REPORTING

Report Date:	DEC-05-2017
Receipt Date:	NOV-28-2017
Collection Date:	NOV-27-2017
Specimen:	Blood
Status:	FINAL

PHYSICIAN

Stephani Christensen
Account: Comprehensive Cancer Centers of Nevada - Wigwam Pkway
Address: 1505 Wigwam Pkwy, Ste 130, Henderson, NV, 89074, United States
Ph: (702) 856-1400 | Fax: (888) 974-3986
Additional Recipient: N/A

Complete Tumor Response Map on page 2

Summary of Somatic Alterations & Associated Treatment Options

KEY Approved in indication | Approved in other indication | Lack of response

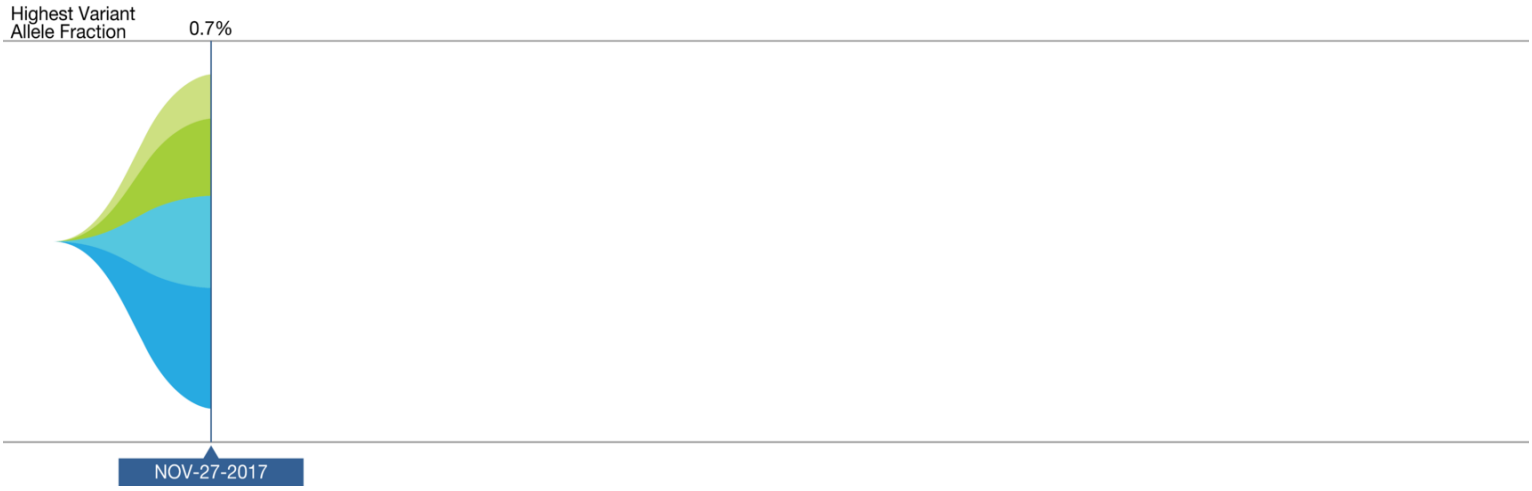
Alteration	% cfDNA or Amplification	Associated FDA-approved therapies	Clinical trial availability (see page 3)
TP53 S241Y	0.7%	None	Yes
TP53 R273H	0.5%	None	Yes
RB1 Splice Site SNV	0.4%	None	No

Variants of Uncertain Significance

TP53 P390fs (0.2%)
The functional consequences and clinical significance of alterations are unknown. Relevance of therapies targeting these alterations is uncertain.

Guardant360 Tumor Response Map

The Guardant360 Tumor Response Map illustrates the mutant allele percentage (% cfDNA) of observed somatic variants at each sample submission time point. Amplifications are not plotted, and only the first and last five test dates are plotted. Please see the Physician Portal (**portal.guardanthealth.com**) for the Tumor Response Map with all test dates.



Alteration	% cfDNA or Amp	
TP53 S241Y	0.7%	
TP53 R273H	0.5%	
RB1 Splice Site SNV	0.4%	
TP53 P390fs	0.2%	Variant of Uncertain Significance §

The table above annotates the variant allele fraction (% cfDNA) detected in this sample, listed in descending order.
§ See definitions section for more detail

Available Clinical Trials (within the same state as the ordering physician)

There may be additional trials not listed here. Visit: **portal.guardanthealth.com** or email **clientservices@guardanthealth.com** with A80160 in the subject line of the email, for additional trials.

Alteration	Trial ID / Contact	Title	Phase	Site(s)
TP53 S241Y	Visit portal.guardanthealth.com for trials not within the same state as the physician's office			
TP53 R273H	Visit portal.guardanthealth.com for trials not within the same state as the physician's office			

More clinical trial options available at **portal.guardanthealth.com**

Definitions

Variant of Uncertain Significance: The functional consequences and clinical significance of alterations are unknown. Relevance of therapies targeting these alterations is uncertain.

Deletion (Del): The following alteration was detected in this patient: TP53 P390fs. Guardant360 detects short deletions in exons of certain genes (see Table 1), including potential splice site-disrupting events.

Splice Site: Splice site variants disrupt the donor and/or acceptor splice site(s), leading to abnormal mRNA splicing and altered protein levels and/or function.

Comments

None

Interpretation

Somatic alterations were detected in the circulating cell-free DNA isolated from this patient's blood specimen. These genomic alterations are cancer-associated somatic variants, some of which have been associated with either increased or reduced clinical response to specific treatments. The percentage of altered cell-free DNA circulating (% cfDNA) in blood is related to the unique tumor biology of each patient. Factors that may affect the % cfDNA of detected somatic alterations include tumor growth, turn over, size, heterogeneity, vascularization, disease progression, and treatment.

Method and Limitations

Guardant360 sequences 73 cancer-associated genes to identify somatic alterations with high sensitivity. Cell-free DNA is extracted from plasma, and genomic alterations are analyzed by massively parallel sequencing of amplified target genes using the Illumina sequencing platforms and hg19 as the reference genome. All exons are sequenced in some genes; only clinically significant exons are sequenced in other genes. The types of genomic alterations detected by Guardant360 include single nucleotide variations, amplifications, fusions, short insertions/deletions, and splice site-disrupting events (see Table 1). This version of the Guardant360 test is not validated for the detection of other types of genomic alterations, such as complex rearrangements or gene deletions. Certain sample or variant characteristics may result in reduced analytic sensitivity, such as low cell-free DNA concentration. Guardant360 cannot discern the source of the circulating cfDNA, and for some variants in the range of ~40 to 60% cfDNA, the test cannot easily distinguish germline variants from somatic alterations. Guardant360 is not validated for the detection of germline or de novo variants that are associated with hereditary cancer risk. Tissue genotyping should be considered when plasma genotyping is negative, if clinically appropriate.

Table 1: Genes on the Guardant360 Panel

Guardant360 reports single nucleotide variants and splice site mutations in all clinically relevant exons in 73 genes and reports other variant types in select genes as indicated below.

AKT1	*ALK* #	*APC* Ω	*AR* †	*ARAF*	*ARID1A* Ω	*ATM* Ω	*BRAF* †	*BRCA1* Ω
BRCA2 Ω	*CCND1* †	*CCND2* †	*CCNE1* †	*CDH1* Ω	*CDK4* †	*CDK6* †	*CDKN2A* Ω	*CTNNB1*
DDR2	*EGFR* †Ω	*ERBB2* †Ω	*ESR1*	*EZH2*	*FBXW7*	*FGFR1* †	*FGFR2* †#	*FGFR3* #
GATA3 Ω	*GNA11*	*GNAQ*	*GNAS*	*HNF1A*	*HRAS*	*IDH1*	*IDH2*	*JAK2*
JAK3	*KIT* †Ω	*KRAS* †	*MAP2K1*	*MAP2K2*	*MAPK1*	*MAPK3*	*MET* †Ω	*MLH1* Ω
MPL	*MTOR* Ω	*MYC* †	*NF1* Ω	*NFE2L2*	*NOTCH1*	*NPM1*	*NRAS*	*NTRK1* #
NTRK3	*PDGFRA* †Ω	*PIK3CA* †	*PTEN* Ω	*PTPN11*	*RAF1* †	*RB1* Ω	*RET* #	*RHEB*
RHOA	*RIT1*	*ROS1* #	*SMAD4* Ω	*SMO*	*STK11* Ω	*TERT* ‡	*TP53* Ω	*TSC1* Ω
VHL Ω								

Ω Guardant360 reports insertion and deletion variants (indels) in this gene.
‡ Guardant360 reports alterations in the promoter region of this gene.
# Guardant360 reports fusion events involving this gene for all known gene partners.
† Guardant360 reports amplifications of this gene.

About the Test

Guardant360 assay was developed and its performance characteristics were determined by Guardant Health, Inc. This test has not been cleared or approved by the U.S. Food and Drug Administration (FDA). The FDA has determined that such clearance or approval is not necessary. This Test may be used for clinical purposes and should not be regarded as investigational or for research only. Guardant Health's clinical reference laboratory is certified under the Clinical Laboratory Improvement Amendments of 1988 (CLIA) as qualified to perform high complexity clinical laboratory testing.

The laboratory report should be considered in context with other clinical criteria (e.g. patient history, physical exam), as well as laboratory, pathology, and imaging studies by a qualified medical professional prior to initiating or changing a patient's treatment plan. The selection of any, all, or none of the drugs associated with potential clinical benefit (or potential lack of clinical benefit) is entirely at the discretion of the treating medical professional. Drugs and trial information are based on the diagnosis as written on the submitted test request form; this information is not based on any supplemental information provided by the requesting medical professional, including pathology reports or other molecular studies Some drugs listed in this report may not be approved or cleared by the FDA for a particular use. Guardant Health makes no endorsement, express or implied, of any product, physician, or procedure contained in this report. This report makes no promises or guarantees that a particular medication will affect (or not affect) the clinical outcome of any patient.

Testing performed at: Guardant Health

Laboratory Director: Arthur Baca, MD PhD | CLIA ID: 05D2070300 | CAP #: 8765297 | 505 Penobscot Drive, Redwood City, CA, 94063, United States

Additional information is available

Any therapeutic annotations are based on publicly available information. This information is described in the "Detailed Therapy Results" and "Relevance of Detected Alterations" sections.

Visit portal.guardanthealth.com or email clientservices@guardanthealth.com with A80160 in the subject line of the email for:

– Additional clinical trials
– Detailed Therapy Results
– Relevance of Detected Alterations
– References

If you would like to receive this additional information with every Guardant360 report, please call client services at 855.698.8887 to opt-in.

Additional information begins on the next page.

List of Available Clinical Trials

Alteration	Trial ID / Contact	Title	Phase	Site (number in parenthesis is count of trial sites)
TP53 S241Y	NCT02576444 Manuel Avedissian, manuel.avedissian@yale.edu, 203-737-3669	OLAParib COmbinations	Phase 2	Boston, MA; New Haven, CT; Nashville, TN
	NCT01827384 Nancy Moore, R.N., nancy.moore@nih.gov, (301) 402-5640	Molecular Profiling-Based Targeted Therapy in Treating Patients With Advanced Solid Tumors	Phase 2	Houston, TX; Saint Louis, MO; Bethesda, MD; Pittsburgh, PA; New Brunswick, NJ; Aurora, CO; Lexington, KY
	NCT02327169 Takeda Study Registration Call Center, globaloncologymedinfo@takeda.com, +1-844-662-8532	A Phase 1B Study of MLN2480 in Combination With MLN0128 or Alisertib, or Paclitaxel, or Cetuximab, or Irinotecan in Adult Patients With Advanced Nonhematologic Malignancies	Phase 1	Houston, TX; Philadelphia, PA; Boston, MA (2); United Kingdom (3); France (3); Spain (3)
	NCT02448589 Takekazu Aoyama, MD PhD, aoyama@taihooncology.com, 1 (609) 750-5300	An Investigation of TAS-119 Monotherapy and in Combination With Docetaxel	Phase 1	Cleveland, OH; Netherlands; Italy; United Kingdom; Spain (2)
	NCT02610075 AstraZeneca Clinical Study Information Center, information.center@astrazeneca.com, 1-877-240-9479	Phase Ib Study to Determine MTD of AZD1775 Monotherapy in Patients With Locally Advanced or Metastatic Solid Tumours.	Phase 1	Denver, CO; Scottsdale, AZ; Nashville, TN
TP53 R273H	NCT02898207	Olaparib and Onalespib in Treating Patients With Solid Tumors That Are Metastatic or Cannot Be Removed by Surgery or Recurrent Ovarian, Fallopian Tube, Primary Peritoneal, or Triple-Negative Breast Cancer	Phase 1	MA (5)
	NCT02503709	Onalespib and CDKI AT7519 in Treating Patients With Solid Tumors That Are Metastatic or Cannot Be Removed by Surgery	Phase 1	Columbus, OH; Bethesda, MD (2); Boston, MA (2)

Detailed Therapy Results

Alteration	Drug	Trade Name	Target	Current Status
TP53 S241Y	ENMD-2076		AuroraA small molecule kinase inhibitor.	Phase 1 (Solid Tumor) Phase 2 (Fibrolamellar hepatocellular carcinoma, Ovarian carcinoma, Breast carcinoma, Fallopian tube adenocarcinoma, Soft tissue sarcoma)
	AMG 900		AuroraA, B, C small molecule kinase inhibitor.	Phase 1 (Solid Tumor) Phase 1 (Acute myelocytic leukemia (AML))
	APR-246		Reactivates mutant p53.	Phase 2 (Ovarian serous carcinoma)
	Alisertib		AuroraA small molecule kinase inhibitor.	Phase 1 (Solid Tumor) Phase 3 (T-cell Lymphoma)
	Kevetrin		Blocks Mdm2-p53 interaction, restoring transcriptional activity of p53.	Phase 1 (Solid Tumor) Phase 2 (Ovarian carcinoma)
	AT9283		AuroraA, B, Jak2, Jak3, Bcr-Abl kinase inhibitor.	Phase 1 (Solid Tumor) Phase 2 (Acute myelocytic leukemia (AML), Multiple myeloma (MM), Chronic myelocytic leukemia (CML), Acute lymphocytic leukemia (ALL))
	MK-1775		Wee1 tyrosine kinase inhibitor.	Phase 2 (Solid Tumor) Phase 2 (Medulloblastoma, Head and neck squamous cell carcinoma (HNSCC), Small cell lung carcinoma (SCLC), Myeloproliferative neoplasm (MPN), Ovarian carcinosarcoma, Breast carcinoma (triple negative), Acute myelocytic leukemia (AML), MDS/MPN, unclassifiable, Peritoneal papillary serous carcinoma, Myelodysplastic Syndrome (MDS))
	AZD2811		Nanoparticle formulation of Aurora kinase B inhibitor barasertib (AZD1152).	Phase 1 (Solid Tumor) Phase 2 (Acute myelocytic leukemia (AML), Myelodysplastic Syndrome (MDS))
	ALT-801		p53-targeted T-cell receptor-IL2 fusion.	Phase 1 (Solid Tumor) Phase 2 (Melanoma, Urothelial carcinoma, Bladder carcinoma, Urethral carcinoma, Multiple myeloma (MM))
	SNS-314		AuroraA, B small molecule kinase inhibitor.	Phase 1 (Solid Tumor)
	SGT-53		TP53 gene therapy delivered via transferrin-targeted nanoparticles.	Phase 1 (Solid Tumor) Phase 2 (Glioblastoma, Glioma, Pancreatic carcinoma)
	TAS-119		Selective AuroraA kinase inhibitor.	Phase 1 (Solid Tumor)
TP53 R273H	AT13387		Small molecule inhibitor of Hsp90.	Phase 1 (Solid Tumor) Phase 2 (GIST (Gastrointestinal stromal tumor), Lymphoma, Non-small cell lung carcinoma (NSCLC), Prostate carcinoma, Lung cancer, Diffuse large B-cell lymphoma (DLBCL))

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Detailed Therapy Results

Alteration	Drug	Trade Name	Target	Current Status
	Ganetespib		Small molecule inhibitor of Hsp90, also may inhibit Kit/Egfr/Bcr-Abl.	Phase 1 (Solid Tumor) Phase 3 (Non-small cell lung carcinoma (NSCLC), Acute myelocytic leukemia (AML), Lung cancer, Myelodysplastic Syndrome (MDS))
	SNX-5422		Hsp90 inhibitor.	Phase 2 (Solid Tumor) Phase 1 (Neuroendocrine carcinoma, Lymphoma, Non-small cell lung carcinoma (NSCLC), Hematologic malignancies, Chronic lymphocytic leukemia (CLL), Lung cancer)
	Luminespib		Hsp90 inhibitor.	Phase 1 (Solid Tumor) Phase 2 (Gastric carcinoma, GIST (Gastrointestinal stromal tumor), Pancreatic carcinoma, Non-small cell lung carcinoma (NSCLC), Breast carcinoma)
	Debio 0932		Small molecule inhibitor of Hsp90.	Phase 1 (Solid Tumor) Phase 2 (Non-small cell lung carcinoma (NSCLC))
	PU-H71		Hsp90 inhibitor.	Phase 1 (Solid Tumor) Phase 1 (Lymphoma, Non-Hodgkin lymphoma (NHL))

Relevance of Detected Alterations

Alteration	Role in Disease	Effect on Drug Sensitivity	Effect on Drug Resistance
TP53 S241Y	Loss of tumor suppressor p53, which is encoded by the TP53 gene, is common in aggressive advanced cancers (1). Carriers of a germline mutation in TP53 have Li-Fraumeni Syndrome, an inherited cancer syndrome resulting in multiple tumors in early adulthood, including breast cancer, brain tumors, and leukemias (2-4). Expression of p53 in normal cells is low; however, TP53 alterations, including those that result in loss of p53 tumor suppressor function, may lead to stabilization and increased expression of p53, particularly in the nucleus, and several studies have shown that it may have oncogenic gain-of-function effects (5-9). Expression of p53 has been implicated in thymic carcinoma development and progression, and has been correlated with more aggressive tumors (10-14).	At present, there are no approved therapies targeting TP53 alterations, despite their high prevalence in cancer. Therapeutic approaches under investigation include gene therapy for TP53 and (dendritic cell-based) TP53 vaccines (15-17). Inhibition of components of the DNA damage checkpoint, including Checkpoint Kinase 1 (Chk1) and Wee1, has been reported to enhance the activity of DNA-damaging agents in preclinical cancer models with deficiency of p53 function (18-20). Clinical trials of the Wee1 inhibitor MK-1775 are currently underway for patients with solid tumors and hematologic malignancies. Studies have reported Aurora kinase A to be activated in cells harboring TP53 mutation, and Aurora kinase A and B inhibitors have been reported to activate wild-type p53 in cellular assays; thus, tumors retaining a wild-type TP53 allele may benefit from Aurora kinase inhibitors (21-26).	Mutations in TP53 may increase resistance to ionizing radiation therapy (27,28).
TP53 R273H	Loss of tumor suppressor p53, which is encoded by the TP53 gene, is common in aggressive advanced cancers (1). Carriers of a germline mutation in TP53 have Li-Fraumeni Syndrome, an inherited cancer syndrome resulting in multiple tumors in early adulthood, including breast cancer, brain tumors, and leukemias (2-4). Expression of p53 in normal cells is low; however, TP53 alterations, including those that result in loss of p53 tumor suppressor function, may lead to stabilization and increased expression of p53, particularly in the nucleus, and several studies have shown that it may have oncogenic gain-of-function effects (5-9). Expression of p53 has been implicated in thymic carcinoma development and progression, and has been correlated with more aggressive tumors (10-14).	Some studies suggest that Hsp90 inhibitors may be effective in tumors with oncogenic TP53 alterations (29-31).	R273H mutant p53 may play a role in drug resistance, particularly methotrexate and doxorubicin, through a dominant gain of function mechanism (32). Mutations in TP53 may increase resistance to ionizing radiation therapy (27). An abstract has reported that TP53 R273H led to reduced sensitivity to gefitinib in a breast cancer and a lung cancer cell line (33).
RB1 Splice Site SNV	RB1 inactivation has been shown to cause epigenetic deregulation of genes involved in several cancer pathways and is thus speculated to play a key role in cancer development (34). Retinoblastoma, a malignant tumor of the retina, arises from mutations in both RB1 alleles. Hereditary retinoblastoma patients carry one RB1 germline mutation, which also increases their risk of developing a second type of cancer later in life (35).	At this time, there are no therapeutic options to target the inactivation of Rb. Preclinical studies are actively investigating possible therapies to address Rb inactivation, exploring avenues such as Aurora kinase inhibitors, Bcl-2 family inhibitors, and Notch pathway activation (36-38). Loss of Rb function has been associated with increased sensitivity to cytotoxic agents in both preclinical studies and in patients with bladder or breast cancer (39,40).	The effect of Rb expression on chemoresistance is complex, as both Rb protein expression and loss of Rb protein have been associated with resistance to chemotherapeutics (39,41-45). Loss of RB1 has been associated with lack of response to Cdk4/6 inhibitors (46-52).

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Relevance of Detected Alterations

Alteration	Role in Disease	Effect on Drug Sensitivity	Effect on Drug Resistance
TP53 P390fs	Loss of tumor suppressor p53, which is encoded by the TP53 gene, is common in aggressive advanced cancers (1). Carriers of a germline mutation in TP53 have Li-Fraumeni Syndrome, an inherited cancer syndrome resulting in multiple tumors in early adulthood, including breast cancer, brain tumors, and leukemias (2-4). Expression of p53 in normal cells is low; however, TP53 alterations, including those that result in loss of p53 tumor suppressor function, may lead to stabilization and increased expression of p53, particularly in the nucleus, and several studies have shown that it may have oncogenic gain-of-function effects (5-9). Expression of p53 has been implicated in thymic carcinoma development and progression, and has been correlated with more aggressive tumors (10-14).	At present, there are no approved therapies targeting TP53 alterations, despite their high prevalence in cancer. Therapeutic approaches under investigation include gene therapy for TP53 and (dendritic cell-based) TP53 vaccines (15-17). Inhibition of components of the DNA damage checkpoint, including Checkpoint Kinase 1 (Chk1) and Wee1, has been reported to enhance the activity of DNA-damaging agents in preclinical cancer models with deficiency of p53 function (18-20). Clinical trials of the Wee1 inhibitor MK-1775 are currently underway for patients with solid tumors and hematologic malignancies. Studies have reported Aurora kinase A to be activated in cells harboring TP53 mutation, and Aurora kinase A and B inhibitors have been reported to activate wild-type p53 in cellular assays; thus, tumors retaining a wild-type TP53 allele may benefit from Aurora kinase inhibitors (21-26). In the case of this uncharacterized variant, the relevance of any available therapeutic approaches is unknown.	Mutations in TP53 may increase resistance to ionizing radiation therapy (27,28).

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