דוח תוצאות בדיקה פתולוגית מס' 25-18290

לתשומת לב הרופא

שם משפחה	שם פרטי
230	

מין: **נקבה** שם האב: **יעקב** תאריך לידה: **09/08/1967** גיל: **58Y** כתובת: **נירים 0 נירים** טלפון: **054-7916540**

תאריך לקיחה: **22/09/25** תאריך קליטה: **10:35 22/09/2025** מס קבלה:

גורם שולח: **נשים אונקולוגיה מרפ סורו** רופא שולח: **ד"ר מאיר עמית**

צוות המכון לפתולוגיה

רופא בכיר: **ד"ר שמואלי בן ציון**

פרטים קליניים:

NGS על ביופסיה מספר 25-16107/2/5 מתאריך 21/8/2025.

הערות כלליות:

בדיקות קודמות:

25-18044,25-16114,25-16107,25-15574

אבחנה:

Molecular Pathology Laboratory Test Results
Oncomine™ Comprehensive Assay (OCA) by NGS

The test was performed on DNA extracted from biopsy #25-16107/2/5.
Tumor comprising 60% of the tissue submitted for analysis, as assessed on an H&E slide.

Test results:

- **TMB score: 12.3 | High | Tier 1**
- MSI: Stable
- Reportable Alterations In Clinically Significant Genes
  - **FGFR2** (Detected): c.755C>G (p.Ser252Trp); see Tier 2 for details
  - **PTEN** (Detected): c.70G>T (p.Asp24Tyr); c.209+5G>C ; see Tier 2 for details
  - AKT1 (Not detected)
  - BRAF (Not detected)
  - CCNE1 (Not detected)
  - DPYD (Not detected)
  - ERBB2 (Not detected)
  - FBXW7 (Not detected)
  - MTAP (Not detected)
  - NRG1 (Not detected)
  - NTRK1 (Not detected)
  - NTRK2 (Not detected)
  - NTRK3 (Not detected)
  - POLE (Not detected)
  - PPP2R1A (Not detected)
  - RET (Not detected)
  - TP53 (Not detected)

דוח תוצאות בדיקה פתולוגית מס' 25-18290

לתשומת לב הרופא

שם משפחה: **אביעזר**	שם פרטי: **כרמית**	ת.ז: **2300713-1**

Genomic alterations found in the sample:

TIER I: VARIANTS OF STRONG CLINICAL SIGNIFICANCE

TMB score: 12.3 | High | Therapeutic

TIER II: VARIANTS OF POTENTIAL CLINICAL SIGNIFICANCE

FGFR2 | p.Ser252Trp | c.755C>G | NM_000141.5 | VAF: 23.90% | Exon 7 | chr10:123279677 | Pathogenic, Potentially Therapeutic

PTEN | p.Asp24Tyr | c.70G>T | NM_000314.8 | VAF: 26.06% | Exon 1 | chr10:89624296 | Pathogenic, Potentially Therapeutic

PTEN | | c.209+5G>C | NM_000314.8 | VAF: 26.36% | Exon 3 | chr10:89685319 | Likely Pathogenic, Potentially Therapeutic

Comment: This is a splice-site alteration that is predicted to be deleterious to protein function by AI models.

TIER III: VARIANTS OF UNCERTAIN CLINICAL SIGNIFICANCE

APC | p.Pro1993Leufs*51 | c.5978del | NM_000038.6 | VAF: 19.95% | Exon 16 | chr5:112177264 | Pathogenic

APC | p.Gln1303* | c.3907C>T | NM_000038.6 | VAF: 22.18% | Exon 16 | chr5:112175198 | Pathogenic

ADAMTS2 | p.Pro224Hisfs*23 | c.669del | NM_014244.5 | VAF: 24.38% | Exon 3 | chr5:178699930 | Likely Pathogenic

CTCF | p.Ala137Leufs*17 | c.409del | NM_006565.4 | VAF: 22.80% | Exon 3 | chr16:67645139 | Likely Pathogenic

PIK3R1 | p.Tyr580* | c.1740C>A | NM_181523.3 | VAF: 22.07% | Exon 13 | chr5:67591147 | Likely Pathogenic

SPOP | p.Arg121Gln | c.362G>A | NM_001007228.2 | VAF: 21.41% | Exon 5 | chr17:47696461 | Likely Pathogenic

KDM6A | p.Pro417Leufs*22 | c.1250del | NM_001291415.2 | VAF: 25.93% | Exon 13 | chrX:44919320 | Likely Pathogenic

CIC | p.Gly838Aspfs*112 | c.2513del | NM_001386298.1 | VAF: 22.05% | Exon 2 | chr19:42778443 | Likely Pathogenic

DPP3 | p.Glu653Serfs*179 | c.1956del | NM_130443.4 | VAF: 27.42% | Exon 17 | chr11:66272154 | VUS

ARID5B | p.Lys967Asnfs*15 | c.2901del | NM_032199.3 | VAF: 24.85% | Exon 10 | chr10:63852117 | VUS

ARID5B | p.Glu456Lysfs*23 | c.1365del | NM_032199.3 | VAF: 25.17% | Exon 9 | chr10:63845621 | VUS

ACVR1B | p.Arg67Cys | c.199C>T | NM_004302.5 | VAF: 8.25% | Exon 2 | chr12:52369156 | VUS

KMT2B | p.Arg1705Gln | c.5114G>A | NM_014727.3 | VAF: 19.86% | Exon 24 | chr19:36221280 | VUS

NF1 | p.Arg135Trp | c.403C>T | NM_001042492.3 | VAF: 23.35% | Exon 4 | chr17:29490318 | VUS

CD276 | p.Ser411Leu | c.1232C>T | NM_001024736.2 | VAF: 47.51% | Exon 6 | chr15:73996676 | VUS

PIK3R1 | p.Glu683Lys | c.2047G>A | NM_181523.3 | VAF: 23.15% | Exon 16 | chr5:67593301 | VUS

KEAP1 | p.Tyr33His | c.97T>C | NM_203500.2 | VAF: 32.69% | Exon 2 | chr19:10610613 | VUS

TMEM233 | p.Ala86Val | c.257C>T | NM_001136534.3 | VAF: 16.87% | Exon 2 | chr12:120067611 | VUS

ARID5B | p.Asp242Asn | c.724G>A | NM_032199.3 | VAF: 15.27% | Exon 4 | chr10:63760071 | VUS

COPY NUMBER VARIANTS

- No CNV to report

דוח תוצאות בדיקה פתולוגית מס' 25-18290

לתשומת לב הרופא

שם משפחה: **אביעזר**	שם פרטי: **כרמית**	ת.ז: **2300713-1**

Fusions found in the sample:

- No fusions found to report.

These results should be taken into consideration with all clinical information concerning the patient's condition in accordance with the standard of care.

General information:

The Ion Torrent™ Oncomine™ Comprehensive Assay v3 is a targeted, next-generation sequencing (NGS) assay that enables the detection of relevant single-nucleotide variants (SNVs), copy number variations (CNVs), gene fusions, and indels. Oncomine™ Comprehensive Panel is used to construct the library and sequencing is performed using Ion Torrent sequencing system.

This NGS test for identifying alterations in cancer related genes in FFPE tumor tissue was validated by the molecular pathology unit in Soroka University Medical Center and approved by the Israeli Ministry of Health.

Validation showed 100% specificity for each mutation tested and a 1% limit of detection.

The test is aimed to detect hotspot mutations in 165genes, CNV variants in 333 genes, CDS in 227 genes and 51 fusions driver genes linked to cancer, such as:

DNA based alterations: *AKT1, ALK, AR, BRAF, BRCA 1/2, CDK4, CTNNB1, DDR2, EGFR, ERBB2, ERBB3, ERBB4, ESR1, FGFR1-4, GNA11, GNAQ, HRAS, IDH1, IDH2, JAK1-3, KIT, KRAS, MAP2K2, MET, MTOR, NRAS, MAP2K1, MAP2K2, MET, MTOR, NRAS, PDGFRA, PIK3CA, RAF1, RET, ROS1, SMO*.

RNA based alterations: *ALK, AXL, BRAF, BRCA1, BRCA2, ERBB2, ERG, ETV1, ETV4, ETV5, FGFR1, FGFR2, FGFR3, MET, NTRK1-3, PDGFRA, PPARG, RAF1, RET, ROS1*.

The test was performed by the molecular laboratory under the direction of Dr. Natalie Aisenberg.

סה"כ 1 דגימות.

תאריך הדפסה:	תאריך הפצה:	תאריך אישור:	
15:57 15/10/2025	**15:57 15/10/2025**	**15:53 15/10/2025**	**ד"ר שמואלי בן ציון** רופא מומחה בפתולוגיה

דוח תוצאות בדיקה פתולוגית מס' 25-18290

לתשומת לב הרופא

שם משפחה : **אביעזר** שם פרטי : **כרמית** ת.ז : **2300713-1**

Soroka Medical Center
Pathology Institute
Report date: 15/10/2025

אכ
Female |
Cancer Type: endometrial carcinoma | **Tumor Purity:** 60.000% | **Tumor Cellularity:** | **Tissue Type:** FFPE

Summary

High (12.3 Muts/Mb) TMB	**Stable** (4.17) MSI	**4** Relevant Biomarkers	**1** Therapies Available	**8** Clinical Trials

Comments

No CNV found to report

Reportable Alterations In Clinically Significant Genes

Gene	Detected	Finding
AKT1	Not detected	
BRAF	Not detected	
CCNE1	Not detected	
DPYD	Not detected	
ERBB2	Not detected	
FBXW7	Not detected	
FGFR2	Detected	c.755C>G (p.Ser252Trp);
MTAP	Not detected	
NRG1	Not detected	
NTRK1	Not detected	
NTRK2	Not detected	
NTRK3	Not detected	
POLE	Not detected	
PPP2R1A	Not detected	
PTEN	Detected	c.70G>T (p.Asp24Tyr); c.209+5G>C;

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אכ Report date: 15/10/2025

RET	Not detected	
TP53	Not detected	

Strong clinical significance - Tier 1

	TMB	Responsive to: **Pembrolizumab | Pembrolizumab | Pembrolizumab | Pembrolizumab | Pembrolizumab |** Resistance to: None	12.3 Muts/Mb

Potential clinical significance - Tier 2

	FGFR2 c.755C>G p.Ser252Trp	chr10:123279677-123279677 Transcript: NM_000141.5 Responsive to: Ponatinib Resistance to: None	23.90% Allelic Frequency
	PTEN c.70G>T p.Asp24Tyr	chr10:89624296-89624296 Transcript: NM_000314.8 Responsive to: Capivasertib Resistance to: None	26.06% Allelic Frequency
	PTEN c.209+5G>C	chr10:89685319-89685319 Transcript: NM_000314.8 Responsive to: Capivasertib Resistance to: None	26.36% Allelic Frequency

Unknown clinical significance - Tier 3

	APC c.5978del p.Pro1993Leufs*51	chr5:112177264-112177265 Transcript: NM_000038.6 Responsive to: None Resistance to: None	19.95% Allelic Frequency
	APC c.3907C>T p.Gln1303*	chr5:112175198-112175198 Transcript: NM_000038.6 Responsive to: None Resistance to: None	22.18% Allelic Frequency

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שם משפחה : **אביעזר** שם פרטי : **כרמית** ת.ז : **2300713-1**

אכ Report date: 15/10/2025

ADAMTS2 c.669del p.Pro224Hisfs*23	chr5:178699930-178699931 Transcript: NM_014244.5 Responsive to: None Resistance to: None	24.38% Allelic Frequency
CTCF c.409del p.Ala137Leufs*17	chr16:67645139-67645140 Transcript: NM_006565.4 Responsive to: None Resistance to: None	22.80% Allelic Frequency
PIK3R1 c.1740C>A p.Tyr580*	chr5:67591147-67591147 Transcript: NM_181523.3 Responsive to: None Resistance to: None	22.07% Allelic Frequency
SPOP c.362G>A p.Arg121Gln	chr17:47696461-47696461 Transcript: NM_001007228.2 Responsive to: None Resistance to: None	21.41% Allelic Frequency
KDM6A c.1250del p.Pro417Leufs*22	chrX:44919320-44919321 Transcript: NM_001291415.2 Responsive to: None Resistance to: None	25.93% Allelic Frequency
CIC c.2513del p.Gly838Aspfs*112	chr19:42778443-42778444 Transcript: NM_001386298.1 Responsive to: None Resistance to: None	22.05% Allelic Frequency
DPP3 c.1956del p.Glu653Serfs*179	chr11:66272154-66272155 Transcript: NM_130443.4 Responsive to: None Resistance to: None	27.42% Allelic Frequency
ARID5B c.2901del p.Lys967Asnfs*15	chr10:63852117-63852118 Transcript: NM_032199.3 Responsive to: None Resistance to: None	24.85% Allelic Frequency
ARID5B c.1365del p.Glu456Lysfs*23	chr10:63845621-63845622 Transcript: NM_032199.3 Responsive to: None Resistance to: None	25.17% Allelic Frequency

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אכ Report date: 15/10/2025

ACVR1B c.199C>T p.Arg67Cys	chr12:52369156-52369156 Transcript: NM_004302.5 Responsive to: None Resistance to: None	8.25% Allelic Frequency
KMT2B c.5114G>A p.Arg1705Gln	chr19:36221280-36221280 Transcript: NM_014727.3 Responsive to: None Resistance to: None	19.86% Allelic Frequency
NF1 c.403C>T p.Arg135Trp	chr17:29490318-29490318 Transcript: NM_001042492.3 Responsive to: None Resistance to: None	23.35% Allelic Frequency
CD276 c.1232C>T p.Ser411Leu	chr15:73996676-73996676 Transcript: NM_001024736.2 Responsive to: None Resistance to: None	47.51% Allelic Frequency
PIK3R1 c.2047G>A p.Glu683Lys	chr5:67593301-67593301 Transcript: NM_181523.3 Responsive to: None Resistance to: None	23.15% Allelic Frequency
KEAP1 c.97T>C p.Tyr33His	chr19:10610613-10610613 Transcript: NM_203500.2 Responsive to: None Resistance to: None	32.69% Allelic Frequency
TMEM233 c.257C>T p.Ala86Val	chr12:120067611-120067611 Transcript: NM_001136534.3 Responsive to: None Resistance to: None	16.87% Allelic Frequency
ARID5B c.724G>A p.Asp242Asn	chr10:63760071-63760071 Transcript: NM_032199.3 Responsive to: None Resistance to: None	15.27% Allelic Frequency
MSI	Responsive to: **None** Resistance to: None	

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שם משפחה : **אביעזר** שם פרטי : **כרמית** ת.ז : **2300713-1**

אכ Report date: 15/10/2025

Relevant Therapy

TMB-HIGH

Relevant Therapy	FDA	NCCN
Pembrolizumab	A	A

(A) In this cancer type (B) Based on well powered studies (C) In other cancer type (D) Based on preclinical studies (-) No evidence
*Showing the most advanced clinical trial phase

FGFR2 | p.Ser252Trp

Relevant Therapy	FDA	NCCN
Ponatinib	-	-

(A) In this cancer type (B) Based on well powered studies (C) In other cancer type (D) Based on preclinical studies (-) No evidence
*Showing the most advanced clinical trial phase

PTEN | p.Asp24Tyr

Relevant Therapy	FDA	NCCN
Capivasertib	C	-

(A) In this cancer type (B) Based on well powered studies (C) In other cancer type (D) Based on preclinical studies (-) No evidence
*Showing the most advanced clinical trial phase

PTEN | c.209+5G>C

Relevant Therapy	FDA	NCCN
Capivasertib	C	-

(A) In this cancer type (B) Based on well powered studies (C) In other cancer type (D) Based on preclinical studies (-) No evidence
*Showing the most advanced clinical trial phase

Relevant Clinical Trials

Details	Status	ID	Phase	Biomarkers
Phase I/IB Safety and Pharmacodynamic Study of Neoadjuvant (NACT) Paclitaxel and Carboplatin With Ipatasertib as Initial Therapy of Ovarian Cancer PTMA 100805	Recruiting	**NCT5276973** https://clinicaltrials.gov/ct2/show/NCT05276973	1	PTEN p.Asp24Tyr PTEN
Phase IB/II Study of Alpelisib in Combination With Paclitaxel in Patients With PIK3CA-altered Metastatic/Recurrent Gastric Cancer	Recruiting	**NCT4526470** https://clinicaltrials.gov/ct2/show/NCT04526470	1|2	PTEN p.Asp24Tyr PTEN

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שם משפחה : **אביעזר** שם פרטי : **כרמית** ת.ז : **2300713-1**

אכ Report date: 15/10/2025

A Multi-Center Phase I Dose Escalation Study of Avutometinib, a RAF/MEK Clamp, in Pediatric Patients With Refractory or Recurrent Solid Tumors Harboring Activating MAPK Pathway Alterations	Recruiting	**NCT6104488** https://clinicaltrials.gov/ct2/show/NCT06104488http://www.mskcc.org	1	NF1 p.Arg135Trp
A Phase II Study of Tazemetostat in Solid Tumors Harboring an ARID1A Mutation	Recruiting	**NCT5023655** https://clinicaltrials.gov/ct2/show/NCT05023655	2	PTEN p.Asp24Tyr PTEN
An Open-Label, Multicenter, First-in-Human, Dose-Escalation and Dose-Expansion, Phase 1/2 Study of BBI-355 and BBI-355 in Combination With Select Targeted Therapies in Subjects With Locally Advanced or Metastatic Solid Tumors With Oncogene Amplifications	Recruiting	**NCT5827614** https://clinicaltrials.gov/ct2/show/NCT05827614	1	FGFR2 p.Ser252Trp
A Phase 2, Open Label Study of REC-4881 in Participants With Unresectable Locally Advanced or Metastatic Cancer With AXIN1 or APC Mutation	Recruiting	**NCT6005974** https://clinicaltrials.gov/ct2/show/NCT06005974	2	APC p.Pro1993Leufs*51 APC p.Gln1303*
A Phase 1/2 Study of FOG-001 in Participants With Locally Advanced or Metastatic Solid Tumors	Recruiting	**NCT5919264** https://clinicaltrials.gov/ct2/show/NCT05919264	1|2	APC p.Pro1993Leufs*51 APC p.Gln1303*
A Multicenter, Open-label, First-in-Human Study of TYRA-200 in Advanced Intrahepatic Cholangiocarcinoma and Other Solid Tumors With Activating FGFR2 Gene Alterations (SURF-201)	Recruiting	**NCT6160752** https://clinicaltrials.gov/ct2/show/NCT06160752	1	FGFR2 p.Ser252Trp

Interpretation

Strong clinical significance - Tier 1

TMB-HIGH

THERAPEUTIC EVIDENCE
Below is list of therapies for which evidence was found associated with the tumor profile

✔ Responsive

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אכ Report date: 15/10/2025

Pembrolizumab FDA Approved

Anti-PD-1 monoclonal antibody PMID: N\A

FDA-Approved pembrolizumab for the treatment of adult and pediatric patients with unresectable or metastatic tumor mutational burden-high (TMB-H) [≥10 mutations/megabase (mut/Mb)] solid tumors that have progressed following prior treatment and who have no satisfactory alternative treatment options.

Pembrolizumab FDA Approved

Anti-PD-1 monoclonal antibody PMID: N\A

FDA-Approved pembrolizumab is indicated for the treatment of adult and pediatric patients with unresectable or metastatic tumor mutational burden-high (TMB-H) [≥10 mutations/megabase (mut/Mb)] solid tumors, as determined by an FDA-approved test, that have progressed following prior treatment and who have no satisfactory alternative treatment options. Clinical Feature: Disease stage: unresectable or metastatic disease

Pembrolizumab FDA Approved

Anti-PD-1 monoclonal antibody PMID: N\A

FDA-Approved pembrolizumab is indicated for the treatment of adult and pediatric patients with unresectable or metastatic tumor mutational burden-high (TMB-H) [≥10 mutations/megabase (mut/Mb)] solid tumors, as determined by an FDA-approved test, that have progressed following prior treatment and who have no satisfactory alternative treatment options. Clinical Feature: Disease stage: unresectable or metastatic disease

Pembrolizumab FDA Approved

Anti-PD-1 monoclonal antibody PMID: N\A

FDA-Approved pembrolizumab for the treatment of adult and pediatric patients with unresectable or metastatic tumor mutational burden-high (TMB-H) [≥10 mutations/megabase (mut/Mb)] solid tumors that have progressed following prior treatment and who have no satisfactory alternative treatment options.

Pembrolizumab Professional Guidelines

Anti-PD-1 monoclonal antibody PMID: N\A

The NCCN Panel recommends pembrolizumab as first-line or subsequent therapy option for advanced, recurrent/metastatic or inoperable Endometrial carcinoma (category 2A, useful in certain circumstances). For the treatment of patients with unresectable or metastatic tumor mutational burden-high (TMB-H) [≥10 mutations/megabase (mut/Mb)] tumors, as determined by a validated and/or FDA-approved test, that have progressed following prior treatment and have no satisfactory alternative treatment options.

Resistance

No responsive therapeutic evidence related to this biomarker was found

DIAGNOSTIC EVIDENCE

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שם משפחה : **אביעזר** שם פרטי : **כרמית** ת.ז : **2300713-1**

אכ Report date: 15/10/2025

Below is list of evidences pertain to tumor profile's diagnostic attributes

No diagnostic evidence related to this biomarker was found

PROGNOSTIC EVIDENCE
Below is list of evidences pertain to tumor profile's prognostic attributes

No prognostic evidence related to this biomarker was found

Potential clinical significance - Tier 2

FGFR2 | p.Ser252Trp

p.Ser252Trp | c.755C>G | NM_000141.5 | CHR10: 123279677 None | VAF: 23.90% | Coverage: 2000 | COSMIC ID: COSM41289;COSV60638319 | rs79184941 | ClinVar ID: RCV000552015, RCV004532334, RCV004527288, RCV000014192, RCV005229786, RCV000014191, RCV002476961, RCV004795407, RCV000263144

GENE SUMMARY
Fibroblast growth factor receptor 2 (FGFR2), is a receptor tyrosine kinase, member of the fibroblast growth factor receptor (FGFR) family. Binding of FGF ligands to FGFR2 activates downstream signaling pathways including RAS-MAPK and PI3K-AKT. Altered Fgfr2 function may lead to increased cell proliferation and tumorigenesis, and FGFR2 amplifying, fusions, overexpression or activating mutations occur in multiple cancers including prostate, lung, gastric, ameloblastomas, uterine, breast, and ovarian cancers. FGFR2-BICC1 fusion is observed in metastatic cholangiocarcinoma, FGFR2-AFF3 fusion in breast cancer, SLC45A3-FGFR2 fusion in prostate cancer and brain metastasis, and FGFR2-CIT fusion identified in a lung adenocarcinoma

VARIANT INTERPRETATION
p.Ser252Trp, a non synonymous variant in the FGFR2, an oncogene.The variant does not reside in any known domain.The variant was reported in COSMIC (COSM41289,COSV60638319) and ClinVar (13272).The variant was classified as a Tier 2 using the ASCO/CAP/AMP Guidelines and as Pathogenic according to the ACMG Guidelines.

THERAPEUTIC EVIDENCE
Below is list of therapies for which evidence was found associated with the tumor profile

✔ Responsive

Ponatinib — Preclinical Studies

Multikinase inhibitor, Tyrosine kinase inhibitor PMID: N\A

"Preclinical study in endometrial cancer cell lines (MFE-296, AN3CA, MFE-280 and Ishikawa). In cell proliferation assays, the three FGFR2 mutant cell lines were more sensitive to the pan-FGFR inhibitor ponatinib (AP24534) than the FGFR2 wild type cell line (Ishikawa) and human embryonic kidney cell line (HEK293). Ponatinib also inhibited FGFR2 kinase activity and phosphorylation (MFE-296 and MFE-280) as well as cell migration and invasion (MFE-296 and AN3CA) of FGFR2 mutated cancer cell lines."

⊘ Resistance

No resistant therapeutic evidence related to this biomarker was found

DIAGNOSTIC EVIDENCE
Below is list of evidences pertain to tumor profile's diagnostic attributes

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דוח תוצאות בדיקה פתולוגית מס' 25-18290

*****לתשומת לב הרופא*****

שם משפחה : **אביעזר** שם פרטי : **כרמית** ת.ז : **2300713-1**

אכ Report date: 15/10/2025

No diagnostic evidence related to this biomarker was found

PROGNOSTIC EVIDENCE
Below is list of evidences pertain to tumor profile's prognostic attributes

No prognostic evidence related to this biomarker was found

PTEN | p.Asp24Tyr

p.Asp24Tyr | c.70G>T | NM_000314.8 | CHR10: 89624296 None | VAF: 26.06% | Coverage: 1017 | COSMIC ID: COSM305668;COSV64288588 | rs786201995 | ClinVar ID: RCV000169787, RCV003454429, RCV004535153

GENE SUMMARY
Phosphatidylinositol 3,4,5-trisphosphate 3-phosphatase (PTEN), is a tumor suppressor with roles in the cell cycle, growth, DNA repair, cell survival and regulation of the Akt-mTOR pathway. PTEN is one of the most frequently mutated genes in human cancer. PTEN somatic alterations including R130G, R130Q, R130*, R233*, T319fs, T267fs, and R173C and loss of function mutations have been found in many types of cancer including, melanoma, endometrial, and prostate. PTEN germline mutations are common in a group of disorders referred to jointly as the 'PTEN hamartoma tumor syndrome (PHTS)', which is associated with glioma, breast and thyroid cancer.

VARIANT INTERPRETATION
p.Asp24Tyr, a non synonymous variant in the PTEN, a tumor suppressor gene.The variant does not reside in any known domain.The variant was reported in COSMIC (COSM305668,COSV64288588) and ClinVar (189398).The variant was classified as a Tier 2 using the ASCO/CAP/AMP Guidelines and as Pathogenic according to the ACMG Guidelines.

THERAPEUTIC EVIDENCE
Below is list of therapies for which evidence was found associated with the tumor profile

✔ Responsive

Capivasertib FDA Approved for Different

Serine/threonine protein kinase inhibitor PMID: N\A

FDA-Approved capivasertib in combination with fulvestrant, is indicated for the treatment of adult patients with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative, locally advanced or metastatic breast cancer with one or more PIK3CA/AKT1/PTEN-alteration as detected by an FDA-approved test following progression on at least one endocrine-based regimen in the metastatic setting or recurrence on or within 12 months of completing adjuvant therapy.

⊘ Resistance

No resistant therapeutic evidence related to this biomarker was found

DIAGNOSTIC EVIDENCE
Below is list of evidences pertain to tumor profile's diagnostic attributes

No diagnostic evidence related to this biomarker was found

PROGNOSTIC EVIDENCE
Below is list of evidences pertain to tumor profile's prognostic attributes

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דוח תוצאות בדיקה פתולוגית מס' 25-18290

*****לתשומת לב הרופא*****

שם משפחה : **אביעזר** שם פרטי : **כרמית** ת.ז : **2300713-1**

אכ Report date: 15/10/2025

No prognostic evidence related to this biomarker was found

PTEN | c.209+5G>C

c.209+5G>C | NM_000314.8 | CHR10: 89685319 None | VAF: 26.36% | Coverage: 1476 | COSMIC ID: | ClinVar ID: RCV001345910, RCV001587366

GENE SUMMARY
Phosphatidylinositol 3,4,5-trisphosphate 3-phosphatase (PTEN), is a tumor suppressor with roles in the cell cycle, growth, DNA repair, cell survival and regulation of the Akt-mTOR pathway. PTEN is one of the most frequently mutated genes in human cancer. PTEN somatic alterations including R130G, R130Q, R130*, R233*, T319fs, T267fs, and R173C and loss of function mutations have been found in many types of cancer including, melanoma, endometrial, and prostate. PTEN germline mutations are common in a group of disorders referred to jointly as the 'PTEN hamartoma tumor syndrome (PHTS)', which is associated with glioma, breast and thyroid cancer.

VARIANT INTERPRETATION
c.209+5G>C, a variant in the PTEN, a tumor suppressor gene.The variant does not reside in any known domain.The variant was reported in ClinVar (1042020).The variant was classified as a Tier 2 using the ASCO/CAP/AMP Guidelines and as Likely Pathogenic according to the ACMG Guidelines.

THERAPEUTIC EVIDENCE
Below is list of therapies for which evidence was found associated with the tumor profile

✔ Responsive

Capivasertib FDA Approved for Different

Serine/threonine protein kinase inhibitor PMID: N\A

FDA-Approved capivasertib in combination with fulvestrant, is indicated for the treatment of adult patients with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative, locally advanced or metastatic breast cancer with one or more PIK3CA/AKT1/PTEN-alteration as detected by an FDA-approved test following progression on at least one endocrine-based regimen in the metastatic setting or recurrence on or within 12 months of completing adjuvant therapy.

⊘ Resistance

No resistant therapeutic evidence related to this biomarker was found

DIAGNOSTIC EVIDENCE
Below is list of evidences pertain to tumor profile's diagnostic attributes

No diagnostic evidence related to this biomarker was found

PROGNOSTIC EVIDENCE
Below is list of evidences pertain to tumor profile's prognostic attributes

No prognostic evidence related to this biomarker was found

General Information

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דוח תוצאות בדיקה פתולוגית מס' 25-18290

*****לתשומת לב הרופא*****

שם משפחה : **אביעזר** שם פרטי : **כרמית** ת.ז : **2300713-1**

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Report date: 15/10/2025

The Ion Torrent™ Oncomine™ Comprehensive Assay v3 is a targeted, next-generation sequencing (NGS) assay that enables the detection of relevant single-nucleotide variants (SNVs), copy number variations (CNVs), gene fusions, and indels. OncomineTM Comprehensive Panel is used to construct the library and sequencing is performed using Ion Torrent Sequencing System.
This Next Generation Sequencing (NGS) test for identifying alterations in cancer related genes in FFPE tumor tissue was validated by the molecular pathology unit in Soroka University Medical Center and approved by Israeli Ministry of Health.
Validation showed 100% specificity for each mutation tested and 1% limit of detection.

דוח תוצאות בדיקה פתולוגית מס' 25-18290

לתשומת לב הרופא

שם משפחה : **אביעזר** שם פרטי : **כרמית** ת.ז : **2300713-1**

Soroka Medical Center
Pathology Institute
Report date: 15/10/2025

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Female |
Cancer Type: | **Tumor Purity:** 60.000% | **Tumor Cellularity:** | **Tissue Type:** FFPE

SUMMARY

Relevant Biomarkers	Therapies Available	Clinical Trials	TMB	MSI
4	1	8	High 12.3 Muts/Mb	Stable 4.17

Reportable Alterations In Clinically Significant Genes

AKT1 (Not detected)
BRAF (Not detected)
CCNE1 (Not detected)
DPYD (Not detected)
ERBB2 (Not detected)
FBXW7 (Not detected)
FGFR2 (Detected): c.755C>G (p.Ser252Trp);
MTAP (Not detected)
NRG1 (Not detected)
NTRK1 (Not detected)
NTRK2 (Not detected)
NTRK3 (Not detected)
POLE (Not detected)
PPP2R1A (Not detected)
PTEN (Detected): c.70G>T (p.Asp24Tyr); c.209+5G>C ;
RET (Not detected)
TP53 (Not detected)

TIER I: VARIANTS OF STRONG CLINICAL SIGNIFICANCE

None identified in the genes covered by this panel.

TIER II: VARIANTS OF POTENTIAL CLINICAL SIGNIFICANCE

FGFR2 | p.Ser252Trp | c.755C>G | NM_000141.5 | VAF: 23.90% | Exon 7 | chr10:123279677 | Pathogenic

PTEN | p.Asp24Tyr | c.70G>T | NM_000314.8 | VAF: 26.06% | Exon 1 | chr10:89624296 | Pathogenic

PTEN | | c.209+5G>C | NM_000314.8 | VAF: 26.36% | Exon 3 | chr10:89685319 | Likely Pathogenic

דוח תוצאות בדיקה פתולוגית מס' 25-18290

לתשומת לב הרופא

שם משפחה : **אביעזר** שם פרטי : **כרמית** ת.ז : **2300713-1**

אכ Report date: 15/10/2025

TIER III: VARIANTS OF UNCERTAIN CLINICAL SIGNIFICANCE

APC | p.Pro1993Leufs*51 | c.5978del | NM_000038.6 | VAF: 19.95% | Exon 16 | chr5:112177264 | Pathogenic

APC | p.Gln1303* | c.3907C>T | NM_000038.6 | VAF: 22.18% | Exon 16 | chr5:112175198 | Pathogenic

ADAMTS2 | p.Pro224Hisfs*23 | c.669del | NM_014244.5 | VAF: 24.38% | Exon 3 | chr5:178699930 | Likely Pathogenic

CTCF | p.Ala137Leufs*17 | c.409del | NM_006565.4 | VAF: 22.80% | Exon 3 | chr16:67645139 | Likely Pathogenic

PIK3R1 | p.Tyr580* | c.1740C>A | NM_181523.3 | VAF: 22.07% | Exon 13 | chr5:67591147 | Likely Pathogenic

SPOP | p.Arg121Gln | c.362G>A | NM_001007228.2 | VAF: 21.41% | Exon 5 | chr17:47696461 | Likely Pathogenic

KDM6A | p.Pro417Leufs*22 | c.1250del | NM_001291415.2 | VAF: 25.93% | Exon 13 | chrX:44919320 | Likely Pathogenic

CIC | p.Gly838Aspfs*112 | c.2513del | NM_001386298.1 | VAF: 22.05% | Exon 2 | chr19:42778443 | Likely Pathogenic

DPP3 | p.Glu653Serfs*179 | c.1956del | NM_130443.4 | VAF: 27.42% | Exon 17 | chr11:66272154 | VUS

ARID5B | p.Lys967Asnfs*15 | c.2901del | NM_032199.3 | VAF: 24.85% | Exon 10 | chr10:63852117 | VUS

ARID5B | p.Glu456Lysfs*23 | c.1365del | NM_032199.3 | VAF: 25.17% | Exon 9 | chr10:63845621 | VUS

ACVR1B | p.Arg67Cys | c.199C>T | NM_004302.5 | VAF: 8.25% | Exon 2 | chr12:52369156 | VUS

KMT2B | p.Arg1705Gln | c.5114G>A | NM_014727.3 | VAF: 19.86% | Exon 24 | chr19:36221280 | VUS

NF1 | p.Arg135Trp | c.403C>T | NM_001042492.3 | VAF: 23.35% | Exon 4 | chr17:29490318 | VUS

CD276 | p.Ser411Leu | c.1232C>T | NM_001024736.2 | VAF: 47.51% | Exon 6 | chr15:73996676 | VUS

PIK3R1 | p.Glu683Lys | c.2047G>A | NM_181523.3 | VAF: 23.15% | Exon 16 | chr5:67593301 | VUS

KEAP1 | p.Tyr33His | c.97T>C | NM_203500.2 | VAF: 32.69% | Exon 2 | chr19:10610613 | VUS

TMEM233 | p.Ala86Val | c.257C>T | NM_001136534.3 | VAF: 16.87% | Exon 2 | chr12:120067611 | VUS

ARID5B | p.Asp242Asn | c.724G>A | NM_032199.3 | VAF: 15.27% | Exon 4 | chr10:63760071 | VUS

דוח תוצאות בדיקה פתולוגית מס' 25-18290

לתשומת לב הרופא

שם משפחה : **אביעזר** שם פרטי : **כרמית** ת.ז : **2300713-1**

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Report date: 15/10/2025