BELAY DIAGNOSTICS

Date: 04/29/2025
Order ID: SumPos-TL-A1

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Summit™ Report

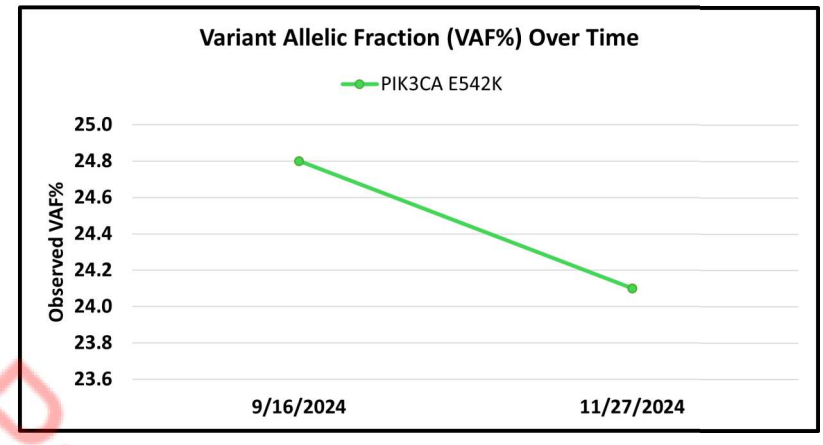
Patient	Specimen	Physician Information
Name: Jane Doe **DOB:**01/01/1990 **Sex Assigned at Birth:** Female **MRN:**11xx22xx33 **Diagnosis:**Metastatic Breast Carcinoma	**Type:**CSF **Collected:**11/27/2025 **Received:**12/02/2024 **Specimen ID:**SumPos-TL-A1	**Institution:**Belay Diagnostics **Referring Physician:**Provider Test

RESULT SUMMARY

POSITIVE

Clinically Significant Alterations Detected	*PIK3CA* E542K (Tier 1A)

Actionability Summary	3 therapeutic responses
	5 trials



Comments
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
PIK3CA p.E542K c.1624G>A	24.1%	Substitution - Missense	Tier 1A	Associated with Drug Response; Potentially Relevant Clinical Trials

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)

chr11q Gain	chr17p Loss	chr21q Loss	chr8p Loss
chr12q Loss	chr17q Loss	chr6p Loss	chr8q Gain
chr16q Loss	chr19q Gain	chr6q Loss	chr9q Loss

ACTIONABILITY SUMMARY

FDA / NCCN Therapies for the Patient's Tumor Type (Tier 1A)

Biomarker	Therapies	Setting	Source(s)

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PIK3CA E542K	capivasertib + fulvestrant	Advanced or metastatic; HR+/HER2-	FDA (Approved), NCCN
PIK3CA E542K	inavolisib + palbociclib + fulvestrant	Recurrent and advanced/metastatic; HR+/HER2-	FDA (Approved), NCCN
PIK3CA E542K	alpelisib + fulvestrant	Subsequent line; HR+/HER2-	FDA (Approved), NCCN

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

Prognostic Implications per NCCN: *None*

Diagnostic Implications per WHO: *None*

CLINICAL TRIALS / INVESTIGATIONAL THERAPIES

***PIK3CA* E542K**

Therapy	Clinical Trial	Location/Sponsor
afuresertib + fulvestrant	**NCT04851613** (Phase 3) Study Evaluating Efficacy & Safety of Afuresertib Plus Fulvestrant in Patients w/ Locally Advanced or Metastatic HR+/HER2- Breast Cancer	Santa Monica, California Laekna Limited wenwen.he@laekna.com
alpelisib + (aromatase inhibitor or fulvestrant)	**NCT04762979** (Phase 2) Alpelisib (BYL719) in Combination With Continued Endocrine Therapy Following Progression on Endocrine Therapy in Hormone Receptor Positive, HER2 Negative, PIK3CA Mutant Metastatic Breast Cancer	Chicago, Illinois Marina N Sharifi msharifi@wisc.edu
gedatolisib + fulvestrant; gedatolisib + palbociclib + fulvestrant	**NCT05486143** (Phase 3) Gedatolisib Plus Fulvestrant With or Without Palbociclib vs Standard-of-Care for the Treatment of Patients With Advanced or Metastatic HR+/HER2- Breast Cancer	Winter Haven, Florida Celcuity, Inc. nzack@celcuity.com
gedatolisib + palbociclib + fulvestrant; gedatolisib + fulvestrant	**NCT05501886** (Phase 3) Gedatolisib Plus Fulvestrant With or Without Palbociclib vs Standard-of-Care for the Treatment of Patients With Advanced or Metastatic HR+/HER2- Breast Cancer (VIKTORIA-1)	Birmingham, Alabama Celcuity Inc VIKTORIA-1_TRIAL@CELCUITY.COM
inavolisib + fulvestrant	**NCT05646862** (Phase 3) A Study Evaluating the Efficacy and Safety of Inavolisib Plus Fulvestrant Compared With Alpelisib Plus Fulvestrant in Participants With HR-Positive, HER2-Negative, PIK3CA Mutated, Locally Advanced or Metastatic Breast Cancer Post CDK4/6i and Endocrine Combination Therapy	York, Pennsylvania Hoffmann-La Roche global-roche-genentech-trials@gene.com

TIER 1A THERAPY DETAILS

***PIK3CA* E542K**

Therapy	Approval / Guideline Summary	Underlying Evidence
alpelisib + fulvestrant	FDA approved for HR-positive, HER2-negative, PIK3CA-mutated, advanced or metastatic breast cancer following progression on or after an endocrine-based regimen. NCCN recommended as Category 1/Preferred intervention.	The FDA approval for alpelisib + fulvestrant was supported by data from the randomized, double-blind, placebo-controlled phase-III trial SOLAR-1 (NCT02437318). SOLAR-1 demonstrated that subsequent-line alpelisib + fulvestrant (n = 169), compared with placebo + fulvestrant (n = 172), improved median PFS (HR = 0.65, p = 0.0013; 11.0 mo. vs. 5.7 mo.) in patients with advanced or metastatic, HR-positive, HER2-negative, PIK3CA-mutated breast carcinoma. The additional endpoints were ORR (35.7% vs. 16.2%) and OS (HR = 0.86, n.s.).

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capivasertib + fulvestrant	FDA approved for adults with HR-positive, HER2-negative, locally advanced or metastatic breast cancer with one or more PIK3CA/AKT1/PTEN alterations, following progression on at least one endocrine-based regimen in the metastatic setting or recurrence on or within 12 months of completing adjuvant therapy. NCCN recommended as Category 1/Preferred intervention.	The FDA approval for capivasertib + fulvestrant was supported by data from the placebo-controlled, double-blind, randomized, phase-III trial CAPItello-291 (NCT04305496). CAPItello-291 demonstrated that subsequent-line capivasertib + fulvestrant (n = 155), compared with placebo + fulvestrant (n = 134), improved PFS (HR: 0.50, p <0.0001; 7.3 mo. vs. 3.1 mo.) in patients with locally advanced or metastatic HR-positive, HER2-negative breast cancer with with one or more PIK3CA/AKT1/PTEN-alterations. Additional endpoints were ORR (26% vs. 8%) and median DoR (10.2 mo. vs. 8.6 mo.).
inavolisib + palbociclib + fulvestrant	FDA approved for adults with endocrine-resistant, PIK3CA-mutated, HR-positive, HER2-negative, locally advanced or metastatic breast cancer, following recurrence on or after completing adjuvant endocrine therapy. NCCN recommended as Category 1/Useful in certain circumstances.	The FDA approval for inavolisib + palbociclib + fulvestrant was supported by data from the double blind, randomized, placebo-controlled, phase-III trial INAVO120 (NCT04191499). INAVO120 demonstrated that inavolisib + palbociclib + fulvestrant (n = 161), compared to placebo + palbociclib + fulvestrant (n = 164), improved PFS (15.0 mo. vs. 7.3 mo., HR = 0.43; p < 0.0001) in patients with endocrine-resistant, PIK3CA-mutated, HR-positive, HER2-negative, locally advanced or metastatic breast cancer following recurrence on or after completing adjuvant endocrine therapy. Additional endpoints include an ORR of 58%, median DoR (18.4 mo.) and OS (not mature with 30% deaths in the overall population).

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

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.

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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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