BELAY DIAGNOSTICS

Date: 07/18/2025
Order ID: CASE 5 LUNG CANCER

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Summit™ Report

Patient Information	Provisional Diagnosis	Specimen	Physician Information
Name: John Smith **DOB:**01/01/2000 **Sex Assigned at Birth:**Male **MRN:**11xx22xx33	**Diagnosis:**Metastatic Lung Adenocarcinoma; Central Nervous System Neoplasm **ICD10:**C79.31, C79.49	**Type:**CSF **Collected:**7/2/2025 **Received:**7/3/2025 **Specimen ID:**CASE 5 LUNG CANCER	**Institution:**Belay Diagnostics **Referring Physician:**Provider Test

RESULT SUMMARY

POSITIVE

Clinically Significant Alterations Detected	*EGFR* E746_P753delinsVS (Tier 1A)
	TP53 E258* (Tier 1A)

Actionability Summary	6 therapeutic responses
	10 trials

Comments

Tumor profiling results from an outside lab for this individual were compared to Summit™ results.

Summit™ detected the previously reported variants in the *EGFR* and *TP53* genes, as well as amplification of chr7q, which includes the *MET* gene, in this sample. Additional variants previously reported in the *ATR*, *CHEK2*, and *DNMT3A* genes are not currently evaluated by Summit™.

While no aneuploidy of clinical significance was detected, a high level of chromosomal loss and gain was observed in this sample.

ALTERATION DETAILS

Clinically Significant Genomic Variants

Alteration	VAF	Type of Alteration	Classification	Clinical Implications
TP53 p.E258* c.772G>T	37.3%	Substitution - Nonsense	Tier 1A	Potentially Relevant Clinical Trials; Diagnostic Implications
EGFR p. E746_P753delinsVS c.2237_2257delinsTCT	56.4%	Complex - deletion inframe	Tier 1A	Associated with Drug Response; Potentially Relevant Clinical Trials; Diagnostic Implications

Aneuploidy Variants (Chromosome Arm Level Loss or Gain): *None*

Clinical Implications: Associated with drug response = related to drug sensitivity or resistance as described in Drug Response section of this report; Potentially relevant clinical trials = gene is related to a trial in the Clinical Trials section of this report; Prognostic Implications = related to prognosis as described in Prognostic Implications section of this report; Diagnostic Implications = related to diagnosis as described in Diagnostic Implications
VAF: Variant Allelic Frequency

Variants of Unknown Significance (Tier 3)

chr10q Loss	chr15q Loss	chr19q Gain	chr4p Gain	chr7q Gain
chr11p Loss	chr16p Loss	chr1q Gain	chr4q Gain	chr8p Loss
chr11q Gain	chr17p Loss	chr20p Loss	chr5p Loss	chr8q Loss
chr12p Gain	chr17q Gain	chr20q Gain	chr5q Gain	chr9p Loss
chr12q Loss	chr18p Loss	chr22q Loss	chr6p Gain	chr9q Loss
chr13q Loss	chr18q Loss	chr2p Gain	chr6q Gain	
chr14q Gain	chr19p Loss	chr2q Gain	chr7p Gain	

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FDA / NCCN Therapies for the Patient's Tumor Type (Tier 1A)			
Biomarker	**Therapies**	**Setting**	**Source(s)**
EGFR E746_P753delinsVS	afatinib; dacomitinib; gefitinib; osimertinib	First line	FDA (Approved), NCCN
EGFR E746_P753delinsVS	erlotinib	Metastatic	FDA (Approved), NCCN
EGFR E746_P753delinsVS	osimertinib	Consolidation	FDA (Approved)

FDA / NCCN Therapies with Resistance / Decreased Response (Tier 1A): *None*

Prognostic Implications per NCCN: *None*

Diagnostic Implications per WHO		
Biomarker	**Diseases**	**Note**
EGFR E746_P753delinsVS	Central Nervous System Neoplasm	EGFR mutations and fusions have been observed in several central nervous system neoplasms. In glioblastoma, IDH-wildtype, about 60% of tumors show evidence of EGFR amplification, mutation, rearrangement, or altered splicing (PMID:24120142), with mutations/fusions often co-occuring with amplification. EGFR gene fusions are observed in 6-13% of cases, typically as part of complex rearrangements at chromosome band 7p11.2 (PMID: 24120142). Fusion partners are mostly neighboring genes of EGFR (e.g. SEPTIN14, PSPH, SEC61G, SDK1). EGFR mutations also define an EGFR-mutant sub-type of diffuse midline glioma, H3 K27-altered. Within EGFR-mutant DMG, most tumors harbor small in-frame insertions/duplications within exon 20, which encodes the intracellular tyrosine kinase domain, whereas others harbor missense mutations in exons encoding parts of the extracellular domain, most commonly p.A289T or p.A289V. EGFR mutations have also been observed in diffuse pediatric-type high-grade glioma, H3-wildtype and IDH-wildtype.
TP53 E258*	Central Nervous System Neoplasm	Among central nervous system neoplasms, detection of TP53 mutations is an essential diagnostic criterion in the diagnosis of medulloblastoma, SHH-activated and TP53-mutant. TP53 mutations are reported in 10-15% of SHH-activated medulloblastomas, over half of which are germline. TP53 mutations are also desirable in the diagnoses of choroid plexus carcinoma (CPC) and astrocytoma, IDH-mutant. About 50% of CPCs carry TP53 mutations, whereas most IDH-mutant astrocytomas show widespread (> 50%) p53 expression (PMID:25040820).

CLINICAL TRIALS / INVESTIGATIONAL THERAPIES

***EGFR* E746_P753delinsVS**		
Therapy	**Clinical Trial**	**Location/Sponsor**
amivantamab + lazertinib + carboplatin + pemetrexed; amivantamab + lazertinib; amivantamab + carboplatin + pemetrexed	NCT05498428 (Phase 2) A Study of Amivantamab in Participants With Advanced or Metastatic Solid Tumors Including Epidermal Growth Factor Receptor (EGFR)-Mutated Non-Small Cell Lung Cancer	La Jolla, California Janssen Research & Development, LLC Participate-In-This-Study1@its.jnj.com
amivantamab + lazertinib + chlorhexidine + clindamycin + (doxycycline or minocycline); amivantamab + lazertinib + ruxolitinib + chlorhexidine + clindamycin + (doxycycline or minocycline); amivantamab + lazertinib + tacrolimus + chlorhexidine + clindamycin + (doxycycline or minocycline)	NCT06120140 (Phase 2) Enhanced Dermatological Care to Reduce Rash and Paronychia in Epidermal Growth Factor Receptor (EGRF)-Mutated Non-Small Cell Lung Cancer (NSCLC) Treated First-line With Amivantamab Plus Lazertinib	Chandler, Arizona Janssen Research & Development, LLC Participate-In-This-Study1@its.jnj.com
amivantamab + lazertinib; amivantamab + (carboplatin or pemetrexed)	NCT06667076 (Phase 2) A Study of Amivantamab in Combination With Lazertinib, or Amivantamab in Combination With Platinum-Based Chemotherapy, for Common Epidermal Growth Factor Receptor (EGFR)-Mutated Locally Advanced or Metastatic Non-Small Cell Lung Cancer (NSCLC)	Daphne, Alabama Janssen Research & Development, LLC Participate-In-This-Study1@its.jnj.com
bevacizumab + osimertinib	NCT04181060 (Phase 3) Osimertinib With or Without Bevacizumab as Initial Treatment for Patients With EGFR-Mutant Lung Cancer	Dublin, California National Cancer Institute (NCI)

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cetrelimab + amivantamab	NCT05908734 (Phase 1/Phase 2) A Study of Combination Therapy With Amivantamab and Cetrelimab in Participants With Metastatic Non-small Cell Lung Cancer	Duarte, California Janssen Research & Development, LLC Participate-In-This-Study1@its.jnj.com
datopotamab deruxtecan + osimertinib; datopotamab deruxtecan	NCT06417814 (Phase 3) *FDA Breakthrough Therapy* *FDA Priority Review* A Study to Investigate the Efficacy and Safety of Dato-DXd With or Without Osimertinib Compared With Platinum Based Doublet Chemotherapy in Participants With EGFR-Mutated Locally Advanced or Metastatic Non-Small Cell Lung Cancer	Fayetteville, Arkansas AstraZeneca information.center@astrazeneca.com
rilvegostomig + pemetrexed + platinum doublet	NCT06627647 (Phase 3) A Global Phase III Study of Rilvegostomig or Pembrolizumab Plus Chemotherapy for First-Line Treatment of Metastatic Non-squamous NSCLC	Anaheim, California AstraZeneca information.center@astrazeneca.com
sacituzumab tirumotecan	NCT06074588 (Phase 3) *FDA Breakthrough Therapy* Sacituzumab Tirumotecan (MK-2870) Versus Chemotherapy in Previously Treated Advanced or Metastatic Nonsquamous Non-small Cell Lung Cancer (NSCLC) With EGFR Mutations or Other Genomic Alterations (MK-2870-004)	Los Angeles, California Merck Sharp & Dohme LLC Trialsites@msd.com
sacituzumab tirumotecan + dexamethasone + acetaminophen + histamine H1 antagonists + histamine H2 antagonists	NCT06305754 (Phase 3) Sacituzumab Tirumotecan (MK-2870) Versus Pemetrexed and Carboplatin Combination Therapy in Participants With Epidermal Growth Factor (EGFR)-Mutated, Advanced Nonsquamous Non-small Cell Lung Cancer (NSCLC) Who Have Progressed on Prior EGFR Tyrosine Kinase Inhibitors (MK-2870-009)	Oakland, California Merck Sharp & Dohme LLC Trialsites@msd.com

TP53* E258		
Therapy	**Clinical Trial**	**Location/Sponsor**
anti-KRAS and anti-TP53 peripheral blood lymphocytes + aldesleukin + cyclophosphamide + fludarabine; anti-KRAS and anti-TP53 peripheral blood lymphocytes + pembrolizumab + aldesleukin + cyclophosphamide + fludarabine	NCT03412877 (Phase 2) Administration of Autologous T-Cells Genetically Engineered to Express T-Cell Receptors Reactive Against Neoantigens in People With Metastatic Cancer	Bethesda, Maryland National Cancer Institute (NCI) IRC@nih.gov

TIER 1A THERAPY DETAILS

***EGFR* E746_P753delinsVS**		
Therapy	**Approval / Guideline Summary**	**Underlying Evidence**
afatinib	FDA approved for first-line treatment of metastatic NSCLC with non-resistant EGFR mutations. NCCN recommended as Category 1/Useful in certain circumstances (for L858R/exon 19 del) or Category 2A/Preferred intervention (for other sensitizing mutations).	The FDA approval for afatinib was supported by data from the open-label, randomized, phase-III trial LUX-Lung 3 (NCT00949650). LUX-Lung 3 demonstrated that first-line afatinib (n = 170), compared with pemetrexed and cisplatin (n = 115), improved median PFS (HR = 0.28; 13.7 mo. vs. 5.6 mo.) and median OS (HR = 0.55; 33.3 mo. vs. 21.1 mo.) in patients with metastatic NSCLC with EGFR exon 19 deletion.
dacomitinib	FDA approved for the first-line treatment of metastatic NSCLC with EGFR exon 19 deletion or exon 21 L858R substitution mutations. NCCN recommended as Category 1/Useful in certain circumstances.	In a Phase III trial (ARCHER 1050) that supported FDA approval, treatment with Vizimpro (dacomitinib) as first-line therapy in patients with non-small cell lung cancer harboring an EGFR exon 19 deletion or EGFR L858R resulted in an improved median progression-free survival (mPFS) of 14.7 months compared to 9.2 months with Iressa (gefitinib), with a mPFS of 12.3 months with dacomitnib vs. 9.8 months with Iressa (gefitinib) among patients with EGFR exon 19 deletions (PMID: 28958502; NCT01777421).
erlotinib	FDA approved for metastatic NSCLC with EGFR exon 19 deletions or exon 21 (L858R) substitution mutations receiving first-line, maintenance, or second or greater line treatment after progression following at least one prior chemotherapy regimen. NCCN recommended as first line therapy (Category 1 /Useful in certain circumstances).	The FDA approval for erlotinib was supported by data from the open-label, phase-III trial EURTAC (ML20650; PMID: 22285168). EURTAC demonstrated that first-line erlotinib, compared with (carboplatin or cisplatin) + (docetaxel or gemcitabine), improved median PFS (HR = 0.34; p < 0.001; 10.4 mo. vs. 5.2 mo.; no. of events, 83% (71/86) vs. 72% (63/88)) in patients with metastatic NSCLC with EGFR Exon 19 Deletion or EGFR L858R. Secondary endpoints were OS (HR = 0.93) and ORR (65% vs. 16%).

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gefitinib	FDA approved for the first-line treatment of metastatic NSCLC with EGFR exon 19 deletions or exon 21 (L858R) substitution mutations. NCCN recommended as Category 1/Useful in certain circumstances.	The FDA approval for gefitinib was supported by two trials: IPASS Study 1 and IPASS Study 2 (NCT00322452; PMID: 19692680). Data from the single-arm, open-label phase-III trial IPASS Study 1 demonstrated that first-line gefitinib had an ORR of 50% (n = 106; CR, 0.9%; PR, 49%) in patients with metastatic NSCLC with EGFR Exon 19 Deletion or EGFR L858R. The secondary endpoint was median DOR (6.0 mo.). Data from the open-label, randomized, phase-III trial IPASS Study 2 demonstrated that first-line gefitinib, compared with carboplatin + paclitaxel, improved median PFS (HR = 0.54; 10.9 mo. vs. 7.4 mo.) and had a better ORR (67% (n = 88) vs. 41% (n = 98)) in patients with metastatic Lung Adenocarcinoma with EGFR Exon 19 Deletion or EGFR L858R.
osimertinib	FDA approved for the first-line treatment of metastatic NSCLC with EGFR exon 19 deletion or exon 21 L858R mutations. NCCN recommended as Category 1 /Preferred intervention.	In a Phase III (FLAURA) trial that supported FDA approval, treatment with Tagrisso (osimertinib) resulted in a longer median progression-free survival compared to treatment with either Tarceva (erlotinib) or Iressa (gefitinib) (18.9 mo vs 10.2 mo) in previously untreated non-small cell lung cancer patients harboring either EGFR L858R or EGFR exon 19 deletion (PMID: 29151359; NCT02296125).
osimertinib	FDA approved for adults with locally advanced, unresectable (stage III) NSCLC with EGFR exon 19 deletions or L858R mutations, whose disease has not progressed during or following platinum-based chemoradiation therapy.	The FDA approval for osimertinib was supported by data from the double blind, randomized, placebo-controlled, phase-III trial LAURA (NCT03521154). LAURA demonstrated that osimertinib (n = 143), compared to placebo (n = 73), improved PFS (39.1 mo. vs. 5.6 mo., HR = 0.16; p < 0.001) in patients with locally advanced, unresectable stage III NSCLC with EGFR exon 19 deletions or exon 21 L858R mutations whose disease had not progressed during or following definitive platinum-based chemoradiation therapy. Additional endpoint includes OS (immature with 36% of pre-specified deaths).

TEST DETAILS

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SNVs and Indels (32 genes, 112 amplicons)			
AKT1 NM_001014432.1	*ERBB2* NM_004448.2	*GNAS* NM_000516.4	*NRAS* NM_002524.4
APC NM_000038.5	*ERBB3* NM_001982.3	*H3-3A* NM_002107.4	*PIK3CA* NM_006218.2
BRAF NM_004333.4	*ERCC2* NM_000400.3	*HRAS* NM_005343.2	*PTEN* NM_000314.4
CD79B NM_000626.2	*FBXW7* NM_033632.3	*IDH1* NM_005896.2	*RAF1* NM_002880.3
CDH1 NM_004360.3	*FGFR2* NM_000141.4	*IDH2* NM_002168.2	*SMAD4* NM_005359.5
CDKN2A NM_000077.4	*FGFR3* NM_000142.4	*KRAS* NM_004985.3	*TERT* NM_198253.2
CTNNB1 NM_001904.3	*FUS* NM_004960.3	*MYD88* NM_002468.4	*TP53* NM_000546.5
EGFR NM_005228.3	*GATA3* NM_001002295.1	*NFE2L2* NM_006164.4	*VHL* NM_000551.3

Aneuploidy (chromosome arm level loss and gain)									
chr1p	chr3p	chr5p	chr7p	chr9p	chr11p	chr13q	chr16q	chr18q	chr20q
chr1q	chr3q	chr5q	chr7q	chr9q	chr11q	chr14q	chr17p	chr19p	chr21q
chr2p	chr4p	chr6p	chr8p	chr10p	chr12p	chr15q	chr17q	chr19q	chr22q
chr2q	chr4q	chr6q	chr8q	chr10q	chr12q	chr16p	chr18p	chr20p	

Methods and Limitations

The Summit™ next-generation sequencing (NGS) test investigates tumor DNA (tDNA) extracted from cerebrospinal fluid (CSF) for clinically relevant single/multi nucleotide variants (SNVs, MNVs, indels) and aneuploidy events associated with primary and metastatic central nervous system (CNS) cancers. Methodology involves targeted duplex sequencing of 32 key genes (SNVs, MNVs and Indels) and low pass whole genome sequencing (>0.1x) for the detection of chromosomal arm level loss or gain, aneuploidy (PMID: 37014860). Post target enrichment libraries, generated from 20-40ng of tDNA, are sequenced on the Illumina NovaSeq XPlus, generating 100 bp paired-end sequence reads. The LOD (limit of detection) for SNVs, MNVs and Indels was determined as 0.3% variant allelic fraction (VAF). Variants (mutations and aneuploidy) are called against the human genome build reference hg19 using the Summit™ Genome Analytics (SGA) pipeline (SNVs, MNVs, and Indels - version 1.0.0 and aneuploidy - version 0.6.0), developed at Belay Diagnostics.

Tertiary analysis is performed using the precision oncology workbench (GenomOncology) based on the joint AMP/ASCO/CAP consensus guidelines for interpretation of sequence variants in cancer (PMID: 27993330). Please reach out to contact@belaydiagnostics.com for additional information or queries.

Disclaimers

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This test was developed, and its performance characteristics determined by Belay Diagnostics Laboratory (CLIA# 14D2302605), which is certified under the Clinical Laboratory Improvement Amendments of 1988 (CLIA) as qualified to perform high complexity testing. This test has not been cleared or approved by the U.S. Food and Drug Administration (FDA). This test may be used for clinical purposes. However, the results of this test do not establish a diagnosis and should not be used alone for diagnosis or patient care decisions or otherwise replace the judgment of a treating physician and must always be interpreted in the context of all relevant clinical and pathological data.

This test is performed only to evaluate for somatic (i.e., tumor-specific) variants within the genes listed and cannot distinguish between germline and somatic alterations with absolute certainty. This test therefore does not report on incidental findings as defined by the American College for Medical Genetics and Genomics (ACMG) (PMID: 37347242). If a germline variant is suspected, follow-up germline testing using non-neoplastic (normal) tissue should be performed by a laboratory permitted to perform germline genetic testing along with genetic counseling. It is possible for a genomic variant to be present yet go undetected by our assay either due to the heterogeneous nature of the specimen or the limits of detection of our assay. Therefore, to the extent a particular genomic variant is not reported, Belay Diagnostics LLC does not guarantee that the variant does not exist in the specimen provided. Likely benign, and benign variants are not reported. For any reported variant of uncertain significance (VUS), if the classification changes, there is no obligation to send out a new report updating this information.

The information presented in the clinical trials and therapeutic sections of this report is compiled from public sources which are continuously updated. While we strive to ensure this information is accurate and complete, we cannot guarantee the accuracy or completeness of this information. This public sourced information is not ranked in order of potential or predicted efficacy and may not be complete. Specific eligibility criteria should be reviewed as applicable. This information may include associations between a genomic variant (or lack of a variant) and one or more therapeutic agents with potential clinical benefit (or lack of clinical benefit), including agents that are being studied in clinical research. The finding of a genomic variant does not necessarily indicate or demonstrate pharmacologic effectiveness (or lack thereof) of any agent or treatment regimen found in public source information. Similarly, the finding of "no clinically significant variant" does not necessarily indicate or demonstrate lack of pharmacologic effectiveness (or lack of effectiveness) of any agent or treatment regimen found in public source information. Belay Diagnostics expressly disclaims, and makes no representation of or warranty of, the accuracy or completeness with respect to the publicly available information included herein or reviewed or collected during creation of this report.

ACTIONABILITY REFERENCES

FDA: U.S. Food & Drug Administration (fda.gov)

NCCN: National Comprehensive Cancer Network® (NCCN®). Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®). © National Comprehensive Cancer Network, Inc. 2024. All rights reserved. The NCCN Guidelines® and illustrations herein may not be reproduced in any form for any purpose without the express written permission of the NCCN. To view the most recent and complete version of the guideline, go online to NCCN.org. NCCN makes no warranties of any kind whatsoever regarding their content, use or application and disclaims any responsibility for their application or use in any way.

WHO: World Health Organization Classification of Tumours online (tumourclassification.iarc.who.int)

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