a particular trials, 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 identified in this report are listed in order of potential clinical significance but not for predicted efficacy of the therapies.

Genes assayed for hotspot mutations:
AKT1, AKT2, AKT3, ALK, AR, ARAF, AXL, BRAF, BTK, CBL, CCND1, CDK4, CDK6, CHEK2, CSF1R, CTNNB1, DDR2, EGFR, ERBB2, ERBB3, ERBB4, ERCC2, ESR1, EZH2, FGFR1, FGFR2, FGFR3, FGFR4, FLT3, FOXL2, GATA2, GNA11, GNAQ, GNAS, H3F3A, HIST1H3B, HNF1A, HRAS, IDH1, IDH2, JAK1, JAK2, JAK3, KDR, KIT, KNSTRN, KRAS, MAGOH, MAP2K1, MAP2K2, MAP2K4, MAPK1, MAX, MDM4, MED12, MET, MTOR, MYC, MYCN, MYD88, NFE2L2, NRAS, NTRK1, NTRK2, NTRK3, PDGFRA, PDGFRB, PIK3CA, PIK3CB, PPP2R1A, PTPN11, RAC1, RAF1, RET, RHEB, RHOA, ROS1, SF3B1, SMAD4, SMO, SPOP, SRC, STAT3, TERT, TOP1, U2AF1, XPO1

Genes assayed with full exon coverage:
ARID1A, ATM, ATR, ATRX, BAP1, BRCA1, BRCA2, CDK12, CDKN1B, CDKN2A, CDKN2B, CHEK1, CREBBP, FANCA, FANCD2, FANCI, FBXW7, MLH1, MRE11, MSH2, MSH6, NBN, NF1, NF2, NOTCH1, NOTCH2, NOTCH3, PALB2, PIK3R1, PMS2, POLE, PTCH1, PTEN, RAD50, RAD51, RAD51B, RAD51C, RAD51D, RB1, RNF43, SETD2, SLX4, SMARCA4, SMARCB1, STK11, TP53, TSC1, TSC2

Genes assayed for copy number variations:
AKT1, AKT2, AKT3, ALK, AR, AXL, BRAF, CCND1, CCND2, CCND3, CCNE1, CDK2, CDK4, CDK6, EGFR, ERBB2, ESR1, FGF19, FGF3, FGFR1, FGFR2, FGFR3, FGFR4, FLT3, IGF1R, KIT, KRAS, MDM2, MDM4, MET, MYC, MYCL, MYCN, NTRK1, NTRK2, NTRK3, PDGFRA, PDGFRB, PIK3CA, PIK3CB, PPARG, RICTOR, TERT

Genes assayed for detection of fusions:
AKT2, ALK, AR, AXL, BRAF, BRCA1, BRCA2, CDKN2A, EGFR, ERBB2, ERBB4, ERG, ESR1, ETV1, ETV4, ETV5, FGFR1, FGFR2, FGFR3, FGR, FLT3, JAK2, KRAS, MDM4, MET, MYB, MYBL1, NF1, NOTCH1, NOTCH4, NRG1, NTRK1, NTRK2, NTRK3, NUTM1, PDGFRA, PDGFRB, PIK3CA, PPARG, PRKACA, PRKACB, PTEN, RAD51B, RAF1, RB1, RELA, RET, ROS1, RSPO2, RSPO3, TERT

DISCLAIMER

This assay is considered a Laboratory Developed Test (LDT). Its performance characteristics have been determined through extensive testing although it has not been cleared by the US Food and Drug Administration and such approval is not required for clinical implementation. Furthermore, any comments included in the report are strictly interpretive and the opinion of the reviewer. This laboratory is certified under the Clinical Laboratory Improvements Amendments (CLIA) for the performance of high-complexity testing

for clinical purposes. The correlative data presented is a result of the curation of published data sources, but may not be exhaustive. The content of this report has not been evaluated or approved by the FDA or other regulatory agencies.

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