REPORTING

Original Report Date:	DEC-08-2017
Amended Date:	AUG-06-2018
Receipt Date:	DEC-01-2017
Collection Date:	NOV-29-2017
Specimen:	Blood
Status:	AMENDED (Preliminary)

PHYSICIAN

John Chan
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Additional Recipient: N/A

Complete Tumor Response Map on page 3

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 4)
BRCA2 R1997fs	4.1%	✓ Niraparib, Olaparib, Rucaparib	Yes
BRAF Amplification	Low (+)	~ Cobimetinib, Regorafenib, Sorafenib, Trametinib	Yes
PDGFRA Amplification	Low (+)	~ Dasatinib, Imatinib, Lenvatinib, Nilotinib, Nintedanib, Olaratumab, Pazopanib, Ponatinib, Regorafenib, Sorafenib, Sunitinib	Yes
TP53 A189G	0.9%	None	Yes
TP53 C275Y	0.2%	None	Yes
TP53 G266R	0.2%	None	Yes
TP53 Splice Site SNV	0.1%	None	Yes
TP53 L43fs	9.8%	None	Yes
BRCA1 R1203Q	0.2%	None	No

Synonymous Alterations
TERT L55L (8.8%)
This sequence change does not alter the amino acid at this position and is unlikely to be a therapeutic target. Clinical correlation is advised.

Comments

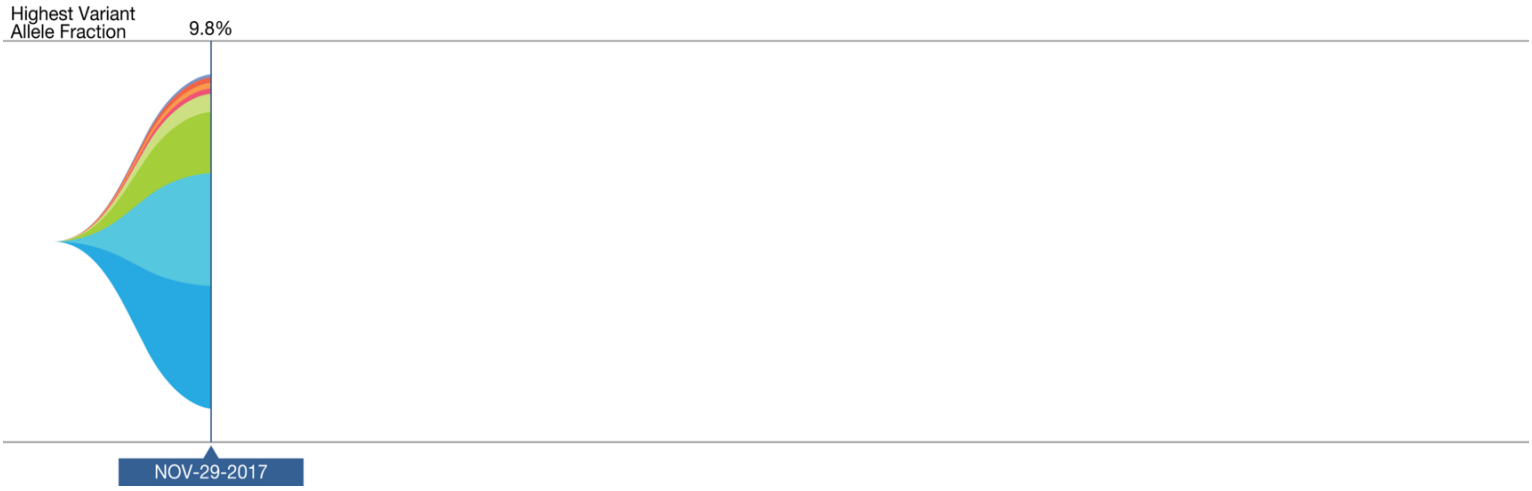
The BRCA2 S1982fs was detected in this patient's sample at an allele fraction suspicious for germline origin. This variant is expected to lead

Comments

to a frame-shift and loss of functional protein, and similar variants at this codon are associated with Hereditary Breast and Ovarian Cancer Syndrome. As Guardant360 is neither intended nor validated for reporting or interpretation of germline variants, this alteration is not reported in the list of somatic variants above, and its verification with an assay validated for germline testing is recommended if this incidental finding is of clinical interest.

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 L43fs	9.8%	
TERT L55L	8.8%	Synonymous Alteration §
BRCA2 R1997fs	4.1%	
TP53 A189G	0.9%	
TP53 C275Y	0.2%	
TP53 G266R	0.2%	
BRCA1 R1203Q	0.2%	
TP53 Splice Site SNV	0.1%	
BRAF Amplification Amplifications not graphed above	Low (+) Plasma Copy Number: 2.3	
PDGFRA Amplification Amplifications not graphed above	Low (+) Plasma Copy Number: 2.2	

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 A80531 in the subject line of the email, for additional trials.

Alteration	Trial ID / Contact	Title	Phase	Site(s)
BRCA2 R1997fs	NCT02264678 AstraZeneca Clinical Study Information Center, information.center@astrazeneca.com, 1-877-240-9479	Ascending Doses of AZD6738 in Combination With Chemotherapy and/or Novel Anti Cancer Agents	Phase 1/ Phase 2	Los Angeles, California Newport, California
	NCT02354586 Beth Zaharoff, Bzaharoff@tesarobio.com, 781-209-5485	A Study of Niraparib in Patients With Ovarian Cancer Who Have Received Three or Four Previous Chemotherapy Regimens	Phase 2	Burbank, California Duarte, California Los Angeles, California San Francisco, California Additional trial sites available
	NCT02655016 Beth Zaharoff, bzaharoff@tesarobio.com, 781-209-5485	A Study of Niraparib Maintenance Treatment in Patients With Advanced Ovarian Cancer Following Response on Front-Line Platinum-Based Chemotherapy	Phase 3	Los Angeles, California San Francisco, California Santa Rosa, California
	NCT02657889 Clinical Trial Management Group, nirap-pembro.combostudy@tesarobio.com, 781-786-7006	Niraparib in Combination With Pembrolizumab in Patients With Triple-negative Breast Cancer or Ovarian Cancer	Phase 1/ Phase 2	Los Angeles, California San Francisco, California Stanford, California
	NCT02889900 AstraZeneca Clinical Study Information Center, information.center@astrazeneca.com, 1-877-240-9479	Efficacy and Safety Study of Cediranib in Combination With Olaparib in Patients With Recurrent Platinum-Resistant Ovarian Cancer	Phase 2	Downey, California Fullerton, California Greenbrae, California Los Angeles, California Additional trial sites available
	Visit portal.guardanthealth.com for trials not within the same state as the physician's office			
BRAF Amplification	NCT02101788	Trametinib in Treating Patients With Recurrent or Progressive Low-Grade Ovarian Cancer or Peritoneal Cavity Cancer	Phase 2/ Phase 3	Auburn, California (2) Berkeley, California Burbank, California Burlingame, California Additional trial sites available
	NCT02465060	NCI-MATCH: Targeted Therapy Directed by Genetic Testing in Treating Patients With Advanced Refractory Solid Tumors, Lymphomas, or Multiple Myeloma	Phase 2	Anaheim, California Antioch, California Auburn, California (2) Bakersfield, California Additional trial sites available
	NCT02703571 Novartis Pharmaceuticals, novartis.email@novartis.com, 1-888-669-6682	Study of Safety and Efficacy of Ribociclib and Trametinib in Patients With Metastatic or Advanced Solid Tumors	Phase 1/ Phase 2	Duarte, California
	Visit portal.guardanthealth.com for trials not within the same state as the physician's office			
PDGFRA Amplification	NCT02571036 Jama Pitman, jpitman@deciphera.com	A Safety, Tolerability and PK Study of DCC-2618 in Patients With Advanced Malignancies	Phase 1	Los Angeles, California Palo Alto, California San Francisco, California
	Visit portal.guardanthealth.com for trials not within the same state as the physician's office			
TP53 A189G	NCT02098343 Roger Tell, MD PhD, Roger.Tell@aprea.com, +46 8 508 845 04	p53 Suppressor Activation in Recurrent High Grade Serous Ovarian Cancer, a Phase Ib/II Study of Systemic Carboplatin Combination Chemotherapy With or Without APR-246	Phase 1/ Phase 2	Los Angeles, California

	NCT02101775	Gemcitabine Hydrochloride With or Without WEE1 Inhibitor MK-1775 in Treating Patients With Recurrent Ovarian, Primary Peritoneal, or Fallopian Tube Cancer	Phase 2	Duarte, California South Pasadena, California
	NCT02272790 AstraZeneca Clinical Study Information Center, information.center@astrazeneca.com, 1-877-240-9479	AZD1775 Plus Chemotherapy in Platinum-Resistant Epithelial Ovarian, Fallopian Tube, or Primary Peritoneal Cancer	Phase 2	La Jolla, California Los Angeles, California San Francisco, California
	Visit portal.guardanthealth.com for trials not within the same state as the physician's office			
TP53 C275Y	NCT02098343 Roger Tell, MD PhD, Roger.Tell@aprea.com, +46 8 508 845 04	p53 Suppressor Activation in Recurrent High Grade Serous Ovarian Cancer, a Phase Ib/II Study of Systemic Carboplatin Combination Chemotherapy With or Without APR-246	Phase 1/ Phase 2	Los Angeles, California
	NCT02101775	Gemcitabine Hydrochloride With or Without WEE1 Inhibitor MK-1775 in Treating Patients With Recurrent Ovarian, Primary Peritoneal, or Fallopian Tube Cancer	Phase 2	Duarte, California South Pasadena, California
	NCT02272790 AstraZeneca Clinical Study Information Center, information.center@astrazeneca.com, 1-877-240-9479	AZD1775 Plus Chemotherapy in Platinum-Resistant Epithelial Ovarian, Fallopian Tube, or Primary Peritoneal Cancer	Phase 2	La Jolla, California Los Angeles, California San Francisco, California
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TP53 L43fs	NCT02101775	Gemcitabine Hydrochloride With or Without WEE1 Inhibitor MK-1775 in Treating Patients With Recurrent Ovarian, Primary Peritoneal, or Fallopian Tube Cancer	Phase 2	Duarte, California South Pasadena, California
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	Visit portal.guardanthealth.com for trials not within the same state as the physician's office			
TP53 G266R	Visit portal.guardanthealth.com for trials not within the same state as the physician's office			
TP53 Splice Site SNV	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

Synonymous Alteration: This sequence change does not alter the amino acid at this position and is unlikely to be a therapeutic target. Clinical correlation is advised.

Amplification: Guardant360 detects amplifications in the genes listed in Table 1. Gene amplification results in increased copies of the gene present in the cfDNA. The reported absolute copy number value represents the average copy number for the detected gene that was detected in circulating cfDNA. With the exception of sex-linked genes such as AR, 2 copies are expected in the absence of amplification. As the absolute number of copies in circulation is dependent on both tumor fraction and the magnitude of the tumor amplification, amplifications are reported on a semi-quantitative scale:

Low (+): Amplification magnitude is below the 50th percentile of amplifications detected by Guardant360.
Medium (++): Amplification magnitude is between the 50th and 90th percentiles.
High (+++): Amplification magnitude is above the 90th percentile.

Insertion (Ins): The following alteration was detected in this patient: BRCA2 R1997fs. Guardant360 detects short insertions in exons of certain genes (see Table 1).

Deletion (Del): The following alteration was detected in this patient: TP53 L43fs. 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.

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.

Amplification was detected in the circulating cell-free DNA isolated from this patient’s blood specimen for the annotated gene(s). Unlike tissue-based gene amplification tests (e.g. IHC or FISH), Guardant360 assesses the total representation of a given gene in all circulating cell-free DNA present in the patient’s blood sample including material derived from the tumor and healthy tissue alike. As such, the absolute level of amplification present in the blood depends both on the tumor-derived cfDNA content and on the degree of amplification within that fraction and cannot be inferred from bulk cfDNA interrogation. For example, a positive Guardant360 test could represent a small population of cells with extremely high levels of the detected gene amplification. Alternatively, it could represent a large population of cells with low to medium levels of the detected gene amplifications. The exact correlation between amplification detected by Guardant360 compared to IHC or FISH and how each test differentially guides patient management is an area of active investigation.

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 A80531 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.