REPORTING

Original Report Date:	JAN-27-2018
Corrected Date:	OCT-24-2018
Receipt Date:	JAN-20-2018
Collection Date:	JAN-19-2018
Specimen:	Blood
Status:	CORRECTED

PHYSICIAN

Jamie Chaft

Account: Memorial Sloan Kettering Cancer Center - 53rd St

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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)
ERBB2 (HER2) Amplification	High (+++)	~ Ado-trastuzumab emtansine, Afatinib, Lapatinib, Neratinib, Pertuzumab, Trastuzumab	Yes
TP53 R273S	9.9%	None	Yes
KRAS Amplification	Low (+)	None	Yes
CCNE1 Amplification	Low (+)	None	Yes
DDR2 C784*	2.6%	None	No

Variants of Uncertain Significance

CDK6 R31S (9.0%), *SMAD4* S171L (0.2%)

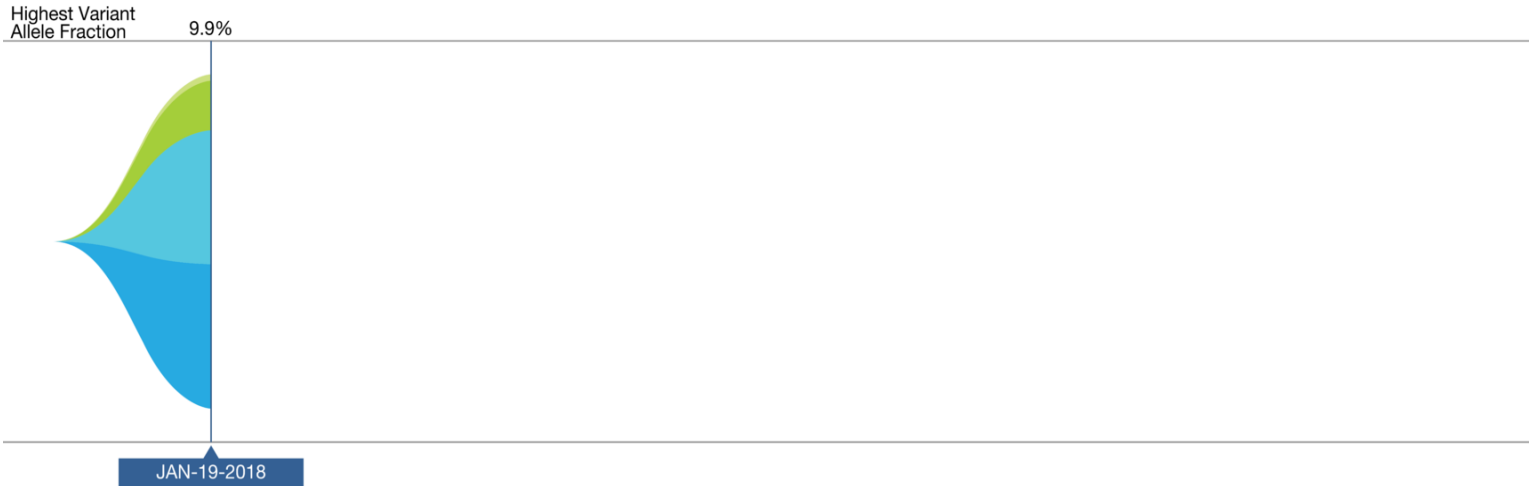
The functional consequences and clinical significance of alterations are unknown. Relevance of therapies targeting these alterations is uncertain.

We evaluated 73 genes, including the following guideline-recommended genes for NSCLC:

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

Guardant360 Tumor Response Map

The Guardant360 Tumor Response Map illustrates the variant allele fraction (% 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 R273S	9.9%	
CDK6 R31S	9.0%	Variant of Uncertain Significance §
DDR2 C784*	2.6%	
SMAD4 S171L	0.2%	Variant of Uncertain Significance §
ERBB2 (HER2) Amplification Amplifications not graphed above	High (+++) Plasma Copy Number: 8.0	
KRAS Amplification Amplifications not graphed above	Low (+) Plasma Copy Number: 2.4	
CCNE1 Amplification Amplifications not graphed above	Low (+) Plasma Copy Number: 2.3	

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 A86684 in the subject line of the email, for additional trials.

Alteration	Trial ID / Contact	Title	Phase	Site(s)
ERBB2 (HER2) Amplification	NCT02091141 California only-PARTICIPATE AT HOME-keep your doctor-For prompt reply contact SCIENCE 37 (213) 529-0657; mypathway@science37.com, Roche ID: ML28897; global-roche-genentech-trials@roche.com, 888-662-6728 (U.S. and Canada)	MY PATHWAY – AN OPEN-LABEL PHASE IIA STUDY EVALUATING TRASTUZUMAB/PERTUZUMAB, ERLOTINIB, VEMURAFENIB/COBIMETINIB, VISMODEGIB, ALECTINIB, AND ATEZOLIZUMAB IN PATIENTS WHO HAVE ADVANCED SOLID TUMORS WITH MUTATIONS OR GENE EXPRESSION ABNORMALITIES PREDICTIVE OF RESPONSE TO ONE OF THESE AGENTS	Phase 2	New York, New York (2)
	NCT02465060	NCI-MATCH: Targeted Therapy Directed by Genetic Testing in Treating Patients With Advanced Refractory Solid Tumors, Lymphomas, or Multiple Myeloma	Phase 2	Bronx, New York (4) Brooklyn, New York Buffalo, New York Glens Falls, New York Additional trial sites available
	NCT02564900 (For Japan sites only) Daiichi Sankyo Contact for Clinical Trial Information, dsclinicaltrial@daiichisankyo.co.jp, +81-3-6225-1111(M-F 9-5 JST)	Study of DS-8201a in Subjects With Advanced Solid Malignant Tumors	Phase 1	New York, New York
	NCT02675829 Bob Li, MD, 646-888-4201	Trial of Ado-Trastuzumab Emtansine for Patients With HER2 Amplified or Mutant Cancers	Phase 2	New York, New York
	Visit portal.guardanthealth.com for trials not within the same state as the physician's office			
TP53 R273S	NCT02134067 Takekazu Aoyama, MD, PhD, aoyama@taihopui.com, 609-750-5331	Dose-escalating, Safety, Tolerability and PK Study of TAS-119 in Combination With Paclitaxel in Patients With Advanced Solid Tumors	Phase 1	New York, New York
	Visit portal.guardanthealth.com for trials not within the same state as the physician's office			
KRAS Amplification	NCT02711345 Novartis Pharmaceuticals, Novartis.email@novartis.com, 1-888-669-6682	A Phase I Clinical Study With Investigational Compound LTT462 in Adult Patients With Specific Advanced Cancers	Phase 1	New York, New York
	NCT03337698 Reference Study ID Number: BO39610 www.roche.com/about_roche/roche_worldwide.htm, global-roche-genentech-trials@gene.com, 888-662-6728 (U.S. and Canada)	A Study Of Multiple Immunotherapy-Based Treatment Combinations In Participants With Metastatic Non-Small Cell Lung Cancer (Morpheus-Non-Small Cell Lung Cancer)	Phase 1/ Phase 2	New York, New York
	Visit portal.guardanthealth.com for trials not within the same state as the physician's office			
CCNE1 Amplification	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.

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.

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

Comments

None

Results reviewed by: Arthur Baca, MD PhD

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. 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, 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 does not preclude MSI-High status in tissue. MSI status is currently not reported for specimens originating from New York State or 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 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.

Table 2: Guardant360 Test Specifications

Alterations	Reportable Range	Allelic Fraction/ Copy Number	Analytical Sensitivity	PPV*
SNVs	≥0.04%	>0.25%	>99.9%	99.6%
		0.05-0.25%	63.8%	92.1%
Indels	≥0.02%	>0.25%	>99.9%	98.0%
		0.05-0.25%	67.8%	88.4%
Fusions	≥0.04%	≥0.3%	100%	100%
		<0.3%	83.0%	100%
CNAs	≥2.12 copies	2.3 copies**	95.0%	100%

Based on cell-free DNA input of 30 ng in patient 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.
**Equivalent to 5% tumor fraction and 8 ERBB2 (HER2) gene copies in tumor. Copy number sensitivity may vary with other genes (2.28 - 2.49 copies).

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: BRCA2 exon 5, RB1 exon 4. Assay sensitivity in these regions may be adversely affected.

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 A86684 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.