REPORTING

Report Date:	NOV-03-2020
Receipt Date:	OCT-23-2020
Collection Date:	OCT-22-2020
Specimen:	Blood
Status:	FINAL

PHYSICIAN
John Miller

Account: Pleasantville Oncology
Address: 1234 Main Street
Anaheim, CA 94063, United States Ph: (123) 456-7890 | Fax: (123) 456-7899
Additional Recipient: N/A

Complete Tumor Response Map on page 3

Summary of Detected Somatic Alterations, Immunotherapy Biomarkers & Associated Treatment Options

KEY ✓ Approved in indication ~ Approved in other indication ⊗ Lack of response

Detected Alteration(s) / Biomarker(s)	Associated FDA-approved therapies	Clinical trial availability (see page 4)	% cfDNA or Amplification
STK11 S216F	~ Everolimus, Temsirolimus	Yes	1.2%
ATM K2331fs	~ Niraparib, Olaparib, Rucaparib, Talazoparib	Yes	0.08%
TP53 H193R	None	Yes	0.2%
TP53 Q165*	None	Yes	0.2%
TP53 R273P	None	No	2.2%

Synonymous Alterations
HRAS E126E (0.4%), *MET* L269L (0.1%)
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

Transplanted solid organs shed cell-free DNA (cfDNA) that is genetically distinct from the recipient into circulation in a manner similar to that of tumors. As such, Guardant360 often cannot determine whether variants detected in cfDNA from a solid organ transplant recipient are derived from the patient's transplant or tumor. In this case, we note the patient's history of lung transplant and have detected several common germline SNPs at sub-germline allele frequencies compatible with transplant-derived cfDNA. The presence of the variants reported above does demonstrate the presence of tumor-derived cell-free DNA; however, the remaining potential transplant or somatic variants are present at similar allele frequencies and, as such, are of uncertain origin. All variants of definite tumor origin are reported above.

Microsatellite status: MSI-High NOT DETECTED. A "Not Detected" result in samples where the highest % cfDNA is < 0.2% is an inconclusive result because it does not preclude MSI-High status in tissue.

Results reviewed by: Martina Lefterova, MD PhD

Additional Biomarkers

Biomarker	Additional Details
Tumor Mutational Burden (TMB)	3.16 mut/MB
MSI-High	NOT DETECTED

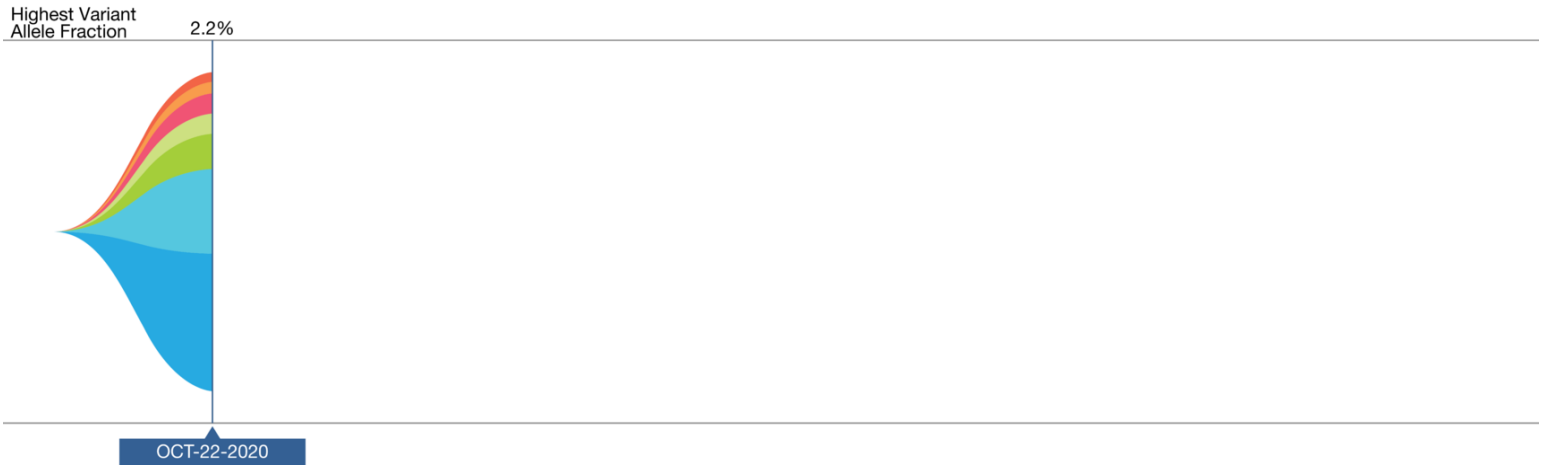
Alterations or biomarkers that were "NOT DETECTED" have been excluded from the summary table above.

We evaluated this sample for 74 genes, including the following guideline-recommended genes for NSCLC

EGFR(T790M and others)	*ALK*	*ROS1*	*BRAF*	*MET*	*ERBB2*(HER2)	*RET*	*NTRK*

Guardant360 Tumor Response Map

The Guardant360 Tumor Response Map illustrates the variant allele fraction (% cfDNA) of observed somatic variants at each sample submission. 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.



Detected Alteration(s) / Biomarker(s)	% cfDNA or Amp	
TP53 R273P	2.2%	
STK11 S216F	1.2%	
HRAS E126E	0.4%	Synonymous Alteration §
TP53 H193R	0.2%	
TP53 Q165*	0.2%	
MET L269L	0.1%	Synonymous Alteration §
ATM K2331fs	0.08%	

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 A0297423 in the subject line of the email, for additional trials.

Alteration	Trial ID / Contact	Title	Phase	Site(s)
STK11 S216F	NCT03334617 AstraZeneca Clinical Study Information Center,information.center@astrazeneca.com,1-877-240-9479	Phase II Umbrella Study of Novel Anti-cancer Agents in Patients With NSCLC Who Progressed on an Anti-PD-1/PD-L1 Containing Therapy	Phase 2	New York, NY
	NCT03366103 See https://clinicaltrials.gov/show/NCT03366103	Navitoclax and Vistusertib in Treating Patients With Relapsed Small Cell Lung Cancer and Other Solid Tumors	Phase 1 /Phase 2	Uniondale, NY Harrison, NY Commack, NY New York, NY
	NCT04250545 See https://clinicaltrials.gov/show/NCT04250545	Testing of the Anti Cancer Drugs CB-839 HCl (Telaglenastat) and MLN0128 (Sapanisertib) in Advanced Stage Non-small Cell Lung Cancer	Phase 1	New York, NY
	Visit portal.guardanthealth.com for trials not within the same state as the physician's office			
ATM K2331fs	NCT02264678 AstraZeneca Clinical Study Information Center,information.center@astrazeneca.com,1-877-240-9479	Ascending Doses of Ceralasertib in Combination With Chemotherapy and/or Novel Anti Cancer Agents	Phase 1 /Phase 2	New York, NY
	NCT03742895 Toll Free Number,Trialsites@merck.com,1-888-577-8839	Efficacy and Safety of Olaparib (MK-7339) in Participants With Previously Treated, Homologous Recombination Repair Mutation (HRRm) or Homologous Recombination Deficiency (HRD) Positive Advanced Cancer (MK-7339-002 / LYNK-002)	Phase 2	Harrison, NY New York, NY (3)
	NCT04095273 Bayer Clinical Trials Contact,clinical-trials-contact@bayer.com,+49 30 300139003	Study to Test How Well Patients With Advanced Solid Tumors Respond to Treatment With the ATR Inhibitor BAY1895344 in Combination With Pembrolizumab, to Find the Optimal Dose for Patients, How the Drug is Tolerated and the Way the Body Absorbs, Distributes and Discharges the Drug	Phase 1	New York, NY
	NCT04123366 Toll Free Number,Trialsites@merck.com,1-888-577-8839	Study of Olaparib (MK-7339) in Combination With Pembrolizumab (MK-3475) in the Treatment of Homologous Recombination Repair Mutation (HRRm) and/or Homologous Recombination Deficiency (HRD)-Positive Advanced Cancer (MK-7339-007/KEYLYNK-007)	Phase 2	Port Jefferson Station, NY
	NCT04173507 See https://clinicaltrials.gov/show/NCT04173507	Combination Treatment (Talazoparib Plus Avelumab) for Stage IV or Recurrent Non-Squamous Non-Small Cell Lung Cancer With STK11 Gene Mutation (A LUNG-MAP Treatment Trial)	Phase 2	Cooperstown, NY Rochester, NY Buffalo, NY Elmira, NY
	Visit portal.guardanthealth.com for trials not within the same state as the physician's office			
TP53 H193R	Visit portal.guardanthealth.com for trials not within the same state as the physician's office			
TP53 Q165*	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.

Deletion (Del): The following alteration was detected in this patient: *ATM* K2331fs. Guardant360 detects short deletions in exons of certain genes (see Table 1), including potential splice site-disrupting events.

***Nonsense mutation:** A point mutation that results in a premature stop codon.

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 74 cancer-associated genes to identify somatic alterations. Cell-free DNA (cfDNA) is extracted from plasma, enriched for targeted regions, and sequenced using the Illumina platform 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 variants, gene amplifications, fusions, short insertions/deletions (longest detected, 70 base pairs), and splice site disrupting events (see Table 1). Microsatellite Instability (MSI) is assessed for all cancer types by evaluating somatic changes in the length of repetitive sequences on the Guardant360 panel. A "Not Detected" result in samples where the highest % cfDNA is < 0.2% is an inconclusive result because it does not preclude MSI-High status in tissue. MSI status is currently not reported for earlier panel versions. 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, such as low cfDNA concentration, may result in reduced analytic sensitivity. Guardant360 cannot discern the source of 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, splice site mutations, and insertion and deletion variants (indels) in all clinically relevant exons in 74 genes and reports other variant types in select genes as indicated below.

AKT1	*ALK* #	*APC*	*AR* †	*ARAF*	*ARID1A*	*ATM*	*BRAF* †	*BRCA1*
BRCA2	*CCND1* †	*CCND2* †	*CCNE1* †	*CDH1*	*CDK12*	*CDK4* †	*CDK6* †	*CDKN2A*
CTNNB1	*DDR2*	*EGFR* †	*ERBB2* †	*ESR1*	*EZH2*	*FBXW7*	*FGFR1* †	*FGFR2* # †
FGFR3 #	*GATA3*	*GNA11*	*GNAQ*	*GNAS*	*HNF1A*	*HRAS*	*IDH1*	*IDH2*
JAK2	*JAK3*	*KIT* †	*KRAS* †	*MAP2K1*	*MAP2K2*	*MAPK1*	*MAPK3*	*MET* †
MLH1	*MPL*	*MTOR*	*MYC* †	*NF1*	*NFE2L2*	*NOTCH1*	*NPM1*	*NRAS*
NTRK1 #	*NTRK3*	*PDGFRA* †	*PIK3CA* †	*PTEN*	*PTPN11*	*RAF1* †	*RB1*	*RET* #
RHEB	*RHOA*	*RIT1*	*ROS1* #	*SMAD4*	*SMO*	*STK11*	*TERT* ‡	*TP53*
TSC1	*VHL*							

‡ Guardant360 reports alterations in the promoter region of this gene.

Guardant360 reports fusion events involving this gene.

† Guardant360 reports amplifications of this gene.

Table 2: Guardant360 Test Specifications

Alterations	Reportable Range	Allelic Fraction/ Copy Number	Analytical Sensitivity	PPV*
SNVs	≥0.04%	0.5-100%	100%	100%
		0.1-0.5%	88.3%	99.4%
Indels	≥0.04%	0.5-100%	99.8%	100%
		0.1-0.5%	73.9%	100%
Fusions**	≥0.04%	0.3-100%	100%	100%
		0.05-0.3%	90.8%	100%
CNAs***	≥2.14 copies	≥2.3 copies	100%	99.6%
MSI	MSI-H DETECTED	>0.1%	95.0%	100%

Based on cell-free DNA input of 30 ng in patient samples or contrived samples. Analytical sensitivity cited above are for targeted, clinically important regions. Sensitivity outside these regions or in highly repetitive sequence contexts may vary.

*Over entire genomic reportable range of Guardant360 panel.

**Based on fusion detection in *ALK*, *NTRK1*, *RET*, *ROS1*.

***Based on *ERBB2* (HER2) and *MET* analytical sensitivity. Copy number sensitivity may vary with other genes.

Regions with insufficient coverage

The following targeted regions failed to meet the minimum coverage required for reliable detection of single nucleotide, insertion-deletion, and fusion variants: None.

About the Test

The 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 interpreted in the context of other clinical information and 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. Drug and trial information are based on the diagnosis 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 the indicated 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 A0297423 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.