Ghulam Sakhi Gurgaon Haryana	DOB: 05/10/1967 Age: 50Y Gender: M PID: QD2206792 Physician:	Molecular Quest Healthcare Pvt. Ltd. 28-29, Electronic City,Sec-18,Udyog Vihar, Phase-04 Gurgaon Haryana Phone: 8588869342

Order#	Collected Date/Time	Reported Date/Time	Status
2270148	11/05/2018	07/06/2018 01:09 PM	Final Report

Order Comments

Medical Oncologist ? Dr. Amish Vora
Molecular Oncologist ? Dr. Amit Verma

Test	Within Range	Out of Range	Biological Ref Range	Units
WATSON GENOMICS FROM QUEST DIAGNOSTICS, CORE	See Attached Report.			

HER2/NEU IMMUNOHISTOCHEMISTRY

DEPT ID NUMBER:
IHC00041318/A

.

GROSS EXAMINATION
Specimen identification (External Block) External ID in case of blocks: **2256/17C**
Number of blocks provided: 01
Test performed on external ID and Internal ID No: **2256/17C IHC00041318/A**

CONTROLS
Reactivity of positive and negative control: Present
All controls showed appropriate reactivity.

Tumor type- carcinoma colon

INTERPRETATION
HER2 OVEREXPRESSION: Negative (Score 0)

Adequacy of sample for evaluation Yes

Antibody Clone/Vendor and Method Used - This test was performed on Paraffin embedded tissue sections using Her

Ghulam Sakhi Gurgaon Haryana	DOB: 05/10/1967 Age: 50Y Gender: M PID: QD2206792 Physician:	Molecular Quest Healthcare Pvt. Ltd. 28-29, Electronic City,Sec-18,Udyog Vihar, Phase-04 Gurgaon Haryana Phone: 8588869342

Order#	Collected Date/Time	Reported Date/Time	Status
2270148	11/05/2018	07/06/2018 01:09 PM	Final Report

2 Neu/C-erb-2 oncoprotein/polyclonal antibody (DAKO) and detection achieved using an HRP-linked polymer system. An antibody other than the FDA approved is used.

Specific testing information:(Cold Ischemic Time, Fixative and Processing): Specimen should be placed in neutral buffered formalin within 1 hour of removal from the patient and fixed for a minimum of 6 but not in excess of 72 hours. Specimen should be processed by routine tissue processing methods.

Comments:
Inappropriate fixation and processing may give erroneous results. False negativity and false positivity is known to occur in case of over fixation and under-fixation.

Test Performed at:

Quest Diagnostics India
A -17, Info City, Sector 34,
Gurgaon, Haryana,
India 122001

This case has been reviewed and Electronically Signed by: Dr. Dixit, Mallika

_____

end of report for Ghulam Sakhi, Order No #2270148, Acc No # 180554245 IHC00041318/A

Dr Anurag Bansal M.D., Associate Director - Medical

Date and Time of Order Received in the Lab: 16/05/2018 02:36 PM

H - High, L - Low, VH - Very High, VL - Very Low, A - Clinically Abnormal, PA - Panic Abnormal

2270148

QUEST DIAGNOSTICS INCORPORATED

PATIENT INFORMATION
SAKHI,GHULAM

DOB: 10/05/1967 Age: 50
SEX: M

ID: 2270148

REPORT STATUS **Final**

ORDERING PHYSICIAN
A VORA/A VERMA
CLIENT INFORMATION
55001
QUEST DIAGNOSTICS INDIA PVT LTD
A17, INFO CITY, GURGAON
SECTOR 34
HARYANA INDIA 122001,

SPECIMEN INFORMATION
SPECIMEN: 83173412
REQUISITION: 550010033417
LAB REF NO:

COLLECTED: 05/11/2018 00:00
RECEIVED: 05/24/2018 00:59
REPORTED: 06/06/2018 18:43

Test Name	In Range	Out of Range	Reference Range	Lab
WATSON GENOMICS,QUEST,CORE				EZ
Tumor Tissue Type:	ADENOCARCINOMA			
Block ID:	2256/17/C			
Diagnosis:	COADREAD METASTATIC LOW-GRADE ADENOCA OF COLON PRIMARY			
Source	LUNG			
Paired Blood Submitted	YES			
Report Germline Consent	NO			
Overall Interpretation	SEE BELOW			

Diagnosis: Colorectal Adenocarcinoma

The following clinically significant alterations were found in this specimen:

1- KRAS G12C
2- BRAF L597Q
3- AKT1 E17K

** no other clinically significant alteration was found in the genes tested.

KRAS SUMMARY
The KRAS G12C mutation is known to be oncogenic. Resistance to Cetuximab is included in the NCCN-Compendium for this indication. Resistance to Panitumumab is also included in the NCCN-Compendium for this indication. There is clinical evidence that the KRAS G12C mutation confers sensitivity to Cobimetinib, Selumetinib, Binimetinib. Mutations in KRAS are associated with poor prognosis in CRC. Patients with tumors positive for mutations affecting codons 12 and 13 of KRAS have shorter OS compared to patients with wild type tumors (median OS 30.2 months for KRAS mutant cases vs 42.7 months for KRAS wild type) (PMID: 24806288) and impaired responses to anti-EGFR inhibitors (Cetuximab and Panitumumab)(PMID: 20619739, 18316791, 19339720, 23182985).

BRAF SUMMARY
The BRAF L597Q mutation is known to be oncogenic. There are no FDA-approved or NCCN-compendium listed treatments specifically for patients with Colorectal Carcinoma harboring the BRAF L597Q mutation. There is clinical evidence that the BRAF L597Q mutation confers sensitivity to Cobimetinib, Trametinib.

AKT1 SUMMARY

PATIENT INFORMATION
SAKHI,GHULAM

REPORT STATUS **Final**

QUEST DIAGNOSTICS INCORPORATED

DOB: 10/05/1967 Age: 50
SEX: M
ID: 2270148

ORDERING PHYSICIAN
A VORA/A VERMA

COLLECTED: 05/11/2018 00:00
REPORTED: 06/06/2018 18:43

Test Name	In Range	Out of Range	Reference Range	Lab
WATSON GENOMICS,QUEST,CORE (Continued)				
Overall Interpretation (Continued)				
The AKT1 E17K mutation is known to be oncogenic. There are no FDA-approved or NCCN-compendium listed treatments specifically for patients with Colorectal Carcinoma harboring any pathogenic AKT1 mutation. There is clinical evidence that pathogenic AKT1 mutations confer sensitivity to AZD5363, ARQ 092.				
MSI SUMMARY The tumor/normal pair samples were examined for microsatellite instability using 5 mononucleotide markers (Bat25, Bat26, NR21, NR24 and NR27). Results indicate microsatellite stable pattern (MSS). There are no FDA-approved or NCCN-compendium listed treatments specifically for patients with Colorectal Carcinoma harboring the MSI Stable. Pre-clinical and clinical evidence are not available for this indication.				
Tumor mutation burden (TMB) for this case is 18 non-synonymous variants per MB coding sequence. In contrast, MSS tumors which in general carry a low TMB are expected to have 12 non-synonymous variants per MB coding sequence (95% Confidence Interval 12-18) and MSI-High tumors which in general carry a high TMB are expected to have 48 non-synonymous variants per MB coding sequence (95% Confidence Interval 42-66). Published literature supports that higher TMB in tumors can help predict response to immunotherapies in certain cancer indications.				
Gene Name #1	SEE BELOW			
	KRAS			
Mutation #1	SEE BELOW			
	G12C			
Alteration Type #1	SEE BELOW			
	MISSENSE MUTATION			
Mutation Frequency #1	SEE BELOW		% Frequency	
	9			
Tumor Type Drugs #1	NO			
Non-Tumor Type Drugs #1	YES			
Clinical Trials #1	YES			
Watson Genomics,Core 2				EZ
Gene Name #2	SEE BELOW			
	BRAF			
Mutation #2	SEE BELOW			
	L597Q			
Alteration Type #2	SEE BELOW			
	MISSENSE MUTATION			

PATIENT INFORMATION
SAKHI,GHULAM

REPORT STATUS **Final**

QUEST DIAGNOSTICS INCORPORATED

DOB: 10/05/1967 Age: 50
SEX: M
ID: 2270148

ORDERING PHYSICIAN
A VORA/A VERMA

COLLECTED: 05/11/2018 00:00
REPORTED: 06/06/2018 18:43

Test Name	In Range	Out of Range	Reference Range	Lab
Watson Genomics,Core 2 (Continued)				
Mutation Frequency #2	SEE BELOW		% Frequency	
	8			
Tumor Type Drugs #2	NO			
Non-Tumor Type Drugs #2	YES			
Clinical Trials #2	YES			
Watson Genomics,Core 3				EZ
Gene Name #3	SEE BELOW			
	AKT1			
Mutation #3	SEE BELOW			
	E17K			
Alteration Type #3	SEE BELOW			
	MISSENSE MUTATION			
Mutation Frequency #3	SEE BELOW		% Frequency	
	20			
Tumor Type Drugs #3	NO			
Non-Tumor Type Drugs #3	NO			
Clinical Trials #3	YES			
Interacting Mutations				EZ
Interacting Mutations	SEE BELOW			
	None			
Additional Mutations	SEE BELOW			
	None			

PATIENT INFORMATION
SAKHI,GHULAM

REPORT STATUS **Final**

QUEST DIAGNOSTICS INCORPORATED

DOB: 10/05/1967 Age: 50
SEX: M
ID: 2270148

ORDERING PHYSICIAN
A VORA/A VERMA

COLLECTED: 05/11/2018 00:00
REPORTED: 06/06/2018 18:43

Test Name	In Range	Out of Range	Reference Range	Lab
Clinical Impact 1				EZ
Gene Function #1	SEE BELOW			

BACKGROUND

KRAS is a GDP/GTP-binding protein with intrinsic GTPase activity that acts as intracellular signal transducer. KRAS is usually tethered to cell membranes and an early molecule in many signal transduction pathways. The protein alternates between an inactive form bound to GDP and an active form bound to GTP. It is activated by receptor tyrosine kinases and a guanine nucleotide-exchange factor (GEF), which then stimulates the RAF-MEK-MAPK pathway. KRAS is inactivated by a GTPase-activating protein (GAP). KRAS is one of the most frequently mutated genes in human cancer. The most common oncogenic Ras mutation found in tumors is an amino acid change from Gly12 to Asp12 (G12D or another amino acid). This mutation prevents the inactivation of the RAS protein. The transforming capacity of KRAS mutants is associated with different degrees of aggressiveness depending on the location of the variant within the protein and the amino acid substation. Codon 12 mutations are more resistant to cell death and have more oncogenic and transforming potential than codon 13 variants (PMID: 11118062). Furthermore, different variants can signal through different downstream effector pathways (PMID: 16679305). Aside from mutations within the highly conserved P-loop (amino acids 10 to 17), switch 1 and switch 2 mutations can also increase the basal activity of KRAS.

Mutation Effect on Gene #1	SEE BELOW			

MUTATION EFFECT
gain-of-function mutation.

The KRAS G12C mutation is known to be oncogenic. The KRAS G12C mutation renders the enzyme less capable of hydrolyzing GTP, leading to constitutive enzymatic activity. Expression of this mutation in cell lines leads to increased activation of signaling downstream of RAS, including the MAPK and PI3K/AKT pathways (PMID: 25705018, 26841430). Breast cancer cell lines expressing this mutation had increased proliferation and colony growth (PMID: 25705018). A conditional mouse model expressing this alteration developed lung hyperplasia (PMID: 16051643). Several targeted therapies have been developed that specifically target this mutant allele (PMID: 26841430, 24256730).
Resistance to Cetuximab is included in the NCCN-Compendium for this indication. Resistance to Panitumumab is also included in the NCCN-Compendium for this indication. There is clinical evidence that the KRAS G12C mutation confers sensitivity to Cobimetinib, Selumetinib, Binimetinib. Mutations in KRAS are associated with poor prognosis in CRC. Patients with tumors positive for mutations affecting codons 12 and 13 of KRAS have shorter OS compared to patients with wild type tumors (median OS 30.2 months for KRAS mutant cases vs 42.7 months for KRAS wild type) (PMID: 24806288) and impaired responses to anti-EGFR inhibitors (Cetuximab and Panitumumab)(PMID: 20619739, 18316791, 19339720, 23182985).

QUEST DIAGNOSTICS INCORPORATED

COLLECTED: 05/11/2018 00:00
REPORTED: 06/06/2018 18:43

PATIENT INFORMATION
SAKHI,GHULAM

DOB: 10/05/1967 Age: 50
SEX: M
ID: 2270148

REPORT STATUS **Final**

ORDERING PHYSICIAN
A VORA/A VERMA

Test Name	In Range	Out of Range	Reference Range	Lab

Clinical Impact 1 (Continued)
Mutation Effect on Gene #1 (Continued)

NCCN
GUIDELINES
Version: 1.2018. Cancer type: Colorectal Carcinoma.
Recommendation
category R1: Numerous studies have shown that patients with colorectal cancer positive for KRAS mutations (exons 2, 3 or 4), do not derive benefit from, treatment with Cetuximab or Panitumumab either alone or in combination with other agents (PMID: 19114683, 18316791, 18946061, 17664471, 25115304, 19339720, 18202412, 17998284, 24024839).

STANDARD THERAPEUTIC
IMPLICATIONS

RESISTANCE INFORMATION

KRAS is associated with resistance
to:

CETUXIMAB
PANITUMUMAB

Highest level of evidence: R1

PROGNOSTIC
IMPLICATIONS
Mutations in KRAS are associated with poor prognosis in CRC.
Patients with tumors positive for mutations affecting codons 12 and 13 of KRAS have shorter OS compared to patients with wild type tumors (median OS 30.2 months for KRAS mutant cases vs 42.7 months for KRAS wild type) (PMID: 24806288) and impaired responses to anti-EGFR inhibitors (Cetuximab and Panitumumab)(PMID: 20619739, 18316791, 19339720, 23182985).

FDA Tumor Drugs #1 — SEE BELOW

None

FDA Non-Tumor Drugs #1 — SEE BELOW

TRAMETINIB
Melanoma

QUEST DIAGNOSTICS INCORPORATED

COLLECTED: 05/11/2018 00:00
REPORTED: 06/06/2018 18:43

PATIENT INFORMATION
SAKHI,GHULAM

DOB: 10/05/1967 Age: 50
SEX: M
ID: 2270148

REPORT STATUS **Final**

ORDERING PHYSICIAN
A VORA/A VERMA

Test Name	In Range	Out of Range	Reference Range	Lab
Clinical Impact 1 (Continued)				
Clinical Trials #1	SEE BELOW			

CLINICAL TRIALS MATCHED FOR VARIANT AND DISEASE
NCT02091141, Phase 2
TITLE:
My Pathway: An Open Label Phase IIa Study Evaluating Trastuzumab/Pertuzumab, Erlotinib, Vemurafenib, and Vismodegib in Patients Who Have Advanced Solid Tumors With Mutations or Gene Expression Abnormalities Predictive of Response to One of These Agents

NCT02465060, Phase 2
TITLE: Molecular Analysis for
Therapy Choice (MATCH)

NCT03087071, Phase 2
TITLE: A Phase II Enrichment
Study of Panitumumab as a Single Agent or in Combination With Trametinib in Cetuximab-Refractory Stage IV Colorectal Cancer Patients

NCT03340558, Phase
2
TITLE: A Pilot Study Investigating the Effect of Atezolizumab Monotherapy and Atezolizumab Plus Cobimetinib on the Tumoral Immunoprofile in Liver Metastases From Colorectal Cancer

NCT03428126, Phase 2
TITLE: Phase II Study
of Durvalumab (MEDI4736) (Anti-PD-L1) and Trametinib (MEKi) in MSS Metastatic Colon Cancer

NCT02079740, Phase 1 or 2
TITLE: 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 Mutation-Positive Advanced Solid Tumors

NCT02613650, Phase 1
TITLE: A Phase
1b Trial of a Combination of FOLFIRI With MEK162 in Patients With Advanced KRAS Positive Metastatic Colorectal Cancers

NCT02703571, Phase 1 or 2
TITLE:
A Phase I/II Study of Safety and Efficacy of Ribociclib (LEE011) in Combination With Trametinib (TMT212) in Patients With Metastatic or Advanced

PATIENT INFORMATION
SAKHI,GHULAM

REPORT STATUS **Final**

QUEST DIAGNOSTICS INCORPORATED

ORDERING PHYSICIAN
A VORA/A VERMA

DOB: 10/05/1967 Age: 50
SEX: M
ID: 2270148

COLLECTED: 05/11/2018 00:00
REPORTED: 06/06/2018 18:43

Test Name	In Range	Out of Range	Reference Range	Lab

Clinical Impact 1 (Continued)
Clinical Trials #1 (Continued)
Solid Tumors

NCT02857270, Phase 1
TITLE: A Phase 1 Study of an ERK1/2
Inhibitor (LY3214996) Administered Alone or in Combination With Other Agents
in Advanced Cancer

NCT02900664, Phase 1
TITLE: Phase Ib, Open-label,
Multi-center Study to Characterize the Safety, Tolerability and
Pharmacodynamics (PD) of PDR001 in Combination With CJM112, EGF816, Ilaris
(Canakinumab) or Mekinist (Trametinib)

NCT02972034, Phase 1
TITLE: A Phase Ib
Study to Evaluate the Safety and Tolerability of MK-8353 in Combination With
Pembrolizumab in Patients With Advanced Malignancies

NCT03162627, Phase
1
TITLE: Evaluation of the Combination of Selumetinib and Olaparib in
Endometrial, Ovarian and Other Solid Tumors With Ras Pathway Alterations, and
Ovarian Tumors With PARP Resistance

NCT03317119, Phase 1
TITLE: A Phase I
Clinical Trial of Trametinib in Combination With TAS-102 in Patients With
Chemotherapy-Resistant RAS-Mutated (PIK3CA/PTEN-Wild-Type) Metastatic
Colorectal Cancer

NCT03374254, Phase 1
TITLE: A Phase 1b Multi-cohort Study
of the Combination of Pembrolizumab (MK-3475) Plus Binimetinib Alone or the
Combination of Pembrolizumab Plus Chemotherapy With or Without Binimetinib in
Participants With Metastatic Colorectal Cancer (KEYNOTE-651)

INVESTIGATIONAL
THERAPEUTIC IMPLICATIONS

COBIMETINIB

Highest level of evidence:
3A

QUEST DIAGNOSTICS INCORPORATED

COLLECTED: 05/11/2018 00:00
REPORTED: 06/06/2018 18:43

PATIENT INFORMATION
SAKHI,GHULAM

DOB: 10/05/1967 Age: 50
SEX: M
ID: 2270148

REPORT STATUS **Final**

ORDERING PHYSICIAN
A VORA/A VERMA

Test Name	In Range	Out of Range	Reference Range	Lab

Clinical Impact 1 (Continued)
Clinical Trials #1 (Continued)

Cobimetinib has not been evaluated for KRAS-mutant disease. However, early results of combination treatment with the PDL1 inhibitor Atezolizumab showed clinical activity in CRC patients (22 KRAS mutant, 1 KRAS wild-type) with an ORR of 17% (4 PR and 5 SD), and 3 responses ongoing at the time of data cutoff (range, 4.0 to 7.7 mo). Response was not associated with baseline PD-L1 expression (Bendell et al. ASCO 2016, # 3502).

SELUMETINIB

Highest level of evidence: 3A
In a phase I study of Selumetinib in KRAS-mutant CRC tumors, 5 out of 14 patients had SD as best response, while 9 patients had PD, demonstrating mild activity for the Drug in this context (PMID: 26666244). An ORR of 4%, median OS of 266 days, and median PFS of 105 days were reported in a phase 2 dose-finding study involving 31 patients with KRAS mutant CRC treated with a combination therapy consisting of Selumetinib and irinotecan. Three patients continued treatment with Selumetinib and irinotecan for over one year (PMID: 25322874).

BINIMETINIB

Highest level of evidence:
3B
Efficacy of Binimetinib in tumors harboring KRAS or BRAF mutations has been tested in a phase 1 trial in patients with advanced solid tumors. Six patients had confirmed oncogenic mutations in KRAS. Two patients had progressive disease, two patients experienced stable disease with mi nor reduction in tumor burden and two remaining patients had partial responses as measured by reduction in tumor burden (PMID: 27071922).

LY3214996

Highest level of evidence: 4
LY3214996 is a highly selective inhibitor of ERK1 and ERK2. Preclinical data have shown that tumor cells with MAPK pathway alterations including BRAF, NRAS or KRAS mutation are sensitivity to LY3214996. In tumor xenograft models, LY3214996 inhibited the PD biomarker p-p90RSK1 and the PD effects correlated with exposure and anti-tumor activity. Oral administration of single-agent LY3214996 significantly inhibited tumor growth in vivo and was well tolerated in BRAF or NRAS mutant Melanoma, BRAF or KRAS mutant CRC, lung and pancreatic cancer xenografts or PDX models (Bhagwat et al. AACR 2017, abstract #4973).

QUEST DIAGNOSTICS INCORPORATED

COLLECTED: 05/11/2018 00:00
REPORTED: 06/06/2018 18:43

PATIENT INFORMATION
SAKHI,GHULAM

DOB: 10/05/1967 Age: 50
SEX: M
ID: 2270148

REPORT STATUS **Final**

ORDERING PHYSICIAN
A VORA/A VERMA

Test Name	In Range	Out of Range	Reference Range	Lab

Clinical Impact 1 (Continued)
Clinical Trials #1 (Continued)
MK-8353

Highest level of evidence: 4
The preclinical data
resulting in advancement of this Drug to clinical development have not been
published.

TRAMETINIB

Highest level of evidence: 4
Trametinib, an oral
selective inhibitor of the MAPK pathway, is FDA-approved for treatment of
BRAF-V600E/K mutant metastatic Melanoma (PMID: 23846731, 22663011).Addition of
MAPK inhibitors to standard treatment is in evaluation for the treatment of
advanced colorectal cancer (PMID: 21690569, 23438367).

LEVELS OF
EVIDENCE
Level 1: FDA-approved drug for this cancer type excluding
chemotherapeutic drugs and hormone therapies
Level 2A: Standard of care
biomarker predictive of response to an FDA-approved drug for this indication
(including biomarkers recommended as standard of care by the NCCN)
Level 2B:
Standard of care biomarker predictive of response to an FDA-approved drug for
a different indication (including biomarkers recommended as standard of care
by the NCCN)
Level 3A: Clinical evidence supports the biomarker as being
predictive of response to a drug for this indication
Level 3B: Clinical
evidence supports the biomarker as being predictive of response to a drug for
a different indication
Level 4: Compelling preclinical evidence supports the
biomarker as being predictive of response to a drug
Level R1: Standard of care
biomarker predictive of resistance to an FDA approved drug for this indication
including biomarkers described by the NCCN

Companion Diagnostics #1 SEE BELOW

None

PATIENT INFORMATION
SAKHI,GHULAM

REPORT STATUS **Final**

QUEST DIAGNOSTICS INCORPORATED

ORDERING PHYSICIAN
A VORA/A VERMA

DOB: 10/05/1967 Age: 50
SEX: M
ID: 2270148

COLLECTED: 05/11/2018 00:00
REPORTED: 06/06/2018 18:43

Test Name	In Range	Out of Range	Reference Range	Lab
Clinical Impact 2				EZ
Gene Function #2	SEE BELOW			

BACKGROUND
BRAF belongs to the RAF family of serine/threonine protein kinases. It is involved in the transduction of mitogenic signals from the cell membrane to the nucleus and plays a role in the postsynaptic responses of hippocampal neurons. BRAF regulates the MAP kinase/ERK signaling pathway, which affects cell division, differentiation, and secretion. BRAF is an oncogene and frequently mutated in cutaneous melanomas, colorectal cancer, thyroid cancers, papillary craniopharyngiomas, lung cancer, and at lower frequency in a wide range of human malignancies.

Mutation Effect on Gene #2	SEE BELOW

MUTATION EFFECT
gain-of-function mutation.

The BRAF L597Q mutation is known to be oncogenic. The L597Q variant has been previously associated with melanoma, multiple myeloma, and CRC and CLL (PMID: 21726664, 24434212, 21289333, 24550227). Functional studies have identified this variant as an oncogenic alteration leading to activation of MEK signaling (PMID: 17525723). There are no FDA-approved or NCCN-compendium listed treatments specifically for patients with Colorectal Carcinoma harboring the BRAF L597Q mutation. There is clinical evidence that the BRAF L597Q mutation confers sensitivity to Cobimetinib, Trametinib.

NCCN GUIDELINES
none

STANDARD THERAPEUTIC IMPLICATIONS
none

FDA Tumor Drugs #2	SEE BELOW
	None
FDA Non-Tumor Drugs #2	SEE BELOW
	TRAMETINIB
	Melanoma

QUEST DIAGNOSTICS INCORPORATED

PATIENT INFORMATION
SAKHI,GHULAM

DOB: 10/05/1967 Age: 50
SEX: M
ID: 2270148

REPORT STATUS **Final**

ORDERING PHYSICIAN
A VORA/A VERMA

COLLECTED: 05/11/2018 00:00
REPORTED: 06/06/2018 18:43

Test Name	In Range	Out of Range	Reference Range	Lab
Clinical Impact 2 (Continued)				
Clinical Trials #2	SEE BELOW			

CLINICAL TRIALS MATCHED FOR VARIANT AND DISEASE
NCT02091141, Phase 2
TITLE:
My Pathway: An Open Label Phase IIa Study Evaluating Trastuzumab/Pertuzumab, Erlotinib, Vemurafenib, and Vismodegib in Patients Who Have Advanced Solid Tumors With Mutations or Gene Expression Abnormalities Predictive of Response to One of These Agents

NCT02465060, Phase 2
TITLE: Molecular Analysis for
Therapy Choice (MATCH)

NCT03087071, Phase 2
TITLE: A Phase II Enrichment
Study of Panitumumab as a Single Agent or in Combination With Trametinib in Cetuximab-Refractory Stage IV Colorectal Cancer Patients

NCT03340558, Phase
2
TITLE: A Pilot Study Investigating the Effect of Atezolizumab Monotherapy and Atezolizumab Plus Cobimetinib on the Tumoral Immunoprofile in Liver Metastases From Colorectal Cancer

NCT03428126, Phase 2
TITLE: Phase II Study
of Durvalumab (MEDI4736) (Anti-PD-L1) and Trametinib (MEKi) in MSS Metastatic Colon Cancer

NCT02079740, Phase 1 or 2
TITLE: 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 Mutation-Positive Advanced Solid Tumors

NCT02428712, Phase 1 or 2
TITLE: A
Phase 1/2a Study to Assess the Safety, Pharmacokinetics, and Pharmacodynamics of PLX8394 in Patients With Advanced, Unresectable Solid Tumors

NCT02613650,
Phase 1
TITLE: A Phase 1b Trial of a Combination of FOLFIRI With MEK162 in Patients With Advanced KRAS Positive Metastatic Colorectal

PATIENT INFORMATION
SAKHI,GHULAM

REPORT STATUS **Final**

QUEST DIAGNOSTICS INCORPORATED

DOB: 10/05/1967 Age: 50
SEX: M
ID: 2270148

ORDERING PHYSICIAN
A VORA/A VERMA

COLLECTED: 05/11/2018 00:00
REPORTED: 06/06/2018 18:43

Test Name	In Range	Out of Range	Reference Range	Lab

Clinical Impact 2 (Continued)
Clinical Trials #2 (Continued)
Cancers

NCT02703571, Phase 1 or 2
TITLE: A Phase I/II Study of Safety and
Efficacy of Ribociclib (LEE011) in Combination With Trametinib (TMT212) in
Patients With Metastatic or Advanced Solid Tumors

NCT02857270, Phase 1
TITLE:
A Phase 1 Study of an ERK1/2 Inhibitor (LY3214996) Administered Alone or in
Combination With Other Agents in Advanced Cancer

NCT02900664, Phase 1
TITLE:
Phase Ib, Open-label, Multi-center Study to Characterize the Safety,
Tolerability and Pharmacodynamics (PD) of PDR001 in Combination With CJM112,
EGF816, Ilaris (Canakinumab) or Mekinist (Trametinib)

NCT02972034, Phase
1
TITLE: A Phase Ib Study to Evaluate the Safety and Tolerability of MK-8353
in Combination With Pembrolizumab in Patients With Advanced
Malignancies

NCT03162627, Phase 1
TITLE: Evaluation of the Combination of
Selumetinib and Olaparib in Endometrial, Ovarian and Other Solid Tumors With
Ras Pathway Alterations, and Ovarian Tumors With PARP Resistance

NCT03317119,
Phase 1
TITLE: A Phase I Clinical Trial of Trametinib in Combination With
TAS-102 in Patients With Chemotherapy-Resistant RAS-Mutated
(PIK3CA/PTEN-Wild-Type) Metastatic Colorectal Cancer

NCT03374254, Phase
1
TITLE: A Phase 1b Multi-cohort Study of the Combination of Pembrolizumab
(MK-3475) Plus Binimetinib Alone or the Combination of Pembrolizumab Plus
Chemotherapy With or Without Binimetinib in Participants With Metastatic
Colorectal Cancer (KEYNOTE-651)

INVESTIGATIONAL THERAPEUTIC
IMPLICATIONS

PATIENT INFORMATION
SAKHI,GHULAM

REPORT STATUS **Final**

QUEST DIAGNOSTICS INCORPORATED

ORDERING PHYSICIAN
A VORA/A VERMA

DOB: 10/05/1967 Age: 50
SEX: M
ID: 2270148

COLLECTED: 05/11/2018 00:00
REPORTED: 06/06/2018 18:43

Test Name	In Range	Out of Range	Reference Range	Lab

Clinical Impact 2 (Continued)
Clinical Trials #2 (Continued)

COBIMETINIB

Highest level of evidence: 3B
Combination therapy
with the BRAF inhibitor Vemurafenib demonstrated significantly improved PFS and OS compared to Vemurafenib monotherapy in metastatic Melanoma (PMID: 27480103, 25265494). Results from the metastatic Melanoma cohort of a phase 1b
dose escalation trial of Cobimetinib and Atezolizumab in 20 non-ocular Melanoma patients with metastatic disease, demonstrated an ORR of 45% percent, with 9 PR, a DCR of 75% (CR plus PR plus SD) and median PFS of 12 months (Miller et al. ASCO 2017, abstract #3057).

TRAMETINIB

Highest level of
evidence: 3B
Trametinib is an orally bioavailable MEK1/2 inhibitor that was FDA-approved in May 2013 for use in patients with BRAF V600E/K-mutant metastatic Melanoma (PMID: 22663011). In a limited cohort study of Trametinib in patients with non-V600E BRAF mutated metastatic Melanoma, 1 patient harboring a BRAF L597Q mutation achieved partial response (6.2 months) upon treatment with Trametinib (PMID: 24933606). In vitro studies of cell lines engineered to express BRAF L597R or L597S mutations demonstrated sensitivity to MEK inhibition as measured by decreased activation of downstream effector proteins upon treatment with Trametinib (PMID: 22798288).

SELUMETINIB

Highest level of evidence: 4
An orally active, small
molecule with potential antineoplastic activity. Selumetinib is an ATP-independent inhibitor of mitogen-activated protein kinase kinase (MEK or MAPK/ERK kinase) 1 and 2. MEK 1 and 2 are dual specificity kinases that are essential mediators in the activation of the RAS/RAF/MEK/ERK pathway, are often upregulated in various cancer cells, and are drivers of diverse cellular responses, including proliferation. Inhibition of both MEK1 and 2 by Selumetinib prevents the activation of MEK1/2 dependent effector proteins and transcription factors, thereby leading to an inhibition of cellular proliferation in various cancers.

BINIMETINIB

QUEST DIAGNOSTICS INCORPORATED

COLLECTED: 05/11/2018 00:00
REPORTED: 06/06/2018 18:43

PATIENT INFORMATION
SAKHI,GHULAM

DOB: 10/05/1967 Age: 50
SEX: M
ID: 2270148

REPORT STATUS **Final**

ORDERING PHYSICIAN
A VORA/A VERMA

Test Name	In Range	Out of Range	Reference Range	Lab

Clinical Impact 2 (Continued)
Clinical Trials #2 (Continued)

Highest level of evidence:
4
Binimetinib is a potent inhibitor of MAPK signaling and clinical activity has been demonstrated in patients with advanced BRAF- as well as NRAS-mutant Melanoma (PMID: 23414587, 28284557).

LY3214996

Highest level of evidence:
4
LY3214996 is a highly selective inhibitor of ERK1 and ERK2. Preclinical data have shown that tumor cells with MAPK pathway alterations including BRAF, NRAS or KRAS mutation are sensitivity to LY3214996. In tumor xenograft models, LY3214996 inhibited the PD biomarker p-p90RSK1 and the PD effects correlated with exposure and anti-tumor activity. Oral administration of single-agent LY3214996 significantly inhibited tumor growth in vivo and was well tolerated in BRAF or NRAS mutant Melanoma, BRAF or KRAS mutant CRC, lung and pancreatic cancer xenografts or PDX models (Bhagwat et al. AACR 2017, abstract #4973).

PLX8394

Highest level of evidence: 4
Preclinical data have shown that PLX8394 is an inhibitor of MAPK activation resulting in growth inhibition of BRAF mutated cancer cells (PMID: 26466569, 28659148).

MK-8353

Highest level of evidence: 4
The preclinical data resulting in advancement of this Drug to clinical development have not been published.

LEVELS OF EVIDENCE
Level 1: FDA-approved drug for this cancer type excluding chemotherapeutic drugs and hormone therapies
Level 2A: Standard of care biomarker predictive of response to an FDA-approved drug for this indication (including biomarkers recommended as standard of care by the NCCN)
Level 2B:
Standard of care biomarker predictive of response to an FDA-approved drug for a different indication (including biomarkers recommended as standard of care

PATIENT INFORMATION
SAKHI,GHULAM

REPORT STATUS **Final**

QUEST DIAGNOSTICS INCORPORATED

ORDERING PHYSICIAN
A VORA/A VERMA

DOB: 10/05/1967 Age: 50
SEX: M
ID: 2270148

COLLECTED: 05/11/2018 00:00
REPORTED: 06/06/2018 18:43

Test Name	In Range	Out of Range	Reference Range	Lab
Clinical Impact 2 (Continued)				
Clinical Trials #2 (Continued)				
by the NCCN) Level 3A: Clinical evidence supports the biomarker as being predictive of response to a drug for this indication Level 3B: Clinical evidence supports the biomarker as being predictive of response to a drug for a different indication Level 4: Compelling preclinical evidence supports the biomarker as being predictive of response to a drug Level R1: Standard of care biomarker predictive of resistance to an FDA approved drug for this indication including biomarkers described by the NCCN				
Companion Diagnostics #2	SEE BELOW			
	None			
Clinical Impact 3				EZ
Gene Function #3	SEE BELOW			

BACKGROUND
AKT1 is a serine-threonine protein kinases and one of the most frequently hyperactivated kinases in cancer with roles in metabolism, proliferation, survival, and angiogenesis. The protein is activated by insulin and various growth and survival factors and plays a role in insulin stimulation of glucose transport and it is involved in cell cycle regulation. It phosphorylates and inactivates tuberin (TSC2), an inhibitor of mTOR within the mTOR-raptor complex. Several substitutions in the Pleckstrin domain have been reported to result in PI3K-independent activation of AKT1 (PMID: 23348505, 19802009), while others did not exceed activity of the wild type protein (PMID: 23237847). The E17K substitution in the Pleckstrin domain is the most prevalent alteration of AKT1 in breast cancer leading to PI3K-independent activation of AKT1 and it is considered an early event in pathogenesis (PMID: 23888070).

PATIENT INFORMATION
SAKHI,GHULAM

REPORT STATUS **Final**

QUEST DIAGNOSTICS INCORPORATED

ORDERING PHYSICIAN
A VORA/A VERMA

DOB: 10/05/1967 Age: 50
SEX: M
ID: 2270148

COLLECTED: 05/11/2018 00:00
REPORTED: 06/06/2018 18:43

Test Name	In Range	Out of Range	Reference Range	Lab
Clinical Impact 3 (Continued)				
Mutation Effect on Gene #3	SEE BELOW			

MUTATION EFFECT
gain-of-function mutation.

The AKT1 E17K mutation is known to be oncogenic. E17K is a highly recurrent mutation and also the most prevalent alteration of AKT1. This variant has been described in several types of cancer but it is most commonly associated with meningioma and ER-positive carcinoma of the breast (PMID: 23334667, 20668451). E17K is located in the N-terminal Pleckstrin homology domain and results in PI3K-independent activation of AKT1 through pathological localization of AKT1 to the plasma membrane. Functionally, it has been shown to induce cellular transformation and leukemogenesis in mice, in agreement with a crucial role in cancer development (PMID: 17611497). There are no FDA-approved or NCCN-compendium listed treatments specifically for patients with Colorectal Carcinoma harboring any pathogenic AKT1 mutation. There is clinical evidence that pathogenic AKT1 mutations confer sensitivity to AZD5363, ARQ 092.

NCCN
GUIDELINES
none

STANDARD THERAPEUTIC IMPLICATIONS
none

FDA Tumor Drugs #3	SEE BELOW			
	None			
FDA Non-Tumor Drugs #3	SEE BELOW			
	None			

PATIENT INFORMATION
SAKHI,GHULAM

REPORT STATUS **Final**

QUEST DIAGNOSTICS INCORPORATED

ORDERING PHYSICIAN
A VORA/A VERMA

DOB: 10/05/1967 Age: 50
SEX: M
ID: 2270148

COLLECTED: 05/11/2018 00:00
REPORTED: 06/06/2018 18:43

Test Name	In Range	Out of Range	Reference Range	Lab
Clinical Impact 3 (Continued)				
Clinical Trials #3	SEE BELOW			

CLINICAL TRIALS MATCHED FOR VARIANT AND DISEASE
NCT02465060, Phase 2
TITLE:
Molecular Analysis for Therapy Choice (MATCH)

NCT02576444, Phase 2
TITLE: A
Phase II Study of the PARP Inhibitor Olaparib (AZD2281) Alone and in
Combination With AZD1775, AZD5363, or AZD2014 in Advanced Solid
Tumors

NCT01226316, Phase 1
TITLE: A Phase I, Open-Label, Multicentre Study
to Assess the Safety, Tolerability, Pharmacokinetics and Preliminary
Anti-tumour Activity of Ascending Doses of AZD5363 Under Adaptable Dosing
Schedules in Patients With Advanced Solid Malignancies.

NCT02476955, Phase
1
TITLE: An Open-label Phase 1b Study of ARQ 092 in Combination With
Carboplatin Plus Paclitaxel in Subjects With Selected Solid
Tumors

NCT02761694, Phase 1
TITLE: A Phase 1 Dose Escalation Study of ARQ 751
in Adult Subjects With Advanced Solid Tumors With AKT1, 2, 3 Genetic
Alterations, Activating PI3K Mutations or PTEN-

INVESTIGATIONAL THERAPEUTIC
IMPLICATIONS

AKT1 can be targeted therapeutically either by drugs that
inhibit AKT itself or important downstream effectors such as mTOR. Sirolimus,
temsirolimus, everolimus, ridaforolimus, deforolimus, AP23573, MK8669, AZD2014
and MLN0128 are inhibitors of mTOR, which is downstream of AKT1 in the
P13K/AKT/mTOR signaling pathway (PMID: 22037041, 24333502). Also known as
rapalogues, these drugs primarily inhibit downstream S6K activity with less of
an effect on 4EBP/EIF4E (PMID: 22037041). Inhibiting mTOR activity downstream
of AKT has no effect on mTOR independent functions of AKT, such as inhibition
of FOXO transcription factors (PMID: 17604717). After extensive preclinical
and clinical investigations, it is generally accepted that single-agent
treatment with rapalogues will be an ineffective therapeutic strategy for most
cancers due to incomplete inhibition of mTOR activity, as well release of
feedback inhibition that leads to heightened upstream signaling via receptor
tyrosine kinases (RTK), PI3K, and AKT (PMID: 16452206). These agents are now

PATIENT INFORMATION
SAKHI,GHULAM

REPORT STATUS **Final**

QUEST DIAGNOSTICS INCORPORATED

ORDERING PHYSICIAN
A VORA/A VERMA

DOB: 10/05/1967 Age: 50
SEX: M
ID: 2270148

COLLECTED: 05/11/2018 00:00
REPORTED: 06/06/2018 18:43

Test Name	In Range	Out of Range	Reference Range	Lab

Clinical Impact 3 (Continued)
Clinical Trials #3 (Continued)
being tested in a wide variety of combination strategies (PMID: 22037041, 25533673, 24481312).

ARQ 092

Highest level of evidence: 3B
ARQ 092 has been shown to inhibit the proliferation of PI3KCA, PIK3R1 or AKT mutant cell lines and xenograft models in preclinical studies. In addition, ARQ092 has demonstrated anti-tumor activity in a phase Ib study in patients with ovarian carcinoma. Two patients with mutations in AKT achieved completed responses (Lakhani et. Al. ASCO 2017 Abstract #2524).

AZD5363

Highest level of evidence: 3B
AZD5363 is an orally available, ATP-competitive pan-AKT inhibitor that targets the PI3K/AKT/mTOR signaling pathway (PMID: 23394218). In two Phase I studies, AZD5363 treatment induced target lesion regression in 20 of 29 evaluable patients (69%) with solid tumors, including one RECIST partial responses (PR) in a patient with endometrioid ovarian cancer (Hyman, D. Et al. AACR-NCI-EORTC International Conference on Molecular Targets and Cancer Therapeutics, Abstract B109, 2015). In this study, decreased AKT1 E17K ctDNA was correlated with tumor response (Abstract: Hyman et al. Abstract# B109, AACR-NCI-EORTC 2015. http://mct.aacrjournals.org/content/14/12_Supplement_2/B109). Another Phase I trial of AZD5363 in Japan showed partial response in 2 of 41 patients, one of these patients with AKT1 E17K-mutated metastatic ovarian cancer exhibited significant shrinkage in her lung metastasis. Notably the patient maintained a stable PR for more than two years (PMID: 26351323). Preclinical studies in vitro have shown that AZD5363 inhibits tumor growth and reduces phosphorylation of PRAS40 and S6 (AKT1 substrates) in breast cancer explants harboring the AKT1 E17K mutation (Davies, B. Et al. Cancer Res. 74 Abstract 5553, 2014).

ARQ751

Highest level of evidence: 4
Preclinical studies have shown that ARQ 751 inhibits proliferation across multiple tumor types with highest potency in leukemia, breast, endometrial, and colorectal cancer cell lines. Inhibition was more prevalent in cancer cell lines containing PIK3CA/PIK3R1 mutations as well as the AKT1 E17K mutation compared to those with wt-PIK3CA/PIK3R1 or PTEN mutations (PMID: 26469692).

PATIENT INFORMATION
SAKHI,GHULAM

REPORT STATUS **Final**

QUEST DIAGNOSTICS INCORPORATED

ORDERING PHYSICIAN
A VORA/A VERMA

DOB: 10/05/1967 Age: 50
SEX: M
ID: 2270148

COLLECTED: 05/11/2018 00:00
REPORTED: 06/06/2018 18:43

Test Name	In Range	Out of Range	Reference Range	Lab
Clinical Impact 3 (Continued)				
Clinical Trials #3 (Continued)				

LEVELS OF
EVIDENCE
Level 1: FDA-approved drug for this cancer type excluding
chemotherapeutic drugs and hormone therapies
Level 2A: Standard of care
biomarker predictive of response to an FDA-approved drug for this indication
(including biomarkers recommended as standard of care by the NCCN)
Level 2B:
Standard of care biomarker predictive of response to an FDA-approved drug for
a different indication (including biomarkers recommended as standard of care
by the NCCN)
Level 3A: Clinical evidence supports the biomarker as being
predictive of response to a drug for this indication
Level 3B: Clinical
evidence supports the biomarker as being predictive of response to a drug for
a different indication
Level 4: Compelling preclinical evidence supports the
biomarker as being predictive of response to a drug
Level R1: Standard of care
biomarker predictive of resistance to an FDA approved drug for this indication
including biomarkers described by the NCCN

Companion Diagnostics #3	SEE BELOW			
	None			
Gene Regions Passing QC				EZ
Gene Regions Passing QC	SEE BELOW			

In this specimen, 896 of 900 regions (>99%) passed our minimal acceptability QC criteria for reporting results, including relevant regions for this test. The coverage of 4 of 900 regions (<1%) was not optimal and the risk of a false-negative result at those regions cannot be ruled out. Details can be provided upon request.

This data was reviewed and interpreted by Anatole Ghazalpour, PhD, FACMG

PATIENT INFORMATION
SAKHI,GHULAM

REPORT STATUS **Final**

QUEST DIAGNOSTICS INCORPORATED

ORDERING PHYSICIAN
A VORA/A VERMA

DOB: 10/05/1967 Age: 50
SEX: M
ID: 2270148

COLLECTED: 05/11/2018 00:00
REPORTED: 06/06/2018 18:43

Test Name	In Range	Out of Range	Reference Range	Lab
Gene Regions Passing QC (Continued)				
Always Statement	SEE BELOW			

This Watson Genomics from Quest Core test is designed to detect mutations present in any FFPE tissue from solid tumors. The test is designed to detect single nucleotide variants (SNVs) and small insertions/deletions (In/Dels) as well as whole gene copy number alterations and translocations in a select group of genes. Results of the test should be correlated with clinical findings. The genes (listed below) were selected based on actionability of mutations identified in those genes using currently available evidence from national and international guidelines and literature. Actionability is defined as information a clinician might find useful to aid in diagnosis, prognosis and/or treatment strategy for a patient. Results of the test should be correlated with clinical findings. Clinical trial information provided in this report is solely for informational purposes for the physician and does not constitute any endorsement or a recommendation for enrollment of patients in any trial by Quest Diagnostics, its affiliates, or its employees.
Only mutations present in the interrogated regions of the genes are reported. The test does not identify mutations present outside the interrogated regions. Normal population variations, promoter and intronic variations (with the exception of the TERT promoter and splice site variants) as well as synonymous single nucleotide polymorphisms (SNPs) are not included in this report. This test has an analytical sensitivity for detecting 5% SNVs and 5% INDEL mutated sequences in a background of non-mutated DNA sequence; two-fold or higher gene amplifications; and homozygous gene deletions.
Insertion/Deletion detection is limited to 10 base insertion and 15 base deletion. Translocation detection is limited to a set of specified acceptor genes at 20% analytical sensitivity. The performance characteristics of the test can change based on adequacy of tumor tissue or pre-analytical variables. (This test was validated on FFPE tissue and whole blood).
The genes tested include: AKT1, AKT2, ALK, AR, AURKA, BAP1, BRAF, BRCA1, BRCA2, CDKN2A, CDKN2B, CTNNB1, DDR2, EGFR, EP300, ERBB2, ERBB3, ERBB4, ESR1, FGFR1, FGFR2, FGFR3, FGFR4, FLT3, HRAS, IDH1, JAK2, KDR, KIT, KRAS, MAP2K1, MET, MTOR, MYC, MYCN, NRAS, NTRK1, PDGFRA, PDGFRB, PIK3CA, PTCH1, PTEN, RET, ROS1, TERT, TMPRSS2, TP53, TSC1, VHL. The genes tested for translocations include ALK, BRAF, EGFR, FGFR2, FGFR3, NTRK1, RET, ROS1, and TMPRSS2.

Microsatellite instability and/or hypermutated phenotype can be reported if identified.
This test was not designed for comprehensive germline mutation analysis or for circulating tumor DNA mutation analysis. When patient consent is provided, and where warranted, limited information is included about whether an alteration detected in the BRCA1, BRCA2, CDKN2A, PTEN, RET, TP53 or VHL genes in the tissue is of germline origin, but this information should be confirmed with specialized germline testing in consultation with a clinician and genetic counseling, if appropriate. Genetic counseling is available at 1.866.GENE.INFO (1.866.436.3463).

For additional information, please refer to

PATIENT INFORMATION
SAKHI,GHULAM

REPORT STATUS **Final**

QUEST DIAGNOSTICS INCORPORATED

ORDERING PHYSICIAN
A VORA/A VERMA

DOB: 10/05/1967 Age: 50
SEX: M
ID: 2270148

COLLECTED: 05/11/2018 00:00
REPORTED: 06/06/2018 18:43

Test Name	In Range	Out of Range	Reference Range	Lab

Gene Regions Passing QC (Continued)
Always Statement (Continued)
http://education.QuestDiagnostics.com/faq/FAQ155
(This link is being provided for informational/educational purposes only.)

This test was developed and its analytical performance characteristics have been determined by Quest Diagnostics Nichols Institute San Juan Capistrano. It has not been cleared or approved by FDA. This assay has been validated pursuant to the CLIA regulations and is used for clinical purposes.
Publications SEE BELOW

Please visit http://ncbi.nlm.nih.gov and enter the PMID number to retrieve reference(s) cited in patient report.

Please visit http://clinicaltrials.gov and enter NCT number to retrieve further information about trials cited in this report.

For more information about the Watson test please visit
https://www.questdiagnostics.com/home/physicians/testing-services/by-test-name
ibm-watson--genomics-from-quest-diagnostics/watson-genomics-for-physicians

---

Performing Laboratory Information:

EZ Quest Diagnostics Nichols Institute 33608 Ortega Hwy San Juan Capistrano CA 92675
Laboratory Director: I Maramica MD, PhD, MBA

Quest Diagnostics | With Watson

Report Status: Final

SAKHI, GHULAM

Patient Information	Specimen Information	Client Information
SAKHI, GHULAM **DOB: 10/05/1967 AGE: 50** Gender: M Phone: NG Patient ID: 83173412	Specimen: 83173412 Requisition: Lab Ref #: 2270148 Collected: 05/11/2018 / 00:00 PDT Received: 05/18/2018 / 03:53 PDT Reported: 06/06/2018 / 18:45 PDT	Client #: 55001 A VORA/A VERMA QUEST DIAGNOSTICS INDIA PVT LT Attn: A17, INFO CITY, GURGAON SECTOR 34 HARYANA INDIA 122001

IBM Watson™ Genomics from Quest Diagnostics®

OVERALL INTERPRETATION **Lab: EZ**

Diagnosis: Colorectal Adenocarcinoma

The following clinically significant alterations were found in this specimen:

1- KRAS G12C 2- BRAF L597Q 3- AKT1 E17K

** no other clinically significant alteration was found in the genes tested.

KRAS SUMMARY

The KRAS G12C mutation is known to be oncogenic. Resistance to Cetuximab is included in the NCCN-Compendium for this indication. Resistance to Panitumumab is also included in the NCCN-Compendium for this indication. There is clinical evidence that the KRAS G12C mutation confers sensitivity to Cobimetinib, Selumetinib, Binimetinib. Mutations in KRAS are associated with poor prognosis in CRC. Patients with tumors positive for mutations affecting codons 12 and 13 of KRAS have shorter OS compared to patients with wild type tumors (median OS 30.2 months for KRAS mutant cases vs 42.7 months for KRAS wild type) (PMID: 24806288) and impaired responses to anti-EGFR inhibitors (Cetuximab and Panitumumab)(PMID: 20619739, 18316791, 19339720, 23182985).

BRAF SUMMARY

The BRAF L597Q mutation is known to be oncogenic. There are no FDA-approved or NCCN-compendium listed treatments specifically for patients with Colorectal Carcinoma harboring the BRAF L597Q mutation. There is clinical evidence that the BRAF L597Q mutation confers sensitivity to Cobimetinib, Trametinib.

AKT1 SUMMARY

The AKT1 E17K mutation is known to be oncogenic. There are no FDA-approved or NCCN-compendium listed treatments specifically for patients with Colorectal Carcinoma harboring any pathogenic AKT1 mutation. There is clinical evidence that pathogenic AKT1 mutations confer sensitivity to AZD5363, ARQ 092.

MSI SUMMARY

The tumor/normal pair samples were examined for microsatellite instability using 5 mononucleotide markers (Bat25, Bat26, NR21, NR24 and NR27). Results indicate microsatellite stable pattern (MSS). There are no FDA-approved or NCCN-compendium listed treatments specifically for patients with Colorectal Carcinoma harboring the MSI Stable. Pre-clinical and clinical evidence are not available for this indication.

Tumor mutation burden (TMB) for this case is 18 non-synonymous variants per MB coding sequence. In contrast, MSS tumors which in general carry a low TMB are expected to have 12 non-synonymous variants per MB coding sequence (95% Confidence Interval 12-18) and MSI-High tumors which in general carry a high TMB are expected to have 48 non-synonymous variants per MB coding sequence (95% Confidence Interval 42-66). Published literature supports that higher TMB in tumors can help predict response to immunotherapies in certain cancer indications.

CLINICIAN PROVIDED INFORMATION **Lab: EZ**

Diagnosis:	METASTATIC LOW-GRADE ADENOCA OF COLON PRIMARY				
Tumor-Tissue Type:	ADENOCARCINOMA	**Specimen Source**	LUNG		
Block/Specimen ID	2256/17/C	**Paired Blood Submitted:**	YES	**Report Germline Consent:**	NO

Quest Diagnostics | With Watson

Report Status: Final

SAKHI, GHULAM

Patient Information	Specimen Information	Client Information
SAKHI, GHULAM **DOB: 10/05/1967 AGE: 50** Gender: M Patient ID: 83173412	Specimen: 83173412 Collected: 05/11/2018 / 00:00 PDT Received: 05/18/2018 / 03:53 PDT Reported: 06/06/2018 / 18:45 PDT	Client #: 55001 A VORA/A VERMA

RESULT SUMMARY **Lab: EZ**

Gene Name	Mutation	Alteration Type	Mutation Frequency	Tumor Type Drugs	Non-Tumor Type Drugs	Clinical Trials
KRAS	G12C	MISSENSE MUTATION	9 % Frequency	NO	YES	YES
BRAF	L597Q	MISSENSE MUTATION	8 % Frequency	NO	YES	YES
AKT1	E17K	MISSENSE MUTATION	20 % Frequency	NO	NO	YES

ADDITIONAL MUTATIONS **Lab: EZ**

None

INTERACTING MUTATIONS **Lab: EZ**

None

KRAS G12C CLINICAL IMPLICATIONS **Lab: EZ**

Gene Function	**BACKGROUND** KRAS is a GDP/GTP-binding protein with intrinsic GTPase activity that acts as intracellular signal transducer. KRAS is usually tethered to cell membranes and an early molecule in many signal transduction pathways. The protein alternates between an inactive form bound to GDP and an active form bound to GTP. It is activated by receptor tyrosine kinases and a guanine nucleotide-exchange factor (GEF), which then stimulates the RAF-MEK-MAPK pathway. KRAS is inactivated by a GTPase-activating protein (GAP). KRAS is one of the most frequently mutated genes in human cancer. The most common oncogenic Ras mutation found in tumors is an amino acid change from Gly12 to Asp12 (G12D or another amino acid). This mutation prevents the inactivation of the RAS protein. The transforming capacity of KRAS mutants is associated with different degrees of aggressiveness depending on the location of the variant within the protein and the amino acid substation. Codon 12 mutations are more resistant to cell death and have more oncogenic and transforming potential than codon 13 variants (PMID: 11118062). Furthermore, different variants can signal through different downstream effector pathways (PMID: 16679305). Aside from mutations within the highly conserved P-loop (amino acids 10 to 17), switch 1 and switch 2 mutations can also increase the basal activity of KRAS.
Mutation Effect on Gene	**MUTATION EFFECT** gain-of-function mutation. The KRAS G12C mutation is known to be oncogenic. The KRAS G12C mutation renders the enzyme less capable of hydrolyzing GTP, leading to constitutive enzymatic activity. Expression of this mutation in cell lines leads to increased activation of signaling downstream of RAS, including the MAPK and PI3K/AKT pathways (PMID: 25705018, 26841430). Breast cancer cell lines expressing this mutation had increased proliferation and colony growth (PMID: 25705018). A conditional mouse model expressing this alteration developed lung hyperplasia (PMID: 16051643). Several targeted therapies have been developed that specifically target this mutant allele (PMID: 26841430, 24256730). Resistance to Cetuximab is included in the NCCN-Compendium for this indication. Resistance to Panitumumab is also

Quest Diagnostics | With Watson

Report Status: Final

SAKHI, GHULAM

Patient Information	Specimen Information	Client Information
SAKHI, GHULAM **DOB: 10/05/1967 AGE: 50** Gender: M Patient ID: 83173412	Specimen: 83173412 Collected: 05/11/2018 / 00:00 PDT Received: 05/18/2018 / 03:53 PDT Reported: 06/06/2018 / 18:45 PDT	Client #: 55001 A VORA/A VERMA

KRAS G12C CLINICAL IMPLICATIONS **Lab: EZ**

	included in the NCCN-Compendium for this indication. There is clinical evidence that the KRAS G12C mutation confers sensitivity to Cobimetinib, Selumetinib, Binimetinib. Mutations in KRAS are associated with poor prognosis in CRC. Patients with tumors positive for mutations affecting codons 12 and 13 of KRAS have shorter OS compared to patients with wild type tumors (median OS 30.2 months for KRAS mutant cases vs 42.7 months for KRAS wild type) (PMID: 24806288) and impaired responses to anti-EGFR inhibitors (Cetuximab and Panitumumab)(PMID: 20619739, 18316791, 19339720, 23182985). NCCN GUIDELINES Version: 1.2018. Cancer type: Colorectal Carcinoma. Recommendation category R1: Numerous studies have shown that patients with colorectal cancer positive for KRAS mutations (exons 2, 3 or 4), do not derive benefit from, treatment with Cetuximab or Panitumumab either alone or in combination with other agents (PMID: 19114683, 18316791, 18946061, 17664471, 25115304, 19339720, 18202412, 17998284, 24024839). STANDARD THERAPEUTIC IMPLICATIONS RESISTANCE INFORMATION KRAS is associated with resistance to: **CETUXIMAB** PANITUMUMAB Highest level of evidence: R1 PROGNOSTIC IMPLICATIONS Mutations in KRAS are associated with poor prognosis in CRC. Patients with tumors positive for mutations affecting codons 12 and 13 of KRAS have shorter OS compared to patients with wild type tumors (median OS 30.2 months for KRAS mutant cases vs 42.7 months for KRAS wild type) (PMID: 24806288) and impaired responses to anti-EGFR inhibitors (Cetuximab and Panitumumab)(PMID: 20619739, 18316791, 19339720, 23182985).
FDA Approved Drugs in Tumor Type	None
FDA Approved Drugs in Other Tumor Type	TRAMETINIB Melanoma
Clinical Trials	CLINICAL TRIALS MATCHED FOR VARIANT AND DISEASE NCT02091141, Phase 2 TITLE: My Pathway: An Open Label Phase IIa Study Evaluating Trastuzumab/Pertuzumab, Erlotinib, Vemurafenib, and Vismodegib in Patients Who Have Advanced Solid Tumors With Mutations or Gene Expression Abnormalities Predictive of Response to One of These Agents NCT02465060, Phase 2 TITLE: Molecular Analysis for Therapy Choice (MATCH)

Quest Diagnostics | With Watson

Report Status: Final

SAKHI, GHULAM

Patient Information	Specimen Information	Client Information
SAKHI, GHULAM **DOB: 10/05/1967 AGE: 50** Gender: M Patient ID: 83173412	Specimen: 83173412 Collected: 05/11/2018 / 00:00 PDT Received: 05/18/2018 / 03:53 PDT Reported: 06/06/2018 / 18:45 PDT	Client #: 55001 A VORA/A VERMA

KRAS G12C CLINICAL IMPLICATIONS **Lab: EZ**

NCT03087071, Phase 2 TITLE: A Phase II Enrichment Study of Panitumumab as a Single Agent or in Combination With Trametinib in Cetuximab-Refractory Stage IV Colorectal Cancer Patients

NCT03340558, Phase

2

TITLE: A Pilot Study Investigating the Effect of Atezolizumab Monotherapy and Atezolizumab Plus Cobimetinib on the Tumoral Immunoprofile in Liver Metastases From Colorectal Cancer

NCT03428126, Phase 2 TITLE: Phase II Study of Durvalumab (MEDI4736) (Anti-PD-L1) and Trametinib (MEKi) in MSS Metastatic Colon Cancer

NCT02079740, Phase 1 or 2 TITLE: 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 Mutation-Positive Advanced Solid Tumors

NCT02613650, Phase 1 TITLE: A Phase 1b Trial of a Combination of FOLFIRI With MEK162 in Patients With Advanced KRAS Positive Metastatic Colorectal Cancers

NCT02703571, Phase 1 or 2

TITLE:

A Phase I/II Study of Safety and Efficacy of Ribociclib (LEE011) in Combination With Trametinib (TMT212) in Patients With Metastatic or Advanced Solid Tumors

NCT02857270, Phase 1 TITLE: A Phase 1 Study of an ERK1/2 Inhibitor (LY3214996) Administered Alone or in Combination With Other Agents in Advanced Cancer

NCT02900664, Phase 1 TITLE: Phase Ib, Open-label, Multi-center Study to Characterize the Safety, Tolerability and Pharmacodynamics (PD) of PDR001 in Combination With CJM112, EGF816, Ilaris (Canakinumab) or Mekinist (Trametinib)

NCT02972034, Phase 1 TITLE: A Phase Ib Study to Evaluate the Safety and Tolerability of MK-8353 in Combination With Pembrolizumab in Patients With Advanced Malignancies

NCT03162627, Phase

1

TITLE: Evaluation of the Combination of Selumetinib and Olaparib in Endometrial, Ovarian and Other Solid Tumors With Ras Pathway Alterations, and Ovarian Tumors With PARP Resistance

NCT03317119, Phase 1 TITLE: A Phase I Clinical Trial of Trametinib in Combination With TAS-102 in Patients With Chemotherapy-Resistant RAS-Mutated (PIK3CA/PTEN-Wild-Type) Metastatic Colorectal Cancer

NCT03374254, Phase 1 TITLE: A Phase 1b Multi-cohort Study of the Combination of Pembrolizumab (MK-3475) Plus Binimetinib Alone or the Combination of Pembrolizumab Plus Chemotherapy With or Without Binimetinib in Participants With Metastatic Colorectal Cancer (KEYNOTE-651)

INVESTIGATIONAL

THERAPEUTIC IMPLICATIONS

Quest Diagnostics | With Watson

Report Status: Final

SAKHI, GHULAM

Patient Information	Specimen Information	Client Information
SAKHI, GHULAM **DOB: 10/05/1967 AGE: 50** Gender: M Patient ID: 83173412	Specimen: 83173412 Collected: 05/11/2018 / 00:00 PDT Received: 05/18/2018 / 03:53 PDT Reported: 06/06/2018 / 18:45 PDT	Client #: 55001 A VORA/A VERMA

KRAS G12C CLINICAL IMPLICATIONS **Lab: EZ**

COBIMETINIB

Highest level of evidence:

3A

Cobimetinib has not been evaluated for KRAS-mutant disease. However, early results of combination treatment with the PDL1 inhibitor Atezolizumab showed clinical activity in CRC patients (22 KRAS mutant, 1 KRAS wild-type) with an ORR of 17% (4 PR and 5 SD), and 3 responses ongoing at the time of data cutoff (range, 4.0 to 7.7 mo). Response was not associated with baseline PD-L1 expression (Bendell et al. ASCO 2016, # 3502).

SELUMETINIB

Highest level of evidence: 3A In a phase I study of Selumetinib in KRAS-mutant CRC tumors, 5 out of 14 patients had SD as best response, while 9 patients had PD, demonstrating mild activity for the Drug in this context (PMID: 26666244). An ORR of 4%, median OS of 266 days, and median PFS of 105 days were reported in a phase 2 dose-finding study involving 31 patients with KRAS mutant CRC treated with a combination therapy consisting of Selumetinib and irinotecan. Three patients continued treatment with Selumetinib and irinotecan for over one year (PMID: 25322874).

BINIMETINIB

Highest level of evidence:

3B

Efficacy of Binimetinib in tumors harboring KRAS or BRAF mutations has been tested in a phase 1 trial in patients with advanced solid tumors. Six patients had confirmed oncogenic mutations in KRAS. Two patients had progressive disease, two patients experienced stable disease with mi nor reduction in tumor burden and two remaining patients had partial responses as measured by reduction in tumor burden (PMID: 27071922).

LY3214996

Highest level of evidence: 4 LY3214996 is a highly selective inhibitor of ERK1 and ERK2. Preclinical data have shown that tumor cells with MAPK pathway alterations including BRAF, NRAS or KRAS mutation are sensitivity to LY3214996. In tumor xenograft models, LY3214996 inhibited the PD biomarker p-p90RSK1 and the PD effects correlated with exposure and anti-tumor activity. Oral administration of single-agent LY3214996 significantly inhibited tumor growth in vivo and was well tolerated in BRAF or NRAS mutant Melanoma, BRAF or KRAS mutant CRC, lung and pancreatic cancer xenografts or PDX models (Bhagwat et al. AACR 2017, abstract #4973).

MK-8353

Highest level of evidence: 4 The preclinical data resulting in advancement of this Drug to clinical development have not been published.

TRAMETINIB

Highest level of evidence: 4 Trametinib, an oral selective inhibitor of the MAPK pathway, is FDA-approved for treatment of BRAF-V600E/K mutant metastatic Melanoma (PMID: 23846731, 22663011).Addition of MAPK inhibitors to standard treatment is in evaluation for the treatment of advanced colorectal cancer (PMID: 21690569, 23438367).

LEVELS OF

Quest Diagnostics | With Watson

Report Status: Final

SAKHI, GHULAM

Patient Information	Specimen Information	Client Information
SAKHI, GHULAM **DOB: 10/05/1967 AGE: 50** Gender: M Patient ID: 83173412	Specimen: 83173412 Collected: 05/11/2018 / 00:00 PDT Received: 05/18/2018 / 03:53 PDT Reported: 06/06/2018 / 18:45 PDT	Client #: 55001 A VORA/A VERMA

KRAS G12C CLINICAL IMPLICATIONS **Lab: EZ**

	EVIDENCE Level 1: FDA-approved drug for this cancer type excluding chemotherapeutic drugs and hormone therapies Level 2A: Standard of care biomarker predictive of response to an FDA-approved drug for this indication (including biomarkers recommended as standard of care by the NCCN) Level 2B: Standard of care biomarker predictive of response to an FDA-approved drug for a different indication (including biomarkers recommended as standard of care by the NCCN) Level 3A: Clinical evidence supports the biomarker as being predictive of response to a drug for this indication Level 3B: Clinical evidence supports the biomarker as being predictive of response to a drug for a different indication Level 4: Compelling preclinical evidence supports the biomarker as being predictive of response to a drug Level R1: Standard of care biomarker predictive of resistance to an FDA approved drug for this indication including biomarkers described by the NCCN
Companion Diagnostics	None

BRAF L597Q CLINICAL IMPLICATIONS **Lab: EZ**

Gene Function	**BACKGROUND** BRAF belongs to the RAF family of serine/threonine protein kinases. It is involved in the transduction of mitogenic signals from the cell membrane to the nucleus and plays a role in the postsynaptic responses of hippocampal neurons. BRAF regulates the MAP kinase/ERK signaling pathway, which affects cell division, differentiation, and secretion. BRAF is an oncogene and frequently mutated in cutaneous melanomas, colorectal cancer, thyroid cancers, papillary craniopharyngiomas, lung cancer, and at lower frequency in a wide range of human malignancies.
Mutation Effect on Gene	**MUTATION EFFECT** gain-of-function mutation. The BRAF L597Q mutation is known to be oncogenic. The L597Q variant has been previously associated with melanoma, multiple myeloma, and CRC and CLL (PMID: 21726664, 24434212, 21289333, 24550227). Functional studies have identified this variant as an oncogenic alteration leading to activation of MEK signaling (PMID: 17525723). There are no FDA-approved or NCCN-compendium listed treatments specifically for patients with Colorectal Carcinoma harboring the BRAF L597Q mutation. There is clinical evidence that the BRAF L597Q mutation confers sensitivity to Cobimetinib, Trametinib. **NCCN GUIDELINES** none STANDARD THERAPEUTIC IMPLICATIONS none
FDA Approved Drugs in Tumor Type	None
FDA Approved Drugs in Other Tumor Type	TRAMETINIB Melanoma
Clinical Trials	CLINICAL TRIALS MATCHED FOR VARIANT AND DISEASE

Quest Diagnostics | With Watson

Report Status: Final

SAKHI, GHULAM

Patient Information	Specimen Information	Client Information
SAKHI, GHULAM **DOB: 10/05/1967 AGE: 50** Gender: M Patient ID: 83173412	Specimen: 83173412 Collected: 05/11/2018 / 00:00 PDT Received: 05/18/2018 / 03:53 PDT Reported: 06/06/2018 / 18:45 PDT	Client #: 55001 A VORA/A VERMA

BRAF L597Q CLINICAL IMPLICATIONS **Lab: EZ**

NCT02091141, Phase 2

TITLE:

My Pathway: An Open Label Phase IIa Study Evaluating Trastuzumab/Pertuzumab, Erlotinib, Vemurafenib, and Vismodegib in Patients Who Have Advanced Solid Tumors With Mutations or Gene Expression Abnormalities Predictive of Response to One of These Agents

NCT02465060, Phase 2 TITLE: Molecular Analysis for Therapy Choice (MATCH)

NCT03087071, Phase 2 TITLE: A Phase II Enrichment Study of Panitumumab as a Single Agent or in Combination With Trametinib in Cetuximab-Refractory Stage IV Colorectal Cancer Patients

NCT03340558, Phase

2

TITLE: A Pilot Study Investigating the Effect of Atezolizumab Monotherapy and Atezolizumab Plus Cobimetinib on the Tumoral Immunoprofile in Liver Metastases From Colorectal Cancer

NCT03428126, Phase 2 TITLE: Phase II Study of Durvalumab (MEDI4736) (Anti-PD-L1) and Trametinib (MEKi) in MSS Metastatic Colon Cancer

NCT02079740, Phase 1 or 2 TITLE: 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 Mutation-Positive Advanced Solid Tumors

NCT02428712, Phase 1 or 2

TITLE: A

Phase 1/2a Study to Assess the Safety, Pharmacokinetics, and Pharmacodynamics of PLX8394 in Patients With Advanced, Unresectable Solid Tumors

NCT02613650, Phase 1 TITLE: A Phase 1b Trial of a Combination of FOLFIRI With MEK162 in Patients With Advanced KRAS Positive Metastatic Colorectal Cancers

NCT02703571, Phase 1 or 2 TITLE: A Phase I/II Study of Safety and Efficacy of Ribociclib (LEE011) in Combination With Trametinib (TMT212) in Patients With Metastatic or Advanced Solid Tumors

NCT02857270, Phase 1

TITLE:

A Phase 1 Study of an ERK1/2 Inhibitor (LY3214996) Administered Alone or in Combination With Other Agents in Advanced Cancer

NCT02900664, Phase 1

TITLE:

Phase Ib, Open-label, Multi-center Study to Characterize the Safety, Tolerability and Pharmacodynamics (PD) of PDR001 in Combination With CJM112, EGF816, Ilaris (Canakinumab) or Mekinist (Trametinib)

NCT02972034, Phase

1

Quest Diagnostics | With Watson

Report Status: Final

SAKHI, GHULAM

Patient Information	Specimen Information	Client Information
SAKHI, GHULAM **DOB: 10/05/1967 AGE: 50** Gender: M Patient ID: 83173412	Specimen: 83173412 Collected: 05/11/2018 / 00:00 PDT Received: 05/18/2018 / 03:53 PDT Reported: 06/06/2018 / 18:45 PDT	Client #: 55001 A VORA/A VERMA

BRAF L597Q CLINICAL IMPLICATIONS **Lab: EZ**

TITLE: A Phase Ib Study to Evaluate the Safety and Tolerability of MK-8353 in Combination With Pembrolizumab in Patients With Advanced Malignancies

NCT03162627, Phase 1 TITLE: Evaluation of the Combination of Selumetinib and Olaparib in Endometrial, Ovarian and Other Solid Tumors With Ras Pathway Alterations, and Ovarian Tumors With PARP Resistance

NCT03317119, Phase 1 TITLE: A Phase I Clinical Trial of Trametinib in Combination With TAS-102 in Patients With Chemotherapy-Resistant RAS-Mutated (PIK3CA/PTEN-Wild-Type) Metastatic Colorectal Cancer

NCT03374254, Phase

1

TITLE: A Phase 1b Multi-cohort Study of the Combination of Pembrolizumab (MK-3475) Plus Binimetinib Alone or the Combination of Pembrolizumab Plus Chemotherapy With or Without Binimetinib in Participants With Metastatic Colorectal Cancer (KEYNOTE-651)

INVESTIGATIONAL THERAPEUTIC

IMPLICATIONS

COBIMETINIB

Highest level of evidence: 3B Combination therapy with the BRAF inhibitor Vemurafenib demonstrated significantly improved PFS and OS compared to Vemurafenib monotherapy in metastatic Melanoma (PMID: 27480103, 25265494). Results from the metastatic Melanoma cohort of a phase 1b dose escalation trial of Cobimetinib and Atezolizumab in 20 non-ocular Melanoma patients with metastatic disease, demonstrated an ORR of 45% percent, with 9 PR, a DCR of 75% (CR plus PR plus SD) and median PFS of 12 months (Miller et al. ASCO 2017, abstract #3057).

TRAMETINIB

Highest level of evidence: 3B Trametinib is an orally bioavailable MEK1/2 inhibitor that was FDA-approved in May 2013 for use in patients with BRAF V600E/K-mutant metastatic Melanoma (PMID: 22663011). In a limited cohort study of Trametinib in patients with non-V600E BRAF mutated metastatic Melanoma, 1 patient harboring a BRAF L597Q mutation achieved partial response (6.2 months) upon treatment with Trametinib (PMID: 24933606). In vitro studies of cell lines engineered to express BRAF L597R or L597S mutations demonstrated sensitivity to MEK inhibition as measured by decreased activation of downstream effector proteins upon treatment with Trametinib (PMID: 22798288).

SELUMETINIB

Highest level of evidence: 4 An orally active, small molecule with potential antineoplastic activity. Selumetinib is an ATP-independent inhibitor of mitogen-activated protein kinase kinase (MEK or MAPK/ERK kinase) 1 and 2. MEK 1 and 2 are dual specificity kinases that are essential mediators in the activation of the RAS/RAF/MEK/ERK pathway, are often upregulated in various cancer cells, and are drivers of diverse cellular responses, including proliferation. Inhibition of both MEK1 and 2 by Selumetinib prevents the activation of MEK1/2 dependent effector proteins and transcription factors, thereby leading to an inhibition of cellular proliferation in various cancers.

BINIMETINIB

Quest Diagnostics | With Watson

Report Status: Final

SAKHI, GHULAM

Patient Information	Specimen Information	Client Information
SAKHI, GHULAM **DOB: 10/05/1967 AGE: 50** Gender: M Patient ID: 83173412	Specimen: 83173412 Collected: 05/11/2018 / 00:00 PDT Received: 05/18/2018 / 03:53 PDT Reported: 06/06/2018 / 18:45 PDT	Client #: 55001 A VORA/A VERMA

BRAF L597Q CLINICAL IMPLICATIONS **Lab: EZ**

	Highest level of evidence: 4 Binimetinib is a potent inhibitor of MAPK signaling and clinical activity has been demonstrated in patients with advanced BRAF- as well as NRAS-mutant Melanoma (PMID: 23414587, 28284557). LY3214996 Highest level of evidence: 4 LY3214996 is a highly selective inhibitor of ERK1 and ERK2. Preclinical data have shown that tumor cells with MAPK pathway alterations including BRAF, NRAS or KRAS mutation are sensitivity to LY3214996. In tumor xenograft models, LY3214996 inhibited the PD biomarker p-p90RSK1 and the PD effects correlated with exposure and anti-tumor activity. Oral administration of single-agent LY3214996 significantly inhibited tumor growth in vivo and was well tolerated in BRAF or NRAS mutant Melanoma, BRAF or KRAS mutant CRC, lung and pancreatic cancer xenografts or PDX models (Bhagwat et al. AACR 2017, abstract #4973). PLX8394 Highest level of evidence: 4 Preclinical data have shown that PLX8394 is an inhibitor of MAPK activation resulting in growth inhibition of BRAF mutated cancer cells (PMID: 26466569, 28659148). MK-8353 Highest level of evidence: 4 The preclinical data resulting in advancement of this Drug to clinical development have not been published. LEVELS OF EVIDENCE Level 1: FDA-approved drug for this cancer type excluding chemotherapeutic drugs and hormone therapies Level 2A: Standard of care biomarker predictive of response to an FDA-approved drug for this indication (including biomarkers recommended as standard of care by the NCCN) Level 2B: Standard of care biomarker predictive of response to an FDA-approved drug for a different indication (including biomarkers recommended as standard of care by the NCCN) Level 3A: Clinical evidence supports the biomarker as being predictive of response to a drug for this indication Level 3B: Clinical evidence supports the biomarker as being predictive of response to a drug for a different indication Level 4: Compelling preclinical evidence supports the biomarker as being predictive of response to a drug Level R1: Standard of care biomarker predictive of resistance to an FDA approved drug for this indication including biomarkers described by the NCCN
Companion Diagnostics	None

AKT1 E17K CLINICAL IMPLICATIONS **Lab: EZ**

Gene Function	**BACKGROUND** AKT1 is a serine-threonine protein kinases and one of the most frequently hyperactivated kinases in cancer with roles in metabolism, proliferation, survival, and angiogenesis.

Quest Diagnostics | With Watson

Report Status: Final

SAKHI, GHULAM

Patient Information	Specimen Information	Client Information
SAKHI, GHULAM **DOB: 10/05/1967 AGE: 50** Gender: M Patient ID: 83173412	Specimen: 83173412 Collected: 05/11/2018 / 00:00 PDT Received: 05/18/2018 / 03:53 PDT Reported: 06/06/2018 / 18:45 PDT	Client #: 55001 A VORA/A VERMA

AKT1 E17K CLINICAL IMPLICATIONS **Lab: EZ**

	The protein is activated by insulin and various growth and survival factors and plays a role in insulin stimulation of glucose transport and it is involved in cell cycle regulation. It phosphorylates and inactivates tuberin (TSC2), an inhibitor of mTOR within the mTOR-raptor complex. Several substitutions in the Pleckstrin domain have been reported to result in PI3K-independent activation of AKT1 (PMID: 23348505, 19802009), while others did not exceed activity of the wild type protein (PMID: 23237847). The E17K substitution in the Pleckstrin domain is the most prevalent alteration of AKT1 in breast cancer leading to PI3K-independent activation of AKT1 and it is considered an early event in pathogenesis (PMID: 23888070).
Mutation Effect on Gene	**MUTATION EFFECT** gain-of-function mutation. The AKT1 E17K mutation is known to be oncogenic. E17K is a highly recurrent mutation and also the most prevalent alteration of AKT1. This variant has been described in several types of cancer but it is most commonly associated with meningioma and ER-positive carcinoma of the breast (PMID: 23334667, 20668451). E17K is located in the N-terminal Pleckstrin homology domain and results in PI3K-independent activation of AKT1 through pathological localization of AKT1 to the plasma membrane. Functionally, it has been shown to induce cellular transformation and leukemogenesis in mice, in agreement with a crucial role in cancer development (PMID: 17611497). There are no FDA-approved or NCCN-compendium listed treatments specifically for patients with Colorectal Carcinoma harboring any pathogenic AKT1 mutation. There is clinical evidence that pathogenic AKT1 mutations confer sensitivity to AZD5363, ARQ 092. NCCN GUIDELINES none **STANDARD THERAPEUTIC IMPLICATIONS** none
FDA Approved Drugs in Tumor Type	None
FDA Approved Drugs in Other Tumor Type	None
Clinical Trials	CLINICAL TRIALS MATCHED FOR VARIANT AND DISEASE NCT02465060, Phase 2 TITLE: Molecular Analysis for Therapy Choice (MATCH) NCT02576444, Phase 2 TITLE: A Phase II Study of the PARP Inhibitor Olaparib (AZD2281) Alone and in Combination With AZD1775, AZD5363, or AZD2014 in Advanced Solid Tumors NCT01226316, Phase 1 TITLE: A Phase I, Open-Label, Multicentre Study to Assess the Safety, Tolerability, Pharmacokinetics and Preliminary Anti-tumour Activity of Ascending Doses of AZD5363 Under Adaptable Dosing Schedules in Patients With Advanced Solid Malignancies.

Quest Diagnostics | With Watson

Report Status: Final

SAKHI, GHULAM

Patient Information	Specimen Information	Client Information
SAKHI, GHULAM **DOB: 10/05/1967 AGE: 50** Gender: M Patient ID: 83173412	Specimen: 83173412 Collected: 05/11/2018 / 00:00 PDT Received: 05/18/2018 / 03:53 PDT Reported: 06/06/2018 / 18:45 PDT	Client #: 55001 A VORA/A VERMA

AKT1 E17K CLINICAL IMPLICATIONS **Lab: EZ**

NCT02476955, Phase

1

TITLE: An Open-label Phase 1b Study of ARQ 092 in Combination With Carboplatin Plus Paclitaxel in Subjects With Selected Solid Tumors

NCT02761694, Phase 1 TITLE: A Phase 1 Dose Escalation Study of ARQ 751 in Adult Subjects With Advanced Solid Tumors With AKT1, 2, 3 Genetic Alterations, Activating PI3K Mutations or PTEN-

INVESTIGATIONAL THERAPEUTIC

IMPLICATIONS

AKT1 can be targeted therapeutically either by drugs that inhibit AKT itself or important downstream effectors such as mTOR. Sirolimus, temsirolimus, everolimus, ridaforolimus, deforolimus, AP23573, MK8669, AZD2014 and MLN0128 are inhibitors of mTOR, which is downstream of AKT1 in the P13K/AKT/mTOR signaling pathway (PMID: 22037041, 24333502). Also known as rapalogues, these drugs primarily inhibit downstream S6K activity with less of an effect on 4EBP/EIF4E (PMID: 22037041). Inhibiting mTOR activity downstream of AKT has no effect on mTOR independent functions of AKT, such as inhibition of FOXO transcription factors (PMID: 17604717). After extensive preclinical and clinical investigations, it is generally accepted that single-agent treatment with rapalogues will be an ineffective therapeutic strategy for most cancers due to incomplete inhibition of mTOR activity, as well release of feedback inhibition that leads to heightened upstream signaling via receptor tyrosine kinases (RTK), PI3K, and AKT (PMID: 16452206). These agents are now being tested in a wide variety of combination strategies (PMID: 22037041, 25533673, 24481312).

ARQ 092

Highest level of evidence: 3B ARQ 092 has been shown to inhibit the proliferation of PI3KCA, PIK3R1 or AKT mutant cell lines and xenograft models in preclinical studies. In addition, ARQ092 has demonstrated anti-tumor activity in a phase Ib study in patients with ovarian carcinoma. Two patients with mutations in AKT achieved completed responses (Lakhani et. Al. ASCO 2017 Abstract #2524).

AZD5363

Highest level of evidence: 3B AZD5363 is an orally available, ATP-competitive pan-AKT inhibitor that targets the PI3K/AKT/mTOR signaling pathway (PMID: 23394218). In two Phase I studies, AZD5363 treatment induced target lesion regression in 20 of 29 evaluable patients (69%) with solid tumors, including one RECIST partial responses (PR) in a patient with endometrioid ovarian cancer (Hyman, D. Et al. AACR-NCI-EORTC International Conference on Molecular Targets and Cancer Therapeutics, Abstract B109, 2015). In this study, decreased AKT1 E17K ctDNA was correlated with tumor response (Abstract: Hyman et al. Abstract# B109, AACR-NCI-EORTC 2015. http://mct.aacrjournals.org/content/14/12-Supplement-2/B109). Another Phase I trial of AZD5363 in Japan showed partial response in 2 of 41 patients, one of these patients with AKT1 E17K-mutated metastatic ovarian cancer exhibited significant shrinkage in her lung metastasis. Notably the patient maintained a stable PR for more than two years (PMID: 26351323). Preclinical studies in vitro have shown that AZD5363 inhibits tumor growth and reduces phosphorylation of PRAS40 and S6 (AKT1 substrates) in breast cancer explants harboring the AKT1 E17K mutation (Davies, B. Et al. Cancer Res. 74 Abstract 5553, 2014).

Quest Diagnostics | With Watson

Report Status: Final

SAKHI, GHULAM

Patient Information	Specimen Information	Client Information
SAKHI, GHULAM **DOB: 10/05/1967 AGE: 50** Gender: M Patient ID: 83173412	Specimen: 83173412 Collected: 05/11/2018 / 00:00 PDT Received: 05/18/2018 / 03:53 PDT Reported: 06/06/2018 / 18:45 PDT	Client #: 55001 A VORA/A VERMA

AKT1 E17K CLINICAL IMPLICATIONS **Lab: EZ**

	ARQ751 Highest level of evidence: 4 Preclinical studies have shown that ARQ 751 inhibits proliferation across multiple tumor types with highest potency in leukemia, breast, endometrial, and colorectal cancer cell lines. Inhibition was more prevalent in cancer cell lines containing PIK3CA/PIK3R1 mutations as well as the AKT1 E17K mutation compared to those with wt-PIK3CA/PIK3R1 or PTEN mutations (PMID: 26469692). LEVELS OF EVIDENCE Level 1: FDA-approved drug for this cancer type excluding chemotherapeutic drugs and hormone therapies Level 2A: Standard of care biomarker predictive of response to an FDA-approved drug for this indication (including biomarkers recommended as standard of care by the NCCN) Level 2B: Standard of care biomarker predictive of response to an FDA-approved drug for a different indication (including biomarkers recommended as standard of care by the NCCN) Level 3A: Clinical evidence supports the biomarker as being predictive of response to a drug for this indication Level 3B: Clinical evidence supports the biomarker as being predictive of response to a drug for a different indication Level 4: Compelling preclinical evidence supports the biomarker as being predictive of response to a drug Level R1: Standard of care biomarker predictive of resistance to an FDA approved drug for this indication including biomarkers described by the NCCN
Companion Diagnostics	None

PUBLICATIONS **Lab: EZ**

Please visit http://ncbi.nlm.nih.gov and enter the PMID number to retrieve reference(s) cited in patient report.

Please visit http://clinicaltrials.gov and enter NCT number to retrieve further information about trials cited in this report.

For more information about the Watson test please visit https://www.questdiagnostics.com/home/physicians/testing-services/by-test-name ibm-watson--genomics-from-quest-diagnostics/watson-genomics-for-physicians

ADDITIONAL INFORMATION **Lab: EZ**

This Watson Genomics from Quest Core test is designed to detect mutations present in any FFPE tissue from solid tumors. The test is designed to detect single nucleotide variants (SNVs) and small insertions/deletions (In/Dels) as well as whole gene copy number alterations and translocations in a select group of genes. Results of the test should be correlated with clinical findings. The genes (listed below) were selected based on actionability of mutations identified in those genes using currently available evidence from national and international guidelines and literature. Actionability is defined as information a clinician might find useful to aid in diagnosis, prognosis and/or treatment strategy for a patient. Results of the test should be correlated with clinical findings. Clinical trial information provided in this report is solely for informational purposes for the physician and does not constitute any endorsement or a recommendation for enrollment of patients in any trial by Quest Diagnostics, its affiliates, or its employees. Only mutations present in the interrogated regions of the genes are reported. The test does not identify mutations present outside the interrogated regions. Normal population variations, promoter and intronic variations (with the exception of the TERT promoter and splice site variants) as well as synonymous single nucleotide polymorphisms (SNPs) are not included in this report. This test has an analytical sensitivity for detecting 5% SNVs and 5% INDEL mutated sequences in a background of non-mutated DNA sequence; two-fold or higher gene amplifications; and homozygous gene deletions. Insertion/Deletion detection is limited to 10 base insertion and 15 base deletion. Translocation detection is limited to a set of specified acceptor genes at 20% analytical sensitivity. The performance characteristics of the test can change based on adequacy of tumor tissue or pre-analytical variables. (This test was validated on FFPE tissue and whole blood). The genes tested include: AKT1, AKT2, ALK, AR, AURKA, BAP1, BRAF, BRCA1, BRCA2, CDKN2A, CDKN2B, CTNNB1, DDR2, EGFR, EP300, ERBB2, ERBB3, ERBB4, ESR1, FGFR1, FGFR2, FGFR3, FGFR4, FLT3, HRAS, IDH1, JAK2, KDR, KIT, KRAS, MAP2K1, MET, MTOR, MYC, MYCN, NRAS, NTRK1, PDGFRA, PDGFRB, PIK3CA, PTCH1, PTEN, RET, ROS1, TERT, TMPRSS2, TP53, TSC1, VHL. The genes tested for translocations include ALK, BRAF, EGFR, FGFR2, FGFR3, NTRK1, RET, ROS1, and TMPRSS2.

Microsatellite instability and/or hypermutated phenotype can be reported if identified. This test was not designed for comprehensive germline mutation analysis or for circulating tumor DNA mutation analysis. When patient consent is provided, and where warranted, limited information is included about whether an alteration detected in the BRCA1, BRCA2, CDKN2A, PTEN, RET, TP53 or VHL genes in the tissue is of germline origin, but this information should be confirmed with specialized germline testing in consultation with a clinician and genetic counseling, if appropriate. Genetic counseling is available at 1.866.GENE.INFO (1.866.436.3463). The Watson Genomics from Quest Diagnostics name and logo are registered trademarks owned by IBM, and used by Quest under license. IBM makes available to Quest certain information to assist Quest in providing this service. This report provided by Quest, is the sole responsibility of Quest, and no relationship is created between the patient or referring physician/institution and IBM or its employees.

For additional information, please refer to http://education.QuestDiagnostics.com/faq/FAQ155 (This link is being provided for informational/educational purposes only.)

This test was developed and its analytical performance characteristics have been determined by Quest Diagnostics Nichols Institute, San Juan Capistrano. It has not been cleared or approved by FDA. This assay has been validated pursuant to the CLIA regulations and is used for clinical purposes.

Quest Diagnostics | With Watson

Report Status: Final

SAKHI, GHULAM

Patient Information	Specimen Information	Client Information
SAKHI, GHULAM **DOB: 10/05/1967 AGE: 50** Gender: M Patient ID: 83173412	Specimen: 83173412 Collected: 05/11/2018 / 00:00 PDT Received: 05/18/2018 / 03:53 PDT Reported: 06/06/2018 / 18:45 PDT	Client #: 55001 A VORA/A VERMA

GENE REGIONS PASSING QC **Lab: EZ**

In this specimen, 896 of 900 regions (>99%) passed our minimal acceptability QC criteria for reporting results, including relevant regions for this test. The coverage of 4 of 900 regions (<1%) was not optimal and the risk of a false-negative result at those regions cannot be ruled out. Details can be provided upon request.

This data was reviewed and interpreted by Anatole Ghazalpour, PhD, FACMG

PERFORMING SITE:

EZ QUEST DIAGNOSTICS/NICHOLS SJC, 33608 ORTEGA HWY, SAN JUAN CAPISTRANO, CA 92675-2042 Laboratory Director: IRINA MARAMICA, MD PHD, CLIA: 05D063352

This is supplemental to your standard report.