REPORTING

Report Date:	JAN-28-2024
Receipt Date:	JAN-23-2024
Collection Date:	JAN-22-2024
Specimen:	Blood
Status:	FINAL

PHYSICIAN

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Additional Recipient: N/A

Complete Tumor Response Map on page 2

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 3)	% cfDNA or Amplification
FGFR3-TACC3 Fusion	✓ Erdafitinib	Yes	2.0%

Comments

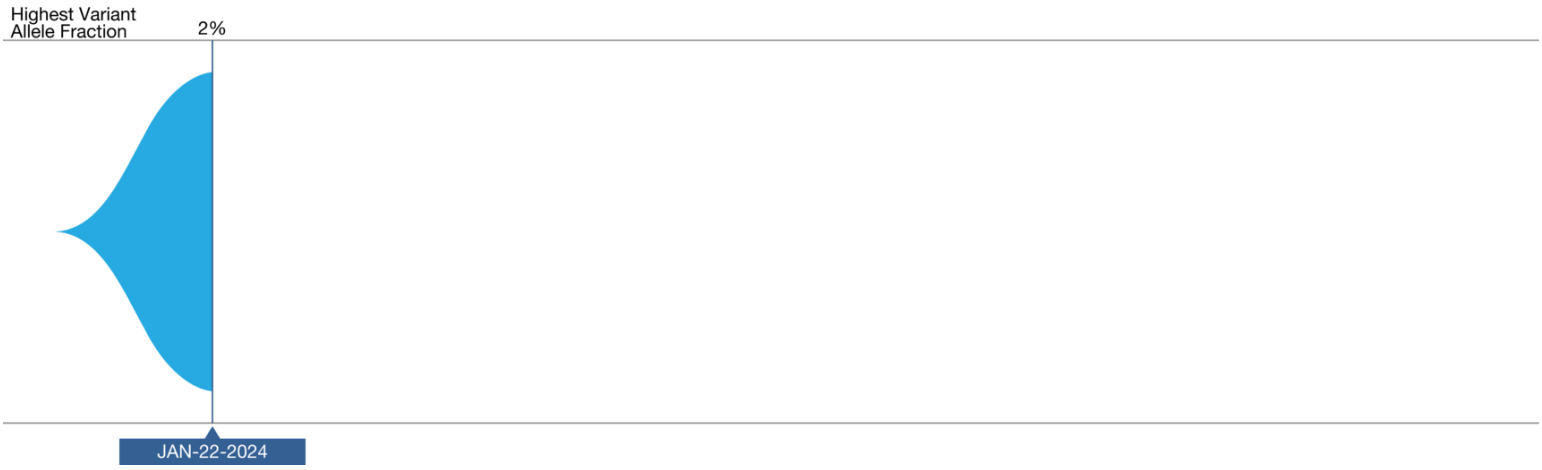
Reported by: DO

Additional Biomarkers

Biomarker	Additional Details
MSI-High	NOT DETECTED

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
FGFR3-TACC3 Fusion	2.0%

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 A0949052 in the subject line of the email, for additional trials.

Alteration	Trial ID / Contact	Title	Phase	Site(s)
FGFR3-TACC3 Fusion	NCT04008797 Eisai Inquiry Service,eisai-chiken_hotline@hhc.eisai.co.jp	A Study of E7386 in Combination With Other Anticancer Drug in Participants With Solid Tumor	Phase 1	Tainan, Taiwan Taoyuan, Taiwan Kao-Hsiung, Taiwan Taipei, Taiwan (2) Additional trial sites available
	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

Fusion: Fusion events are gene rearrangements that fuse two previously distinct genes into a single genetic unit. Guardant360 detects fusions in the genes listed in Table 1.

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.

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: Martina Lefterova, MD PhD | CLIA ID: 05D2070300 | CAP #: 8765297 | 505 Penobscot Drive, Redwood City, CA, 94063, USA

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 A0949052 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)
FGFR3-TACC3 Fusion	NCT04008797 Eisai Inquiry Service,eisai-chiken_hotline@hhc.eisai.co.jp	A Study of E7386 in Combination With Other Anticancer Drug in Participants With Solid Tumor	Phase 1	Los Angeles, CA; Houston, TX; Oklahoma City, OK; West Palm Beach, FL; La Jolla, CA; New York, NY; Aurora, CO; Sarasota, FL; Nashville, TN; Charleston, SC; Santa Monica, CA; Kansas City, MO; Dallas, TX (2); Japan (12); Taiwan (6); Korea, Republic of (5); France (5)
	NCT04565275 Olivia Yang,olivia.yang@INNOCAREPHARMA.COM,+1 (609) 524-0684	A Study of ICP-192 in Patients With Advanced Solid Tumors	Phase 1 /Phase 2	Tucson, AZ; Houston, TX; Minneapolis, MN; La Jolla, CA; Columbus, OH; Lake Success, NY; Aurora, CO; Bronx, NY; Orange City, FL; Australia (7)
	NCT04601857 Taiho Oncology, INC, clinicaltrialinfo@taihooncology.com,1-609-250-7336	Futibatinib and Pembrolizumab Combination in the Treatment of Advanced or Metastatic Urothelial Carcinoma	Phase 2	Las Vegas, NV; Detroit, MI; San Francisco, CA; France (6); Spain (8)
	NCT05544552 Jennifer M Davis,TyraClinicalTrials@tyra.bio,(619)728-4805	Safety and Preliminary Anti-Tumor Activity of TYRA-300 in Advanced Urothelial Carcinoma and Other Solid Tumors With FGFR3 Gene Alterations	Phase 1 /Phase 2	Seattle, WA; Boston, MA; New York, NY; Worcester, MA; Nashville, TN; Durham, NC; France (3); Australia (6); Spain (3)
	NCT05614739 Patient Advocacy, clinicaltrials@loxooncology.com,855-569-6305	A Study of LOXO-435 in Participants With Cancer With a Change in a Gene Called FGFR3	Phase 1	Orlando, FL; Oklahoma City, OK; Philadelphia, PA; Saint Louis, MO; Chicago, IL; Baltimore, MD; Myrtle Beach, SC; Santa Monica, CA; Houston, TX; Duarte, CA; Detroit, MI; Chapel Hill, NC; Boston, MA; Atlanta, GA; Pittsburgh, PA; Dallas, TX; Salt Lake City, UT; Nashville, TN; New York, NY (3); Norway; United Kingdom; France; Canada (2); Japan (4); Korea, Republic of (4); Australia (2); Germany (2); Spain (2)
	NCT05627063 May Litt,may.litt@abbisko.com,+1 5033091243	A Study to Assess Safety, Tolerability, and Pharmacokinetics of ABSK121-NX in Patients With Advanced Solid Tumors	Phase 1	Las Vegas, NV; Detroit, MI; Canton, OH; China (6)

Detailed Therapy Results

Alteration	Drug	Trade Name	Target	Current Status
FGFR3-TACC3 Fusion	ABSK121-NX		Pan-Fgfr inhibitor.	Phase 1 (Solid Tumor)
	AL8326		Aurora kinase B/VEGFRs/Fgfr multi-kinase inhibitor.	Phase 1 (Solid Tumor) Phase 2 (Small cell lung carcinoma (SCLC))
	Anlotinib		Multi-tyrosine kinase inhibitor of VEGFR-1/2/3, Fgfr1-4, Pdgfr-beta, and Kit.	Phase 1 (Solid Tumor) Phase 3 (Gastric carcinoma, Non-small cell lung carcinoma (NSCLC), Thyroid carcinoma, Colorectal carcinoma (CRC), Soft tissue sarcoma)
	AZD4547		Pan-Fgfr inhibitor.	Phase 2 (Urothelial carcinoma) Phase 2 (Gastric carcinoma, Glioma, Non-small cell lung carcinoma (NSCLC), Gastroesophageal junction carcinoma, Esophageal carcinoma, Breast carcinoma, Multiple myeloma (MM), Lung cancer, Upper gastrointestinal carcinoma, Mesothelioma)
	B-701		Anti-Fgfr3 antibody.	Phase 2 (Urothelial carcinoma)
	Debio 1347		Fgfr1/2/3 inhibitor.	Phase 1 (Solid Tumor) Phase 2 (Breast carcinoma)
	Derazantinib		Fgfr1/2/3 inhibitor.	Phase 1 (Solid Tumor) Phase 2 (Cholangiocarcinoma)
	E7090		Fgfr1/2/3 kinase inhibitor.	Phase 1 (Solid Tumor) Phase 2 (Cholangiocarcinoma)
	Erdafitinib	Balversa	Pan-Fgfr inhibitor.	Phase 3 (Urothelial carcinoma) FDA Approved in other indications (Urothelial carcinoma with a susceptible FGFR3 alteration)
	Futibatinib	Lytgobi	Covalent pan-Fgfr kinase inhibitor.	Phase 2 (Urothelial carcinoma) FDA Approved in other indications (FGFR2-rearranged cholangiocarcinoma)
	Gunagratinib		Covalent pan-Fgfr inhibitor.	Phase 2 (Urothelial carcinoma) Phase 2 (Solid Tumor, Brain and Central Nervous System Tumors)
	HMPL-453		Fgfr1/2/3 inhibitor.	Phase 2 (Solid Tumor) Phase 2 (Brain and Central Nervous System Tumors)
	KIN-3248		Irreversible pan-Fgfr inhibitor.	Phase 1 (Urothelial carcinoma) Phase 1 (Solid Tumor, Brain and Central Nervous System Tumors)
	Lenvatinib	Lenvima	Multi-kinase inhibitor targeting VEGF, FGF, and SCF receptors.	Phase 3 (Urothelial carcinoma) FDA Approved in other indications (Thyroid carcinoma, well differentiated, Hepatocellular carcinoma (HCC))
	LOXO-435		Fgfr3-specific inhibitor.	Phase 1 (Urothelial carcinoma) Phase 1 (Solid Tumor)
	Lucitanib		Oral inhibitor of Fgfr1,2,3, VEGFR-1,2,3, Pdgfr-alpha, and Pdgfr-beta.	Phase 2 (Solid Tumor) Phase 2 (Small cell lung carcinoma (SCLC))
	LY2874455		Pan-Fgfr inhibitor.	Phase 1 (Solid Tumor) Phase 1 (Acute myeloid leukemia (AML))
	LY3076226		Anti-Fgfr3 antibody drug conjugate.	Phase 1 (Solid Tumor) Phase 1 (Bladder urothelial (transitional cell) carcinoma)
	Nintedanib	Vargatef	Multitargeted kinase inhibitor (VEGFRs, Fgfrs, Pdgfrs, Lyn, Lck, Src, Ret, Flt3).	Phase 2 (Urothelial carcinoma) FDA Approved in other indications (Idiopathic pulmonary fibrosis)
	ODM-203		Fgfr/VEGFR inhibitor.	Phase 1 (Solid Tumor)

Detailed Therapy Results

Alteration	Drug	Trade Name	Target	Current Status
	Pazopanib	Votrient	VEGFR-1,2,3/Kit/Pdgfrs/Fgfrs small molecule kinase inhibitor.	Phase 2 (Urothelial carcinoma) FDA Approved in other indications (Renal cell carcinoma, Soft tissue sarcoma)
	Pemigatinib	Pemazyre	Fgfr1/2/3 inhibitor.	Phase 2 (Urothelial carcinoma) FDA Approved in other indications (FGFR2-rearranged cholangiocarcinoma, FGFR1-rearranged myeloid /lymphoid neoplasm)
	Ponatinib	Iclusig	Bcr-Abl/VEGFR-1,2,3/Fgfrs/Kit/Tie-2/Flt3 kinase inhibitor.	Phase 2 (Solid Tumor) FDA Approved in other indications (Chronic myeloid leukemia, BCR-ABL1 positive, Acute lymphoblastic leukemia (Ph+) (ALL-Ph+))
	PRN1371		Pan-Fgfr inhibitor.	Phase 1 (Solid Tumor)
	Rogaratinib		Fgfr1/2/3 inhibitor.	Phase 3 (Urothelial carcinoma) Phase 2 (Lung squamous cell carcinoma)
	TT-00434		Fgfr1/2/3 inhibitor.	Phase 1 (Solid Tumor)
	TYRA-300		Fgfr3-specific inhibitor.	Phase 2 (Solid Tumor)

Relevance of Detected Alterations

Alteration	Role in Disease	Effect on Drug Sensitivity	Effect on Drug Resistance
FGFR3-TACC3 Fusion	Gain of function mutations in FGFRs have been reported in several cancer types. [1,2]. The presence of an FGFR3 abnormality (mutation, amplification, or overexpression) can result in an overabundance or overactivity of Fgfr3 protein, which may drive tumorigenesis. [3-5]. FGFR3 mutation has been associated with Fgfr3 overexpression in bladder urothelial carcinoma samples, although Fgfr3 overexpression without FGFR3 mutation has also been reported in muscle-invasive tumors. [6-8]. FGFR3 mutations have been reported to occur early during bladder urothelial transformation, and to be more frequent in low stage and low grade bladder lesions. [8-16]. FGFR3 mutations have been significantly correlated with TERT promoter mutations, and shorter relative telomere lengths as compared with non-mutated samples, in a cohort of 327 bladder urothelial carcinoma samples. [17].	FGFR3 amplification or mutations may lead to activation of Fgfr3 and may therefore confer sensitivity to Fgfr family inhibitors. [3,18]. Erdafitinib is a pan-FGFR inhibitor that has been FDA-approved for the treatment of patients with locally advanced or metastatic urothelial carcinoma who experienced disease progression during or after at least one line of systemic therapy and have a susceptible FGFR3 alteration, as determined by an FDA-approved companion diagnostic test. Erdafitinib is not recommended for the treatment of patients who are eligible for and have not received prior PD-1/PD-L1 inhibitor therapy [19]. Several multi-kinase inhibitors that target Fgfrs, including pazopanib, ponatinib, and lenvatinib, have been approved for certain indications and continue to be studied in clinical trials. [20-24]. Additional agents that target Fgfrs are also being studied in clinical trials. [25-31].	Preclinical and clinical studies suggest that FGFR3-TACC3 fusion may result in resistance to Egfr-targeted therapies. [32,33].

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