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Email: custcare@biodesix.com

PATIENT & PHYSICIAN INFORMATION

Patient:
First Last

MRN:
1010100

Physician:
Dr. First Last

Date of Birth:
Sep 04, 1990

Gender:
Male

Facility:
Order Facility

Tumor:
Lung

Specimen Type:
Whole Blood

Address:
Street Address, City, State, Country

GSNGS Accession No:
GSNGSXXXXXXXXXX

Stage:
Advanced

Phone:
000-000-0000

Fax:
000-000-0000

External Specimen ID:
1234567

Date Collected:
Sep 24, 2023

Date Received:
Sep 25, 2023

Date Reported:
Sep. 25, 2023

GENESTRAT NGS® TEST RESULTS

Relevant Biomarkers

Tier	Genomic Alteration	Relevant Therapies (In this cancer type)	Relevant Therapies (In other cancer type)	Clinical Trials
IA	*EGFR L858R* Allele Frequency: 0.75%	**afatinib** [1] **dacomitinib** [1] **erlotinib** [1] **erlotinib + ramucirumab** [1] **gefitinib** [1] **osimertinib** [1] bevacizumab + erlotinib	None	21

Public data sources included in relevant therapies: FDA[1], NCCN

See "Classification and Levels of Evidence" section for tier definitions.

Alerts informed by public data sources: Contraindicated, Resistance, Breakthrough, Fast Track, Not recommended

EGFR L858R	**patritumab deruxtecan** [1]

Public data sources included in alerts: FDA[1], NCCN

LABORATORY DIRECTOR

Donald Joe Chaffin, M.D., CAP Accredited CLIA Laboratory Director

The Laboratory Director approval applies to the detection of the molecular variants in this assay.

GENESTRAT NGS® PANEL DETAILS

Relevant Lung Cancer Findings

Gene	Finding	Gene	Finding
ALK	None detected	MET	None detected
BRAF	None detected	NTRK1	None detected
EGFR	***EGFR L858R***	NTRK3	None detected
ERBB2	None detected	RET	None detected
KRAS	None detected	ROS1	None detected

Genes Assayed

Single Nucleotide Variants (SNVs) and Insertion/Deletions (Indels): AKT1, ALK, APC, AR, ARAF, BRAF, CHEK2, CTNNB1, DDR2, EGFR, ERBB2 (HER2), ERBB3, ESR1, FGFR1, FGFR2, FGFR3, FGFR4, FLT3, FBXW7, GNA11, GNAQ, GNAS, HRAS, IDH1, IDH2, KIT, KRAS, MAP2K1, MAP2K2, MET, MTOR, NRAS, NTRK1, NTRK3, PDGFRA, PIK3CA, PTEN, RAF1, RET, ROS1, SF3B1, SMAD4, SMO, TP53

Fusions and Skipping Variants: ALK, BRAF, ERG, ETV1, FGFR1, FGFR2, FGFR3, MET, NTRK1, NTRK3, RET, ROS1

Copy Number Amplifications: CCND1, CCND2, CCND3, CDK4, CDK6, EGFR, ERBB2 (HER2), FGFR1, FGFR2, FGFR3, MET, MYC

Biomarker Descriptions

EGFR (epidermal growth factor receptor)

Background: The EGFR gene encodes the epidermal growth factor receptor (EGFR) tyrosine kinase, a member of the ERBB/human epidermal growth factor receptor (HER) family. In addition to EGFR/ERBB1/HER1, other members of the ERBB/HER family include ERBB2/HER2, ERBB3/HER3, and ERBB4/HER4[1]. EGFR ligand induced dimerization results in kinase activation and leads to stimulation of oncogenic signaling pathways including the PI3K/AKT/MTOR and RAS/RAF/MEK/ERK pathways. Activation of these pathways promote cell proliferation, differentiation, and survival[2,3].

Alterations and prevalence: Recurrent somatic mutations in the tyrosine kinase domain (TKD) of EGFR are observed in approximately 10-20% of lung adenocarcinoma, and at higher frequencies in never-smoker, female, and Asian populations[4,5,6,7]. The most common mutations occur near the ATP-binding pocket of the TKD and include short in-frame deletions in exon 19 (EGFR exon 19 deletion) and

Biomarker Descriptions (continued)

the L858R amino acid substitution in exon 21[8]. These mutations constitutively activate EGFR resulting in downstream signaling, and represent 80% of the EGFR mutations observed in lung cancer. A second group of less prevalent activating mutations include E709K, G719X, S768I, L861Q, and short in-frame insertion mutations in exon 20[9,10,11,12]. EGFR activating mutations in lung cancer tend to be mutually exclusive to KRAS activating mutations[13]. In contrast, a different set of recurrent activating EGFR mutations in the extracellular domain include R108K, A289V and G598V and are primarily observed in glioblastoma[8,14]. Amplification of EGFR is observed in several cancer types including 30% of glioblastoma, 12% of esophageal cancer, 10% of head and neck cancer, 5% of bladder cancer, and 5% of lung squamous cell carcinoma[5,6,7,14,15]. Deletion of exons 2-7, encoding the extracellular domain of EGFR (EGFRvIII), results in overexpression of a ligand-independent constitutively active protein and is observed in approximately 30% of glioblastoma[16,17,18].

Potential relevance: Approved first-generation EGFR tyrosine kinase inhibitors (TKIs) include erlotinib[19] (2004) and gefitinib[20] (2015), which block the activation of downstream signaling by reversible interaction with the ATP-binding site. Although initially approved for advanced lung cancer, the discovery that drug sensitivity was associated with exon 19 and exon 21 activating mutations allowed first-generation TKIs to become subsequently approved for front-line therapy in lung cancer tumors containing exon 19 or exon 21 activating mutations. Second-generation TKIs afatinib[21] (2013) and dacomitinib[22] (2018) bind EGFR and other ERBB/HER gene family members irreversibly and were subsequently approved. First- and second-generation TKIs afatinib, dacomitinib, erlotinib, and gefitinib are recommended for the treatment NSCLC harboring EGFR exon 19 insertions, exon 19 deletions, point mutations L861Q, L858R, S768I, and codon 719 mutations, whereas most EGFR exon 20 insertions, except p.A763_Y764insFQEA, confer resistance to the same therapies[23,24,25,26]. However, in 2021, the irreversible tyrosine kinase inhibitor, mobocertinib[27]was FDA approved for the treatment of NSCLC with EGFR exon 20 insertion mutations. Additionally, in 2022, the FDA granted breakthrough therapy designation to the irreversible EGFR inhibitors, CLN-081 (TPC-064)[28] and sunvozertinib[29], for locally advanced or metastatic non-small cell lung cancer harboring EGFR exon 20 insertion mutations. In lung cancer containing EGFR exon 19 or 21 activating mutations, treatment with TKIs is eventually associated with the emergence of drug resistance[30]. The primary resistance mutation that emerges following treatment with first-generation TKI is T790M, accounting for 50-60% of resistant cases[8]. Third generation TKIs were developed to maintain sensitivity in the presence of T790M. Osimertinib[31] (2015) is an irreversible inhibitor indicated for metastatic EGFR T790M positive lung cancer and for the first-line treatment of metastatic NSCLC containing EGFR exon 19 deletions or exon 21 L858R mutations. Like first-generation TKIs, treatment with osimertinib is associated with acquired resistance. In this case, resistance is associated with the C797S mutation and occurs in 22-44% of cases[30]. The T790M and C797S mutations may be each selected following sequential treatment with a first-generation TKI followed by a third-generation TKI or vice versa[32]. T790M and C797S can occur in either cis or trans allelic orientation[32]. If C797S is observed following progression after treatment with a third-generation TKI in the first-line setting, sensitivity may be retained to first-generation TKIs[32]. If C797S co-occurs in trans with T790M following sequential treatment with first- and third-generation TKIs, patients may exhibit sensitivity to combination first- and third-generation TKIs, but resistance to third-generation TKIs alone[32,33]. However, C797S occurring in cis conformation with T790M, confers resistance to first- and third-generation TKIs[32]. Fourth-generation TKIs are in development to overcome acquired C797S and T790M resistance mutations after osimertinib treatment. EGFR targeting antibodies including cetuximab (2004), panitumumab (2006), and necitumumab (2016) are under investigation in combination with EGFR-targeting TKIs for efficacy against EGFR mutations. The bispecific antibody, amivantamab[34], targeting EGFR and MET was approved (2021) for NSCLC tumors harboring EGFR exon 20 insertion mutations. CPO301[35] received a fast track designation (2023) from the FDA for EGFR mutations in patients with metastatic NSCLC who are relapsed/refractory or ineligible for EGFR targeting therapy such as 3rd-generation EGFR inhibitors including osimertinib. The Oncoprex immunogene therapy quaratusugene ozeplasmid[36] in combination with osimertinib received a fast track designation from the FDA (2020) for NSCLC tumors harboring EGFR mutations that progressed on osimertinib alone. BDTX-189[37] was granted a fast track designation (2020) for the treatment of solid tumors harboring an EGFR exon 20 insertion mutation.

Clinical Trials Summary

EGFR L858R

NCT ID	Title	Phase
NCT04988295	A Phase III, Open-Label, Randomized Study of Amivantamab and Lazertinib in Combination With Platinum-Based Chemotherapy Compared With Platinum-Based Chemotherapy in Patients With EGFR-Mutated Locally Advanced or Metastatic Non-Small Cell Lung Cancer After Osimertinib Failure	III
NCT03833154	A Phase III, Randomized, Placebo-controlled, Double-blind, Multi-center, International Study of Durvalumab With Stereotactic Body Radiation Therapy (SBRT) for the Treatment of Patients With Unresected Stage I/II, Lymph-node Negative Non-small Cell Lung Cancer (PACIFIC-4/RTOG-3515)	III
NCT05120349	A Phase III, Double-blind, Randomised, Placebo-Controlled, International Study to Assess the Efficacy and Safety of Adjuvant Osimertinib Versus Placebo in Participants With EGFR Mutation-positive Stage IA2-IA3 Non-small Cell Lung Cancer, Following Complete Tumour Resection	III
NCT04181060	Randomized Phase III Study of Combination Osimertinib (AZD9291) and Bevacizumab Versus Osimertinib (AZD9291) Alone as First-Line Treatment for Patients With Metastatic EGFR-Mutant Non-Small Cell Lung Cancer (NSCLC)	III
NCT04351555	A Phase III, Randomised, Controlled, Multi-center, 3-Arm Study of Neoadjuvant Osimertinib as Monotherapy or in Combination With Chemotherapy Versus Standard of Care Chemotherapy Alone for the Treatment of Patients With Epidermal Growth Factor Receptor Mutation Positive, Resectable Non-small Cell Lung Cancer	III
NCT04765059	A Phase III, Randomized, Double-Blind, Placebo-Controlled Study of Platinum Plus Pemetrexed Chemotherapy Plus Osimertinib Versus Platinum Plus Pemetrexed Chemotherapy Plus Placebo in Patients With EGFRm, Locally Advanced or Metastatic NSCLC Who Have Progressed Extracranially Following First-Line Osimertinib Therapy (COMPEL)	III
NCT05338970	HERTHENA–Lung02: Phase III, Randomized, Open-label Study of Patritumab Deruxtecan Versus Platinum-Based Chemotherapy in Metastatic or Locally Advanced Non-Small Cell Lung Cancer (NSCLC) With Epidermal Growth Factor Receptor (EGFRm) Mutation After Failure treatment with epidermal growth factor (EGFR) tyrosine kinase inhibitors (TKIs)	III
NCT05261399	A Phase III, Randomised, Open-Label Study of Savolitinib in Combination With Osimertinib Versus Platinum-Based Doublet Chemotherapy in Participants With EGFR Mutated, MET-Overexpressed and/or Amplified, Locally Advanced or Metastatic Non-Small Cell Lung Cancer Who Have Progressed on Treatment With Osimertinib (SAFFRON).	III
NCT05498428	A Phase II, Open-Label, Parallel Cohort Study of Subcutaneous Amivantamab in Multiple Regimens in Patients With Advanced or Metastatic Solid Tumors Including EGFR-mutated Non-Small Cell Lung Cancer	II
NCT03586453	A Phase II Study of Osimertinib With On-study and Post-progression Biopsy in the First Line Treatment of EGFR Inhibitor naive Advanced EGFR Mutant Lung Cancer	II
NCT05526755	An Open-label, Single-arm, Phase II, Multinational, Multicentre Study to Assess the Efficacy and Safety of 5 Years of Osimertinib in Participants With EGFRm-positive Stage II-IIIB NSCLC, Following Complete Tumour Resection with or Without Adjuvant Chemotherapy	II

Clinical Trials Summary (continued)

EGFR L858R (continued)

NCT ID	Title	Phase
NCT03778229	A Phase II Study Assessing the Efficacy of Osimertinib in Combination With Savolitinib in Patients With EGFRm+ and MET+, Locally Advanced or Metastatic Non Small Cell Lung Cancer Who Have Progressed Following Treatment With Osimertinib.	II
NCT04940299	A Phase II Study to Assess the Safety and Efficacy of Tocilizumab in Combination With Ipilimumab and Nivolumab in Patients With Advanced Melanoma, Non-Small Cell Lung Cancer, or Urothelial Carcinoma	II
NCT04965090	A Phase II Single-Arm Study of Amivantamab (JNJ-61186372) and Lazertinib in Metastatic EGFR-mutant Lung Cancer With Progressive or New CNS Metastases on Previous Treatment	II
NCT05642572	A Randomized Phase II Study of INC280 (Capmatinib) Plus Osimertinib With or Without Ramucirumab in Participants With EGFR-Mutant, MET-Amplified Stage IV or Recurrent Non-Small Cell Lung Cancer (Lung-MAP Sub-Study)	II
NCT03944772	A Biomarker-directed Phase II Platform Study in Patients with Advanced Non-Small Lung Cancer Whose Disease Has Progressed on First-Line Osimertinib Therapy	II
NCT04120454	An Investigator-Sponsored Phase II Single Arm Trial of Ramucirumab and Pembrolizumab in Patients With EGFR Mutant Non-Small Cell Lung Cancer	II
NCT05184712	A Randomized, Double-blind, Multi-center, Phase III Study of AK112 or Placebo Combined With Pemetrexed and Carboplatin in Patients With EGFR-mutant Locally Advanced or Metastatic Non-squamous NSCLC Who Have Failed to EGFR-TKI Treatment	III
NCT04958811	A Phase II Open-label Multi-cohort Study Evaluating the Efficacy of Tiragolumab With Atezolizumab Plus Bevacizumab in Previously-Treated Advanced Non-squamous NSCLC	II
NCT03786692	TH-138: Phase II Randomized Trial of Carboplatin + Pemetrexed + Bevacizumab, With or Without Atezolizumab in Stage IV Non-squamous NSCLC Patients Who Harbor a Sensitizing EGFR Mutation or Have Never Smoked	II
NCT04410796	A Phase II Randomized Study of Osimertinib Versus Osimertinib Plus Chemotherapy for Patients With Metastatic EGFR-Mutant Lung Cancers That Have Detectable EGFR-Mutant cfDNA in Plasma After Initiation of Osimertinib	II

Note: Phase I clinical trials are not included if available.

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CLASSIFICATION AND LEVELS OF EVIDENCE

The variant classification system used in this report is based on joint consensus recommendations of the Association for Molecular Pathology, American Society of Clinical Oncology, and the College of American Pathologists. Tiers IA, IB, IIC, and IID are reported in descending order of clinical importance, and Tiers III and IV are not reported.

IA	IB	IIC	IID
Variants with strong clinical significance	*Variants with strong clinical significance*	*Variants with potential clinical significance*	*Variants with potential clinical significance*
Level A variants have an FDA-approved therapy and are included in professional guidelines for patient's tumor type.	Level B variants have well-powered studies with consensus from experts in the field for patient's tumor type.	Level C variants have FDA-approved therapies for different tumor types or investigational therapies. Multiple small, published studies with some consensus.	Level D variants have preclinical trials or a few case reports without consensus.

III: Variants of unknown clinical significance. | **IV:** Variants deemed benign or likely benign.

References: Li M. et al. *JMD.* Volume 19, Issue 1, P4-23, January 2017. | Li M. et al. *JMD.* Volume 25, Issue 2, P69-86, February 2023.

GENESTRAT NGS® ANALYSIS DESCRIPTION

TEST DESCRIPTION: The GeneStrat NGS genomic test is a qualitative laboratory developed test designed to aid physicians by providing molecular characterization of cancer patients' disease. The test has been validated for the detection of somatic mutations from cell-free DNA and RNA (cfDNA and cfRNA) derived from plasma samples using established targeted next generation sequencing methodology.

LIMITATIONS AND DISCLAIMER:
- Specific validated SNV and indel variant types relevant to oncology are reported from the genes assayed.
- The test has been validated to 0.5% Variant Allele Frequency for SNVs and indels.
- The limit of detection for fusion/skipping variants and copy number amplifications were 42 copies and 1.4 fold change, respectively.
- Reported variants may be either somatic (not inherited) or germline (inherited). The GeneStrat NGS genomic test cannot discern the source of the cfDNA and cfRNA, and for some variants in the range of ~40 to 60% minor allele frequency, the test cannot easily distinguish germline variants from somatic alterations. If a reported alteration is suspected to be germline, confirmatory testing should be considered.
- Variants found in circulation may be due to clonal hematopoiesis of indeterminate potential (CHIP). Accordingly, results are adjunctive to the ordering physician's workup and should be evaluated by a qualified healthcare professional in combination with the patient's clinical history, other diagnostic tests, and clinicopathological factors.
- For patients that test negative for all variants, tissue based testing is recommended.
- The GeneStrat NGS genomic test was developed and its performance characteristics determined by Biodesix, Inc. as a laboratory developed test. It has not been cleared or approved by the U.S. Food and Drug Administration. The FDA does not require this test to go through premarket FDA review. This test is used for clinical purposes and should not be regarded as investigational or for research. This laboratory is certified under the Clinical Laboratory Improvement Amendments (CLIA) as qualified to perform high-complexity clinical laboratory testing.
- The GeneStrat NGS genomic test results are intended to assist with decisions related to patient management and provide supplementary information. This test is not a stand-alone diagnostic assay.
- Values obtained with a different assay method or kit cannot be used interchangeably.
- Results cannot be interpreted as absolute evidence of the presence or absence of malignant disease.

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