Keshav Sarda MOLECULAR QUEST HEA LTD PLAT NO 28 29 SECTOR GURGAON Gurgaon Haryana		DOB: 24/04/1953 Gender: M PID: QD2205525 Physician:DR.SANT(Age: 65Y OSH		t Healthcare Pvt. Ltd. ic City,Sec-18,Udyog 9342
Order#	Collected Date/Time		Reported Da	Reported Date/Time Status	
2270147	11/	05/2018	15/06/2018	15/06/2018 08:12 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.			

end of report for Keshav Sarda, Order No #2270147, Acc No # 180546852

Sansel ma

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

Date and Time of Order Received in the Lab: 15/05/2018 02:09 PM

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

Autolims Version 3.02 On 21/06/2018

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	PATIENT INFORMATION	REPORT STATUS Final
QUEST DIAGNOSTICS INCORPORATED SPECIMEN INFORMATION SPECIMEN: 83173413 REQUISITION: 550010033418 LAB REF NO: COLLECTED: 05/11/2018 00:00 RECEIVED: 05/24/2018 01:05	SARDA,KESHAV DOB: 04/24/1953 Age: 65 SEX: M ID: 2270147	ORDERING PHYSICIAN A VORA/A VERMA CLIENT INFORMATION 55001 QUEST DIAGNOSTICS INDIA PVT LTD A17, INFO CITY, GURGAON SECTOR 34 HARYANA INDIA 122001,
RECEIVED: 05/24/2018 01:05 REPORTED: 06/14/2018 22:33		
Test Name	In Range Out of Range	Reference Range Lab
Tumor Tissue Type: Block ID: Diagnosis: Source Paired Blood Submitted Report Germline Consent Overall Interpretation Diagnosis: Colorectal Adenocarcin The following clinically signific		
1- KRAS wildtype 2- NRAS wildtype 3- TP53 R175H KRAS and NRAS SUMMARY		
Both KRAS and NRAS SOLVARI Both KRAS and NRAS are wildtype (stage IV colorectal cancer influe antibody therapies cetuximab and for the treatment of KRAS wildtyp chemotherapy or alone following p	nces patient responses to the panitumumab. These drugs are F e colorectal tumors together w	anti-EGFR DA-approved ith
TP53 SUMMARY The TP53 R175H mutation is known or NCCN-compendium listed treatme Colorectal Carcinoma harboring a evidence that the patogenic TP53 Transferrin Receptor-Targeted Lip	nts specifically for patients pathogenic TP53 mutation. Ther mutation confers sensitivity t	with e is clinical
MSI SUMMARY The tumor/normal pair samples we using 5 mononucleotide markers (B indicate microsatellite stable pa NCCN-compendium listed treatments Carcinoma harboring the MSI Stabl are not available for this indica	at25, Bat26, NR21, NR24 and NR ttern (MSS). There are no FDA- specifically for patients wit e tumor. Pre-clinical and clin	27). Results approved or h Colorectal
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	PATIENT INFORMATION	REPORT STATUS Final	
CUEST DIAGNOSTICS INCORPORATED COLLECTED: 05/11/2018 00:00 REPORTED: 06/14/2018 22:33	SARDA, KESHAV DOB: 04/24/1953 Age: 65 SEX: M ID: 2270147	ORDERING PHYSICIAN A VORA/A VERMA	
Test Name	In Range Out of Range	Reference Range	Lab
coding sequence. In contrast, expected to have 12 non-synony Confidence Interval 12-18) and TMB are expected to have 48 no (95% Confidence Interval 42-66		a low TMB are nce (95% carry a high ng sequence that higher	
	WD 3 G		
Mutation #1	KRAS SEE BELOW		
Alteration Type #1	wildtype SEE BELOW		
Mutation Frequency #1	WILDTYPE SEE BELOW	% Frequency	
Tumor Type Drugs #1 Non-Tumor Type Drugs #1 Clinical Trials #1	0 YES NO NO		
Watson Genomics,Core 2 Gene Name #2	SEE BELOW		ΕZ
Mutation #2	NRAS SEE BELOW		
Alteration Type #2	wildtype SEE BELOW		
Mutation Frequency #2	WILDTYPE SEE BELOW	% Frequency	
Tumor Type Drugs #2 Non-Tumor Type Drugs #2 Clinical Trials #2	0 YES NO NO		
Watson Genomics,Core 3 Gene Name #3	SEE BELOW		EZ
Mutation #3	TP53 SEE BELOW		
Alteration Type #3	R175H SEE BELOW		
	MISSENSE MUTATION		
GARDA,KESHAV - 83173413		Page 2 - Continued on Pa	ige 3

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	PATIENT INFORMATION		REPORT STATUS Final	
QUEST DIAGNOSTICS INCORPORATED	SARDA, KESHAV DOB: 04/24/1953 SEX: M	Age: 65	ORDERING PHYSICIAN A VORA/A VERMA	
REPORTED: 06/14/2018 22:33	ID: 2270147			
Test Name	In Range Out o	f Range	Reference Range	Lab
Watson Genomics,Core 3 (Continued) Mutation Frequency #3	SEE BELOW		% Frequency	
Tumor Type Drugs #3 Non-Tumor Type Drugs #3 Clinical Trials #3	l0 NO NO YES			
Interacting Mutations Interacting Mutations	SEE BELOW			EZ
Additional Mutations	None SEE BELOW			
	None			
Clinical Impact 1 Gene Function #1	SEE BELOW			EZ
BACKGROUND				
KRAS is a GDP/GTP-binding prote that acts as intracellular sigr membranes and an early molecula protein alternates between an i bound to GTP. It is activated k nucleotide-exchange factor (GEI pathway. KRAS is inactivated by of the most frequently mutated oncogenic Ras mutation found ir Asp12 (G12D or another amino ac the RAS protein. The transformi different degrees of aggressive within the protein and the amir resistant to cell death and hav than codon 13 variants (PMID: 1 signal through different downst from mutations within the highl switch 1 and switch 2 mutations KRAS.	al transducer. KRAS in many signal tra nactive form bound y receptor tyrosine), which then stimu a GTPase-activation genes in human cance tumors is an amino id). This mutation ng capacity of KRAS ness depending on t o acid substation. e more oncogenic an 1118062). Furthermor ream effector pathw y conserved P-loop	is usually nsduction p to GDP and . kinases an lates the R g protein (" er. The mos acid changy prevents th mutants is he location Codon 12 mu d transform re, differe: ays (PMID: (amino acid	tethered to cell athways. The an active form d a guanine AF-MEK-MAPK GAP). KRAS is one t common e from Gly12 to e inactivation of associated with of the variant tations are more ing potential nt variants can 16679305). Aside s 10 to 17),	

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REPORTED: 06/14/2018 22	DOB: 04/24/1953 DOB: 04/24/1953 SEX: M ID: 2270147		REPORT STATUS Final ORDERING PHYSICIAN A VORA/A VERMA	
Test Name Clinical Impact 1 (Continu	5	of Range	Reference Range	Lab
Mutation Effect on Gene				
	MUTATION EFFECT No clinically significant mut	ation was fou	und in KRAS	
	NCCN GUIDELINES			
	Patients with any known KRAS NRAS mutation should not be t panitumumab.			
	STANDARD THERAPEUTIC IMPLICAT	TIONS		
	The absence of a mutation in the RAS genes is clinical expands approved treatments available to treat IV colorectal cancer influences patient rest therapies cetuximab and panitumumab. The treatment of KRAS wildtype colorectal tumo alone following progression through standard of the ligands epiregulin and amphiregulin of patients, and retrospective data analysis a epiregulin and amphiregulin is associated we associated with no benefit (PMID: 19738)	this tumor. sponses to the sese drugs are ors together w chemotherapy. may allow for suggest that h	RAS status in stage e anti-EGFR antibody e FDA-approved for the with chemotherapy or . Expression levels further selection of high expression of and low expression is	

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			PATIENT INFO: SARDA, KE			REPORT STATUS Final	
QUEST DIAGNOST	TICS INCORPORATED					ORDERING PHYSICIAN	
			DOB: 04/24 SEX: M	1/1953	Age: 65	A VORA/A VERMA	
COLLECTED: REPORTED:	05/11/2018 06/14/2018	00:00 22:33	ID: 227014	17			
Test Name			In Range	Out of	Range	Reference Range	Lab
	Impact 1 (Con mor Drugs #1	tinued)	SEE BELOW				
enroll either intrav progre fluord patier There to par differ the BS diseas EGFR e betwee EGFR e which (BSC) mCRC. 6.9 r panitu CETUXI The ap patier	Led 463 patient c best support venously, ever ession followi opyrimidine, i hts receiving were 19 parti- hitumumab, the rence in OS be SC alone arm c es progression expression in en either the expression (PM assessed the vs BSC on OS In wild-type months for BSC imumab (PMID: IMAB, Colorecta oproval was ba ts enrolled i	l Carcinoma sed on retrospe n the CRYSTAL t	tic CRC. Pat alone or BSC ll patients chemotherapy oxaliplatin. 60 days for %) among the e duration w tudy arms. A receive pani nvestigator. lls with no ells express Efficacy was t of panitum with chemo- n OS for pan RAS mutatic	ients we plus pa vere req regimer The mea patient 231 pat vas 17 we proxima tumumab Most pa evidence sing EGFF s also sh umab plu refracto itumumak ons did r	ere randomly anitumumab, quired to have as containing an PFS was 9 is receiving ients randd eeks. There ately 75% of after a det atients" ture of a corre for the int own in a pl as best supp ory wild-typ o plus BSC w not benefit	y assigned to 6 mg/kg ave disease ng a 96 days for g BSC alone. omly assigned was no 6 patients in termination of mors exhibited elation tensity of nase 3 trial, portive care pe KRAS exon 2 was 10.0 vs from s from dies, CA225025	
and EM cetux: OS, PI benef: was ar chemot 89% c patien wild t median FOLFII overal 8.9 m an upo months months muth 27722 OPUS, tumors plus f treate BSC ar was 3.	AR 62 202-047 imab to chemot <i>FS</i> , and ORR in it, or even por open-label t cherapy for me of patients (1 hts had mutant cype group of <i>PFS</i> for pati <i>RI</i> was 9.5 mon <i>D</i> population, months compare lated analysis for patients for patients tumors, no i 2750). Retrosp by KRAS mutat <i>CA225025</i> wa best supportive ad mCRC. The m d BSC groups 8 and 1.9 mon	(OPUS), according herapy or best a patients with a tential harm, in trial in patient dastatic disease 079) and 676 pa tumors. Retross 23.5 months com- ents with wild ths compared to PFS in patient d to 8.1 months with an additi- treated with con- treated with con-	ng to KRAS m supportive c KRAS wild-ty n patients w s with mCRC e. KRAS muta tients had K pective anal pared to 19. type tumors 8.1 months. s treated wi in patients onal 162 eve etuximab plu OLFIRI alone noted by the of two supp orted the ef randomized th BSC alone 6 versus 5.0 d type tumor ximab plus E	nutation are (BSC ope tumor with KRAS who had tion sta RAS wild sysis sho 5 months treated ORR was threated ORR was treated or was treated or back s FOLFIF a dditio trial the in patis of months S, respenses and the south of th	status. The c) resulted cs, whereas mutant turn not receive atus was avail type turmoo wed a media s for FOLFII with cetuxis 567 vs 398 dimab plus H with FOLFI e median OS RI compared a subgroup v on of cetuxis studies, CA2 of cetuzimal hat compared in the cetus in the cetus the BSC group	e addition of in improved there was no mors. CRYSTAL ed prior ailable from rs, while 403 an OS for the RI alone. The imab plus &. In the FOLFIRI was IRI alone. In was 19.6 with 18.5 with KRAS imab (PMID: 225025, and o in wild type d cetuximab previously uximab plus ne median PFS aps,	

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	PATIENT INFORMATION SARDA, KESHAV	REPORT STATUS Final	
QUEST DIAGNOSTICS INCORPORATED COLLECTED: 05/11/2018 00:00 REPORTED: 06/14/2018 22:33	DOB: 04/24/1953 Age: 65 SEX: M ID: 2270147	ORDERING PHYSICIAN A VORA/A VERMA	
Test Name	In Range Out of Range	Reference Range	Lab
Clinical Impact 1 (Continued) FDA Tumor Drugs #1 (Continued) cetuximab in combination with FOLF treatment of metastatic CRC. Retro performed on 93% of patients (315/ ORR was 57% in patients treated wi in patients treated with FOLFOX-4. months and median OS was 22.8 vers (N=136/315), no improvements in OS treated with cetuximab plus FOLFOX FOLFOX-4 alone (PMID: 21228335).	spective analysis of KRAS statu 337). In the wild-type subgroup th cetuximab plus FOLFOX-4 comp The median PFS was 8.3 compare us 18.5 months. In the KRAS mut , PFS, or ORR were observed in	ns was (N=179/315), aared to 34% ed with 7.2 .ant subgroup patients	
FDA Non-Tumor Drugs #1	SEE BELOW		
Clinical Trials #1	None SEE BELOW		
Companion Diagnostics #1	None SEE BELOW		
	None		
Clinical Impact 2 Gene Function #2	SEE BELOW		EZ
the active (GTP-bound) ar molecular switch mediatir kinases (RTK) to the nucl cascades. NRAS mutations genes in Melanoma found i 16291983). The most comm and 13. Mutations in NRAS 20736745), AML (PMID: 23	tide binding protein that cycles ad inactive (GDP-bound) form. If ag signals from ligand activates eus through a complex network of are by far the predominant alt. In approximately 15% of all turn non mutation occurs in codon 61 3 are also associated with up to 634996), Multiple Myeloma (PMID of the lung (PMID: 12460918).	t functions as a d receptor tyrosine of downstream signaling eration among RAS ors (PMID: , followed by codon 12 o 6% of CRC (PMID:	

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	PATIENT INFORMATION		REPORT STATUS Final	
QUEST DIAGNOSTICS INCORPORATED COLLECTED: 05/11/2018 00:00 REPORTED: 06/14/2018 22:33	SARDA, KESHAV DOB: 04/24/1953 SEX: M ID: 2270147	Age: 65	ORDERING PHYSICIAN A VORA/A VERMA	
Test Name	In Range Out	of Range	Reference Range	Lab
Clinical Impact 2 (Continued) Mutation Effect on Gene #2	SEE BELOW			
	MUTATION EFFECT No clinically significa	ant mutation	was found in NRAS	
			lon (exon 2 or non-exon 2) or d with either cetuximab or	-
	STANDARD THERAPEUTIC IN CETUXIMAB PANITUMUMAB	IPLICATIONS		
FDA Tumor Drugs #2	SEE BELOW			
enrolled 463 patients with either best supportive care intravenously, every other progression following one o fluoropyrimidine, irinoteca patients receiving panitumu There were 19 partial respo to panitumumab, the median difference in OS between th the BSC alone arm crossed o disease progression by the EGFR expression in 10% of t between either the proporti EGFR expression (PMID: 1747 which assessed the treatmen (BSC) vs BSC on OS in 377 p mCRC. In wild-type RAS mCRC 6.9 months for BSC. Patien panitumumab (PMID: 27736842	(BSC) alone or BSC plus week. All patients were m r more chemotherapy regin n, and oxaliplatin. The m mab and 60 days for patie nses (8%) among the 231 p response duration was 17 e two study arms. Approxi ver to receive panitumuma study investigator. Most umor cells with no evider on of cells expressing EC 5878). Efficacy was also t effect of panitumumab p atients with chemo-refrac , median OS for panitumum ts with RAS mutations dic	panitumumab, required to h mens contain: mean PFS was ents receivin weeks. There that a set of a corre- set of a corre- SFR or the in shown in a p polus best sup ctory wild-ty mab plus BSC	6 6 mg/kg have disease lng a 96 days for ng BSC alone. domly assigned a was no of patients in etermination of umors exhibited relation ntensity of ohase 3 trial, oportive care ype KRAS exon 2 was 10.0 vs	
CETUXIMAB,Colorectal Carcin The approval was based on r patients enrolled in the CR and EMR 62 202-047 (OPUS), cetuximab to chemotherapy o OS, PFS, and ORR in patient benefit, or even potential was an open-label trial in chemotherapy for metastatic	etrospective analyses of YSTAL trial and in two su according to KRAS mutatio r best supportive care (F s with KRAS wild-type tur harm, in patients with KR patients with mCRC who ha	apportive stu on status. Th BSC) resulted mors, whereas RAS mutant tu ad not receive	ndies, CA225025 ne addition of d in improved s there was no umors. CRYSTAL ved prior	
SARDA,KESHAV - 83173413			Page 7 - Continued on Page	8
Autolims Version 3.02 C	Dn 21/06/2018	All Righ	ts Reserved	

		PATIENT INFORMATION SARDA, KESHAV		REPORT STATUS Final
QUEST DIAGNOSTICS INCORPORATED		DOB: 04/24/1953	Aqe: 65	ORDERING PHYSICIAN A VORA/A VERMA
COLLECTED: 05/11/2018 REPORTED: 06/14/2018	00:00 22:33	SEX: M ID: 2270147	Age. 05	

Out of Range

Reference Range

Lab

Test Name

Clinical Impact 2 (Continued)

FDA Tumor Drugs #2 (Continued) 89% of patients (1079) and 676 patients had KRAS wild type tumors, while 403 patients had mutant tumors. Retrospective analysis showed a median OS for the wild type group of 23.5 months compared to 19.5 months for FOLFIRI alone. The median PFS for patients with wild type tumors treated with cetuximab plus FOLFIRI was 9.5 months compared to 8.1 months. ORR was 567 vs 39%. In the overall population, PFS in patients treated with cetuximab plus FOLFIRI was 8.9 months compared to 8.1 months in patients treated with FOLFIRI alone. In an updated analysis with an additional 162 events, the median OS was 19.6 months for patients treated with cetuximab plus FOLFIRI compared with 18.5 months for patients treated with FOLFIRI alone. In the subgroup with KRAS mutant tumors, no improvement was noted by the addition of cetuximab (PMID: 27722750). Retrospective analysis of two supportive studies, CA225025, and OPUS, by KRAS mutation status supported the efficacy of cetuzimab in wild type tumors: CA225025 was an open-label randomized trial that compared cetuximab plus best supportive care (BSC) with BSC alone in patients with previously treated mCRC. The median OS was 8.6 versus 5.0 months in the cetuximab plus BSC and BSC groups in patients wild type tumors, respectively. The median PFS was 3.8 and 1.9 months in the cetuximab plus BSC and the BSC groups, respectively. OPUS was a randomized open-label phase II study that compared cetuximab in combination with FOLFOX-4 to FOLFOX-4 alone as first-line treatment of metastatic CRC. Retrospective analysis of KRAS status was performed on 93% of patients (315/337). In the wild-type subgroup (N=179/315), ORR was 57% in patients treated with cetuximab plus FOLFOX-4 compared to 34% in patients treated with FOLFOX-4. The median PFS was 8.3 compared with 7.2 months and median OS was 22.8 versus 18.5 months. In the KRAS mutant subgroup (N=136/315), no improvements in OS, PFS, or ORR were observed in patients treated with cetuximab plus FOLFOX-4 compared with patients treated with FOLFOX-4 alone (PMID: 21228335).

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In Range

FDA Non-Tumor Drugs #2	SEE BELOW
Clinical Trials #2	None SEE BELOW
Companion Diagnostics #2	None SEE BELOW
	None

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			PATIENT INFO SARDA, KI			REPORT STATUS Final	
QUEST DIAGNOSTICS INC	ORPORATED					ORDERING PHYSICIAN	
COLLECTED: 05/11	L/2018	00:00	DOB: 04/2 SEX: M		Age: 65	A VORA/A VERMA	
REPORTED: 06/14	1/2018	22:33	ID: 22701	47			
Test Name			In Range	Out of	Range	Reference Range	Lab
Clinical Impact Gene Function			SEE BELOW				ΕZ
	that of repain apopto phosph regula funct is the	canscription fa control tumor s c, senescence a osis. Activatio norylation by A ates more than lons such as ce e most frequent are associated	uppressing fund apoptosis, n of TP53 beg TM, ATR, CHK 100 genes that 11 cycle area ly altered ge	unctions , whilst gins thro L and MAP at contro est, DNA ene in hu	such as ce the activa ugh a numb Ks. The TP l critical repair, se man cancer	ber of genes 11 cycle arrest, DNA tion of TP53 often leads to er of mechanisms including 53 tumor suppressor gene tumor suppressing nescence and apoptosis. It is and missense mutations cur in more than 50% of	
Mutation Eff	ect on	Gene #3	SEE BELOW				
The TP53 known to alteratic histidine domain ar the mutar (PMID: 27 TP53 (PMI thermodyr lacks wil apoptosis adenocarc variant h cancer-pr causative has been There are for patie There is sensitive	R175H be onco ons of 7 a substi- nd loss at prote 7589690) CD: 8633 namicall cd-type as R175H frinoma of nas been redispose a no FDA ents wit clinica ty to A	ein has gained in addition t 8021, 9364015, Ly stable and c TP53 function H is most commo of the esophagu h associated wi sing syndrome (hese disorders ated with a her A-approved or N	than 320 entr n 175 results onal activity the ability to o having a da 10519380). It ompletely der and is unable nly associate s and stomach th Li-Fraumer PMID: 9047394 (ClinVar). Th editary cance CCN-compendit arcinoma hark t the patoger	ries in t s in unfo y (PMID: to bind t to bind t to bind t to sign hatured a e to indu ed with C a, as wel hi syndro 4, 185115 he germli er predis predis coring a hic TP53	he COSMIC lding of t 8510927, 1 o and inhi egative ef ificantly t 37C. Fur ce cell cy RC, PDAC, l as HNSCC me (LFS) a 70) and cl ne variant posing syn treatment pathogenic mutation c	database. The he DNA-binding 7401432), while bit P63 and P73 fect on wild type less thermore, it cle arrest or breast carcinoma, . The germline nd hereditary assified as of this mutation drome (ClinVar). s specifically TP53 mutation. onfers	
NCCN GUII none STANDARD none		EUTIC IMPLICATI	ONS				
SARDA,KESHAV - 83	3173413					Page 9 - Continued on Page	10

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	PATIENT INFORMATION		REPORT STATUS Final	
QUEST DIAGNOSTICS INCORPORATED COLLECTED: 05/11/2018 00:00 REPORTED: 06/14/2018 22:33	SARDA, KESHAV DOB: 04/24/1953 SEX: M ID: 2270147		ORDERING PHYSICIAN A VORA/A VERMA	
Test Name	In Range Out	of Range	Reference Range	Lab
Clinical Impact 3 (Continued) FDA Tumor Drugs #3	SEE BELOW			
FDA Non-Tumor Drugs #3	None SEE BELOW			
Clinical Trials #3	None SEE BELOW			
CLINICAL TRIALS MATCHED FOR VARIA NCT02576444, Phase 2	NT AND DISEASE			
TITLE: A Phase II Study of the PARP Inhil Combination With AZD1775, AZD5363 Tumors			and in	
NCT01748825, Phase 1 TITLE: A Phase I Study of Single-a (MK-1775), a Weel Inhibitor, in Pa Tumors		ced Refractor	y Solid	
NCT02095132, Phase 1 or 2 TITLE: A Phase 1/2 Study of AZD17 (MK-1775) in Combination With Ora Young Adults With Relapsed or Ref:	l Irinotecan in Ch		scents, and	
NCT02354547, Phase 1 TITLE: A Phase I Study of SGT-53, Children With Refractory or Recur:		e-p53 Complex	:, in	
NCT02617277, Phase 1 TITLE: A Phase I Study Assessing (Pharmacokinetics of AZD1775 in Con Advanced Solid Tumours	1.	-	ents With	
NCT03313557, Phase 1 TITLE: An Open-label, Non-randomised, Multicentre Study Safety and Tolerability of AZD177 Pharmacology Studies				
INVESTIGATIONAL THERAPEUTIC IMPLI	CATIONS			
P53-directed therapies are currently in early p	phase trials, base	d on preclini	cal studies	
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	2270147			
	PATIENT INFORMATION		REPORT STATUS Final	
QUEST DIAGNOSTICS INCORPORATED	DOB: 04/24/1953 Ag	e: 65	ordering physician A VORA/A VERMA	
COLLECTED: 05/11/2018 00:00 REPORTED: 06/14/2018 22:33	SEX: M ID: 2270147			
Test Name	In Range Out of Ra	inge	Reference Range	Lab
Clinical Impact 3 (Continued) Clinical Trials #3 (Continued) aiming to restore wildtype p53 fur of oncogenic mutant p53 (PMID: 24) research on p53, restoring its fur task and difficult to translate in strategies have been utilized in a cells. These strategies include in restoring wildtype activity to p55 function, however, as of yet, non- translated into advanced clinical 16690321).	651012). Despite the sub action within cancer cel nto clinical benefit. No an attempt to restore p5 mpairing the activity of 3 mutant forms or mimick e of these approaches ha	ostantia lls is a onethele 53 funct p53 re- ting p53 ave succ	l body of challenging ss, multiple ion in cancer gulators, downstream	
TRANSFERRIN RECEPTOR-TARGETED LIP	DSOMAL P53 CDNA			
Highest level of evidence: 3B Clinical activity of this Drug way Phase I clinical trial in 11 pati- effects were observed and seven pu- adenoid cystic carcinoma had his resectable after one treatment cy- 23609015). Combination therapy w advanced cancers. The combination activity in 12 patients evaluable patients achieved PR with tumor r patients had SD with significant a (PMID: 27357628).	ents with refractory dis atients demonstrated SD. status changed from unre cle. The median survival ith docetaxel was tested treatment was well-tole for analysis was observ eductions of -47%, -51%,	sease. M One pa esectabl was 34 in 14 erated a ved. Thr and -7	tient with e to 0 days (PMID: patients with nd clinical ee of these 9%. Two other	
AZD1775				
Highest level of evidence: 3B In a phase II study of AZD1775 plus carboplatin in par refractory or resistant to first- including one patient (5%) with a months and 12.6 months, respective response for more than 31 and 42 m 27998224).	line platinum based ther prolonged CR. Median PF ely, with two patients h	rapy, th 7S and O naving o	e ORR was 43%, S were 5.3	
LEVELS OF EVIDENCE Level 1: FDA-approved drug for th excluding chemotherapeutic drugs a Level 2A: Standard of care biomarker predictive of resp indication (including biomarkers : NCCN) Level 2B: Standard of care biomart FDA-approved drug for a different	and hormone therapies onse to an FDA-approved recommended as standard ker predictive of respon	of care	by the	
SARDA, KESHAV - 83173413	indication (including f	orollar Ke	Page 11 - Continued on	Page 12

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Test Name In Range Out of Range Reference Range Lab Clinical Impact 3 (Continued) Clinical Trials #3 (Continued) Set Standard of care by the NCCN) Set Standard of care by the NCCN) Set Standard of care by the NCCN Set Standard of care by the biomarker as being predictive of response to a drug for this indication Set Standard of care biomarker as being predictive of response to a drug Set Standard of care biomarker predictive of response to a drug Set Standard of care biomarker predictive of response to a drug Set Standard of care biomarker predictive of response to a drug Set Standard of care biomarker predictive of response to a drug Set Standard of care biomarker s described by the NCCN Companion Diagnostics #3 SET SELOW Set SELOW Set	Clinical Impact 3 (Continued) Clinical Trials #3 (Continued) as standard of care by the NCCN) Level 3A: Clinical evidence suppor biomarker as being predictive of r Level 3B: Clinical evidence supports th to a drug for a different indicati Level 4: Compelling preclinical ev supports the biomarker as being pr Level R1: Standard of care biomarker predict for this indication including biom	rts the response to a drug for this ind he biomarker as being predictive ion vidence redictive of response to a drug tive of resistance to an FDA app markers described by the NCCN	ication e of response

None

Gene Regions Passing QC Gene Regions Passing QC

SEE BELOW

In this specimen, 868 of 900 regions (>96%) passed our minimal acceptability QC criteria for reporting results, including relevant regions for this test. The coverage of 32 of 900 regions (<4%) was not optimal and the risk of a false-negative result at those regions cannot be ruled out. Details can be

This data was reviewed and interpreted by Anatole Ghazalpour, PhD, FACMG Always Statement SEE BELOW

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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%

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SARDA, KESHAV - 83173413

			PATIENT INFORMATION		REPORT STATUS Final	
QUEST DIAGNOST	ICS INCORPORATED		DOB: 04/24/1953 Age: 65		ordering physician A VORA/A VERMA	
COLLECTED: REPORTED:	05/11/2018 06/14/2018	00:00 22:33	SEX: M ID: 2270147			

Out of Range

Reference Range

Lab

Test Name

Gene Regions Passing QC (Continued)

Always Statement (Continued)

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.

In Range

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).

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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.

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SARDA, KESHAV - 83173413

QUEST DIAGNOSTICS INCORPORATED COLLECTED: 05/11/2018 00:00 REPORTED: 06/14/2018 22:33	PATIENT INFORMATION SARDA, KESHAV DOB: 04/24/1953 Age: 65 SEX: M ID: 2270147	REPORT STATUS Final ORDERING PHYSICIAN A VORA/A VERMA				
Test Name	In Range Out of Range	Reference Range Lab				
Gene Regions Passing QC (Continued) 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-watsongenomics-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



Report Status: Final SARDA, KESHAV

Lab: EZ

Patient Information	Specimen Information	Client Information
SARDA, KESHAV	Specimen: 83173413 Requisition:	Client #: 55001 A VORA/A VERMA
DOB: 04/24/1953 AGE: 65 Gender: M Phone: NG Patient ID: 83173413	Lab Ref #: 2270147 Collected: 05/11/2018 / 00:00 PDT Received: 05/18/2018 / 03:53 PDT Reported: 06/14/2018 / 22:33 PDT	QUEST DIAGNOSTICS INDIA PVT LT Attn: A17, INFO CITY, GURGAON SECTOR 34 HARYANA INDIA 122001

IBM Watson Genomics from Quest Diagnostics®

OVERALL INTERPRETATION

Diagnosis: Colorectal Adenocarcinoma

The following clinically significant results were found in this specimen:

1- KRAS wildtype 2- NRAS wildtype 3- TP53 R175H

KRAS and NRAS SUMMARY Both KRAS and NRAS are wildtype (not mutated) in this sample. RAS status in stage IV colorectal cancer influences patient responses to the anti-EGFR antibody therapies cetuximab and panitumumab. These drugs are FDA-approved for the treatment of KRAS wildtype colorectal tumors together with chemotherapy or alone following progression through standard chemotherapy. TP53 SUMMARY

The TP53 R175H mutation is known to be oncogenic. There are no FDA-approved or NCCN-compendium listed treatments specifically for patients with Colorectal Carcinoma harboring a pathogenic TP53 mutation. There is clinical evidence that the patogenic TP53 mutation confers sensitivity to AZD1775, Transferrin Receptor-Targeted Liposomal p53 cDNA.

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 tumor. Pre-clinical and clinical evidence are not available for this indication.

Tumor mutation burden (TMB) for this case is 6 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 POORLY DIFFERENTIATED ADENOCA-HINDGUT						
Tumor-Tissue Type:	ADENOCARCINOMA		Speci	men Source	ABDOMINAL	WALL	
Block/Specimen ID	18011098	Paired Blood Subm	itted:	YES	Report Germli	ne Consent:	NO
RESULT SUMMARY							Lab: EZ
Gene Name	Mutation	Alteration Type	Mu	tation Frequency	Tumor Type Drugs	Non-Tumor Type Drugs	Clinical Trials
KRAS	wildtype	WILDTYPE	0 %	Frequency	YES	NO	NO
NRAS	wildtype	WILDTYPE	0 %	Frequency	YES	NO	NO
ТР53	R175H	MISSENSE MUTATION	10	% Frequency	NO	NO	YES
ADDITIONAL MUTATION	IS	·					Lab: EZ
None							

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INTERACTING MUTATIONS

None

KRAS wildtype 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
	No clinically significant mutation was found in KRAS
	NCCN
	GUIDELINES
	Patients with any known KRAS mutation (exon 2 or non-exon 2) or NRAS mutation should not be treated with either cetuximab or panitumumab.
	STANDARD THERAPEUTIC IMPLICATIONS
	The absence of a mutation in the RAS genes is clinically important because it expands approved treatments available to treat this tumor. RAS status in stage IV colorectal cancer influences patient responses to the anti-EGFR antibody therapies cetuximab and panitumumab. These drugs are FDA-approved for the treatment of KRAS wildtype colorectal tumors together with chemotherapy or alone following progression through standard chemotherapy. Expression levels of the ligands epiregulin and amphiregulin may allow for further selection of patients, and retrospective data analysis suggest that high expression of epiregulin and amphiregulin is associated with response and low expression is associated with no benefit (PMID: 19738126, 26867820).
FDA Approved Drugs in Tumor Type	PANITUMUMAB, Colorectal Carcinoma The approval is based on the results of a single, open label study that enrolled 463 patients with metastatic CRC. Patients were randomly assigned to either best supportive care (BSC) alone or BSC plus panitumumab, 6 mg/kg intravenously, every other week. All patients were required to have disease progression following one or more chemotherapy regimens containing a fluoropyrimidine, irinotecan, and oxaliplatin. The mean PFS was 96 days for patients receiving panitumumab and 60 days for patients receiving BSC alone. There were 19 partial responses (8%) among the 231 patients randomly assigned to panitumumab, the median response duration was 17 weeks. There was no difference in OS between the two study arms. Approximately 75% of patients in the BSC

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KRAS wildtype CLINICAL IMPLICATIONS

Lab: EZ

	alone arm crossed over to receive panitumumab after a determination of disease progression by the study investigator. Most patients" tumors exhibited EGFR expression in 10% of tumor cells with no evidence of a correlation between either the proportion of cells expressing EGFR or the intensity of EGFR expression (PMID: 17475878). Efficacy was also shown in a phase 3 trial, which assessed the treatment effect of panitumumab plus best supportive care (BSC) vs BSC on OS in 377 patients with chemo-refractory wild-type KRAS exon 2 mCRC. In wild- type RAS mCRC, median OS for panitumumab plus BSC was 10.0 vs 6.9 months for BSC. Patients with RAS mutations did not benefit from panitumumab (PMID: 27736842).
	CETUXIMAB,Colorectal Carcinoma The approval was based on retrospective analyses of tumor samples from patients enrolled in the CRYSTAL trial and in two supportive studies, CA225025 and EMR 62 202-047 (OPUS), according to KRAS mutation status. The addition of cetuximab to chemotherapy or best supportive care (BSC) resulted in improved OS, PFS, and ORR in patients with KRAS wild-type tumors, whereas there was no benefit, or even potential harm, in patients with KRAS mutant tumors. CRYSTAL was an open-label trial in patients with mCRC who had not received prior chemotherapy for metastatic disease. KRAS mutation status was available from 89% of patients (1079) and 676 patients had KRAS wild type tumors, while 403 patients had mutant tumors. Retrospective analysis showed a median OS for the wild type group of 23.5 months compared to 19.5 months for FOLFIRI was 9.5 months compared to 8.1 months. ORR was 567 vs 39%. In the overall population, PFS in patients treated with FOLFIRI alone. In an updated analysis with an additional 162 events, the median OS was 19.6 months for patients treated with cetuximab plus FOLFIRI compared with 18.5 months for patients treated with FOLFIRI alone. In an updated analysis with an additional 162 events, the median OS was 19.6 months for patients treated with cetuximab plus FOLFIRI compared with 18.5 months for patients treated with FOLFIRI alone. In the subgroup with KRAS mutant tumors, no improvement was noted by the addition of cetuximab [02:7722750]. Retrospective analysis of two supportive studies, CA225025, and OPUS, by KRAS mutation status supported the efficacy of cetuzimab in wild type tumors, respectively. The median PFS was 3.8 and 1.9 months in the cetuximab plus BSC and the BSC groups, respectively. OPUS was a randomized open-label phase II study that compared cetuximab in combination with FOLFOX-4 to FOLFOX-4 alone as first-line treatment of metastatic CRC. Retrospective analysis of KRAS status was performed on 93% of patients (315/337). In the wild-type subgroup (N=179/315
FDA Approved Drugs in Other Tumor Type	None
Clinical Trials	None
Companion Diagnostics	None
NRAS wildtype CLINICAL IMPLICATIONS	Lab: EZ
Gene Function	BACKGROUND
	1

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NRAS wildtype CLINICAL IMPLICATIONS

Lab: EZ

NKAS WILLTYPE CEINICAE IMPEICATIONS	
	NRAS is a guanine-nucleotide binding protein that cycles between the active (GTP-bound) and inactive (GDP-bound) form. It functions as a molecular switch mediating signals from ligand activated receptor tyrosine kinases (RTK) to the nucleus through a complex network of downstream signaling cascades. NRAS mutations are by far the predominant alteration among RAS genes in Melanoma found in approximately 15% of all tumors (PMID: 16291983). The most common mutation occurs in codon 61, followed by codon 12 and 13. Mutations in NRAS are also associated with up to 6% of CRC (PMID: 20736745), AML (PMID: 23634996), Multiple Myeloma (PMID: 24434212) and few
	cases of adenocarcinoma of the lung (PMID: 12460918).
Mutation Effect on Gene	MUTATION EFFECT
	No clinically significant mutation was found in NRAS
	NCCN
	GUIDELINES
	Patients with any known KRAS mutation (exon 2 or non-exon 2) or NRAS mutation should not be treated with either cetuximab or panitumumab.
	STANDARD THERAPEUTIC IMPLICATIONS
	CETUXIMAB
	PANITUMUMAB
FDA Approved Drugs in Tumor Type	PANITUMUMAB, Colorectal Carcinoma The approval is based on the results of a single, open label study that enrolled 463 patients with metastatic CRC. Patients were randomly assigned to either best supportive care (BSC) alone or BSC plus panitumumab, 6 mg/kg intravenously, every other week. All patients were required to have disease progression following one or more chemotherapy regimens containing a fluoropyrimidine, irinotecan, and oxaliplatin. The mean PFS was 96 days for patients receiving panitumumab and 60 days for patients receiving BSC alone. There were 19 partial responses (8%) among the 231 patients randomly assigned to panitumumab, the median response duration was 17 weeks. There was no difference in OS between the two study arms. Approximately 75% of patients in the BSC alone arm crossed over to receive panitumumab after a determination of disease progression by the study investigator. Most patients" tumors exhibited EGFR expression in 10% of tumor cells with no evidence of a correlation between either the proportion of cells expressing EGFR or the intensity of EGFR expression (PMID: 17475878). Efficacy was also shown in a phase 3 trial, which assessed the treatment effect of panitumumab plus best supportive care (BSC) vs BSC on OS in 377 patients with chemo-refractory wild-type KRAS exon 2 mCRC. In wild-type RAS mCRC, median OS for panitumumab plus BSC was 10.0 vs 6.9 months for BSC.
	CETUXIMAB, Colorectal Carcinoma The approval was based on retrospective analyses of tumor samples from patients enrolled in the CRYSTAL trial and in two supportive studies, CA225025 and EMR 62 202-047 (OPUS), according to KRAS mutation status. The addition of cetuximab to chemotherapy or best supportive care (BSC) resulted in improved OS, PFS, and ORR in patients with KRAS wild-type tumors, whereas there was no benefit, or even potential harm, in patients with KRAS mutant tumors. CRYSTAL was an open-label trial in patients with mCRC who had not received prior chemotherapy for metastatic disease. KRAS mutation status was available from 89% of patients (1079) and 676 patients had KRAS wild type tumors, while 403 patients had mutant tumors. Retrospective analysis showed a median

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SARDA, KESHAV	Specimen: 83173413 Collected: 05/11/2018 / 00:00 PDT	Client #: 55001 A VORA/A VERMA
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NRAS wildtype CLINICAL IMPLICATIONS

Lab: EZ

	OS for the wild type group of 23.5 months compared to 19.5 months for FOLFIRI alone. The median PFS for patients with wild type tumors treated with cetuximab plus FOLFIRI was 9.5 months compared to 8.1 months. ORR was 567 vs 39%. In the overall population, PFS in patients treated with cetuximab plus FOLFIRI was 9.5 months compared to 8.1 months. ORR was 567 vs 39%. In the overall population, PFS in patients treated with FOLFIRI alone. In an updated analysis with an additional 162 events, the median OS was 19.6 months for patients treated analysis with an additional 162 events, the median OS was 19.6 months for patients treated with cetuximab plus FOLFIRI compared with 18.5 months for patients treated with FOLFIRI alone. In the subgroup with KRAS mutant tumors, no improvement was noted by the addition of cetuximab (PMID: 27722750). Retrospective analysis of two supportive studies, CA225025, and OPUS, by KRAS mutation status supported the efficacy of cetuzimab in wild type tumors: CA225025 was an open-label randomized trial that compared cetuximab plus best supportive care (BSC) with BSC alone in patients with previously treated mCRC. The median OS was 8.6 versus 5.0 months in the cetuximab plus BSC and the BSC groups, respectively. OPUS was a randomized open-label phase II study that compared cetuximab in combination with FOLFOX-4 to FOLFOX-4 alone as first-line treatment of metastatic CRC. Retrospective analysis of KRAS status was performed on 93% of patients (315/337). In the wild-type subgroup (N=179/315), ORR was 57% in patients treated with cetuximab plus FOLFOX-4 compared to 34% in patients treated with patients treated with reated with cetuximab plus FOLFOX-4 alone as first-line treated with FOLFOX-4 alone (PMID) 21228335).
FDA Approved Drugs in Other Tumor Type	None
Clinical Trials	None
Companion Diagnostics	None
TP53 R175H CLINICAL IMPLICATIONS	Lab: EZ

Gene Function	BACKGROUND	
	The transcription factor TP53 regulates a large number of genes that control tumor suppressing functions such as cell cycle arrest, DNA repair, senescence and apoptosis, whilst the activation of TP53 often leads to apoptosis. Activation of TP53 begins through a number of mechanisms including phosphorylation by ATM, ATR, CHK1 and MAPKs. The TP53 tumor suppressor gene regulates more than 100 genes that control critical tumor suppressing functions such as cell cycle arrest, DNA repair, senescence and apoptosis. It is the most frequently altered gene in human cancers and missense mutations that are associated with an aggressive phenotype occur in more than 50% of cancers.	
Mutation Effect on Gene	MUTATION EFFECT	
	loss-of-function mutation.	
	The TP53 R175H mutation is known to be oncogenic. The R175H mutation is one of the most common alterations of TP53 with more than 320 entries in the COSMIC database. The histidine substitution at codon 175 results in unfolding of the DNA-binding domain and loss of transcriptional activity (PMID: 8510927, 17401432), while the mutant protein has gained the ability to bind to and inhibit P63 and P73 (PMID: 27589690) in addition to having a dominant negative effect on wild type TP53 (PMID: 8633021, 9364015, 10519380). It is	

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Report Status: Final SARDA, KESHAV

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TP53 R175H CLINICAL IMPLICATIONS

Lab: EZ

	significantly less thermodynamically stable and completely denatured at 37C. Furthermore, it lacks wild-type TP53 function and is unable to induce cell cycle arrest or apoptosis. R175H is most commonly associated with CRC, PDAC, breast carcinoma, adenocarcinoma of the esophagus and stomach, as well as HNSCC. The germline variant has been associated with Li-Fraumeni syndrome (LFS) and hereditary cancer-predisposing syndrome (PMID: 9047394, 18511570) and classified as causative for these disorders (ClinVar). The germline variant of this mutation has been associated with a hereditary cancer predisposing syndrome (ClinVar). There are no FDA-approved or NCCN-compendium listed treatments specifically for patients with Colorectal Carcinoma harboring a pathogenic TP53 mutation. There is clinical evidence that the patogenic TP53 mutation confers sensitivity to AZD1775, Transferrin Receptor-Targeted Liposomal p53 cDNA.
	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
	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
	NCT01748825, Phase 1 TITLE: A Phase I Study of Single-agent AZD1775 (MK-1775), a Wee1 Inhibitor, in Patients With Advanced Refractory Solid Tumors
	NCT02095132, Phase 1 or 2 TITLE: A Phase 1/2 Study of AZD1775 (MK-1775) in Combination With Oral Irinotecan in Children, Adolescents, and Young Adults With Relapsed or Refractory Solid Tumors
	NCT02354547, Phase
	1
	TITLE: A Phase I Study of SGT-53, a TfRscFv-Liposome-p53 Complex, in Children With Refractory or Recurrent Solid Tumors
	NCT02617277, Phase
	1
	TITLE: A Phase I Study Assessing the Safety, Tolerability and Pharmacokinetics of AZD1775 in Combination With MEDI4736 in Patients With Advanced Solid Tumours
	NCT03313557, Phase 1 TITLE: An Open-label, Non-randomised, Multicentre Study to Allow Continued Access to and Assess the Safety and Tolerability of AZD1775 for Patients Enrolled in AZD1775 Clinical Pharmacology Studies
	INVESTIGATIONAL THERAPEUTIC IMPLICATIONS

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TP53 R175H CLINICAL IMPLICATIONS

Lab: EZ

significant shrinkage of tumor volumes of 25% and 16% (PMID: 27357628). AZD1775 Highest level of evidence: 3B In a phase II study of AZD1775 plus carboplatin in patients with TP53-mutated ovarian cancer refractory or resistant to first-line platinum based therapy, the ORR was 43%, including one patient (5%) with a prolonged CR. Median PFS and OS were 5.3 months and 12.6 months, respectively, with two patients having ongoing response for more than 31 and 42 months at data cutoff (PMID: 27998224). 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 care biomarkers recommended as standard of care by the NCCN) Level 3B: 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		
 Highest level of evidence: 3B Clinical activity of this Drug was demonstrated in afirst-in-man Phase I clinical trial in 11 patients with refractory disease. Minimal side effects were observed and seven patients demonstrated SD. One patient with adenoid cystic carcinoma had his status changed from unresectable to resectable after one treatment cycle. The median survival was 340 days (PMID: 23809015). Combination therapy with docetaxel was tested in 14 patients with advanced cancers. The combination treatment was well-tolerated and clinical activity in 12 patients evaluable for analysis was observed. Three of these patients achieved PR with tumor reductions of -47%51%, and -79%. Two other patients had SD with significant shrinkage of tumor volumes of 25% and 16% (PMID: 27357628). AZD1775 Highest level of evidence: 3B In a phase II study of AZD1775 plus carboplatin in patients with TP53-mutated ovarian cancer refractory or resistant to first-line platinum based therapy, the ORR was 43%, including one patient (5%) with a prolonged CR. Median PFS and OS were 5.3 months and 12.6 months, respectively, with two patients having ongoing response for more than 31 and 42 months at data cutoff (PMID: 27998224). LEVELS OF EVIDENCE Level 11: FDA-approved drug for this cancer type excluding chemotherapeutic drugs and hormone therapies Level 2A: Standard of care biomarkers recommended as standard of care by the NCCN) Level 2B: Standard of care biomarkers recommended as standard of care by the NCCN) Level 3A: Clinical evidences supports the biomarker as being predictive of response to a drug for this indication (including biomarkers as being predictive of response to a drug for this sindication Level 38: Clinical evidence supports the biomarker as being predictive of response to a drug for this sindication Level 38: Clinical evidence supports the biomarker as being predictive of response to a drug for a different indication Level 38: C		aiming to restore wildtype p53 function or to inhibit the downstream function of oncogenic mutant p53 (PMID: 24651012). Despite the substantial body of research on p53, restoring its function within cancer cells is a challenging task and difficult to translate into clinical benefit. Nonetheless, multiple strategies have been utilized in an attempt to restore p53 function in cancer cells. These strategies include impairing the activity of p53 regulators, restoring wildtype activity to p53 mutant forms or mimicking p53 downstream function, however, as of yet, none of these approaches have successfully translated into advanced clinical trials
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	Companion Diagnostics	None

PUBLICATIONS

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-questdiagnostics/watson-genomics-for-physicians

CLIENT SERVICES: 866-894-6920 (Opt#1)

SPECIMEN: 83173413

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Lab: EZ

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Report Status: Final SARDA, KESHAV

Patient Information	Specimen Information	Client Information
SARDA, KESHAV	Specimen: 83173413 Collected: 05/11/2018 / 00:00 PDT	Client #: 55001 A VORA/A VERMA
DOB: 04/24/1953 AGE: 65 Gender: M Patient ID: 83173413	Received: 05/18/2018 / 03:53 PDT Reported: 06/14/2018 / 22:33 PDT	

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 polymorphism (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, ALX, AR,

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, CDRV2A, 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.

GENE REGIONS PASSING QC

Lab: EZ

In this specimen, 868 of 900 regions (>96%) passed our minimal acceptability QC criteria for reporting results, including relevant regions for this test. The coverage of 32 of 900 regions (<4%) 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.

CLIENT SERVICES: 866-894-6920 (Opt#1)

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