T.C. SAĞLIK BAKANLIĞI

NESİLLER
GENETİK HASTALIKLAR DEĞERLENDİRME MERKEZİ
Laboratuvar Ruhsat No: GHDM.SM/34.09/01
MOLEKÜLER GENETİK ANALİZ RAPORU

nesiller
GENETİK HASTALIKLAR DEĞERLENDİRME MERKEZİ

TÜRKÇE RAPOR ÖZETİ VE BULGULARIN YORUMLANMASI

Adı ve Soyadı	: [redacted]	**Protokol No**	: [redacted]
TC Kimlik No	: [redacted]	**Doğum Tarihi / Cinsiyet**	: 07.05.2003 / K
Numune Türü	: Parafin Blok	**Çalışılan Test**	: Focus CGP
Gönderen Doktor	: [redacted]	**Gönderen Kurum**	: -
İstem Tarihi	: 06.11.2025 11:21	**Numune Alım Tarihi**	: 06.11.2025 16:44
Uzman Onay Tarihi	: 21.11.2025 15:43	**Numune Kabul Tarihi**	: 06.11.2025 16:45
Endikasyon	: Kaposi sarkomu		

SONUÇ:

Genomik Değişiklikler	Onaylı/Önerilen Tedaviler (hastanın tümör tipi)	Onaylı/Önerilen Tedaviler (farklı tümör tipi)
I-A EWSR1::CREM (exon 7::exon 5...	none	none
II-C combination MSS, TMB Low	none	none
I-B present in combination TMB Low	none	none
II-C other biomarker HRDsig Negative	none	Excluded from report
II-C present in combination MSS	none	none
other biomarker Genomic LOH Undetermined	none	none

Bu rapor özeti 21.11.2025 tarihinde sonuçlanan **Foundation Medicine /Avenio Tumor Tissue CGP V2** analiz raporu incelenerek yazılmıştır.

Kaposi sarkomu tanılı hastamızın tümör dokusundan elde edilen DNA ile yapılan çalışmada klinik açıdan önemli olabilecek **EWRS1-CREM füzyonu** tespit edilmiştir.

Tümör Mutasyon Yükü (TMB): **1.21 (Düşük)**

Mikrosatellit İnstabilite (MSI) Statüsü: MSS (Stabil)

HRD Statüsü: **Negatif**

Adı ve Soyadı	: [redacted]	**Protokol No**	: [redacted]

AÇIKLAMA:

Hastamızda 149 okuma sayısı ile doğrulanan **EWSR1–CREM füzyonu** saptanmıştır. EWSR1, DNA/RNA bağlayan FET ailesi bir protein, CREM ise CREB ailesinden bir transkripsiyon faktörüdür; aralarındaki bu füzyon, farklı mezenkimal ve epitelyal tümörlerde tanımlanmış, onkojenik bir şimerik transkripsiyon faktörü oluşumu ile ilişkilendirilmiştir. Bu füzyonun; hücre siklusu, proliferasyon, migrasyon ve özellikle poliamin metabolizmasını düzenleyen genlerde ekspresyon değişikliklerine yol açarak tümör gelişimine katkıda bulunabildiği gösterilmiştir.

EWSR1–CREM füzyonu, Kaposi sarkomu için özgül veya tanı koydurucu bir genetik imza değildir ve bu tümör tipinde prognostik ya da tedavi yanıtını öngören doğrulanmış bir biyobelirteç olarak kabul edilmemektedir. Bu nedenle saptanan füzyon, tümörün klonal/neoplastik doğasını destekleyen; ancak mevcut kılavuzlar ışığında tek başına tedavi seçimini veya standart klinik yaklaşımı değiştirmeyen bir moleküler bulgu olarak yorumlanmalıdır. EWSR1/FET–CREB ailesi füzyonlarını doğrudan hedefleyen, Kaposi sarkomu için onaylanmış bir tedavi bulunmamaktadır.

Hastamızın DNA'sından yapılan incelemede tümör mutasyon yükü (TMB) düşük ve mikrosatellit statüsü stabil (MSS) olarak bulunmuştur. TMB düşük MSS vakaların, TMB yüksek vakalara göre, immün checkpoint inhibitör tedavisine daha az yanıt vermekte ve klinik fayda bu yönde daha az olmaktadır.

Bu raporda verilen sonuçlar sadece bakılan genler ve bölgeler için yazılmış olup çalışılmayan genlerdeki mutasyonların varlığını dışlamaz. Sonuçların hastanın klinik bulguları ile birlikte değerlendirilmesi önerilir.

NOT: Orijinal rapor, bu rapor özetinin devamındadır.

DR. GÜLAY ÖZGÖN

TIBBİ GENETİK UZMANI

1-Bu belge 5070 sayılı elektronik imza kanununa göre güvenli elektronik imza ile imzalanmıştır.
2- Bu rapor, laboratuvarın yazılı izni olmadan kısmen kopyalanıp çoğaltılamaz.
3-Analiz sonuçları yukarıda verilen örnek için geçerlidir.
4-" * " Bu parametre TS EN ISO 15189 standardı doğrultusunda TÜRKAK tarafından akredite edilmiştir.

Belge Doğrulama Kodu: {4F7B6562-BA98-454D-927C-E959ECC4355D}
Belge Doğrulama Linki : www.nesiller.com - Kullanıcı Kodu ve Şifrenizi Bilmiyorsanız eğer Lütfen Bizimle Temasa Geçiniz.

19 Mayis Mahallesi Çoruh Sokak No:32 D:1
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Case ID **30572-RD**	Patient sex **Female**	Disease **Kaposi's sarcoma**	Tumor purity **70%**	Ordering physician
Patient MRN **30572**	Patient DOB **07/05/2003**	Sample type **Formalin Fixed Paraffin Embedded Tissue Scroll**	Sample collection date **02/09/2025**	Ordering institution not specified
Patient name **R.D**	Patient ethnicity not specified	Sample site not specified	Sample receipt date not specified	Ordering institution ID not specified

Report summary: **Kaposi's sarcoma**

1 Clinically significant biomarker
4 Other biomarkers
1 Combination

0 Relevant therapies

22 Clinical trials

Variants & other biomarkers	Therapies approved/recommended in current disease	Therapies approved/recommended in other disease
I-A **EWSR1::CREM** (exon 7::exon 5...	none	none
II-C combination **MSS**, **TMB** Low	none	none
I-B present in combination **TMB** Low	none	none
II-C other biomarker **HRDsig** Negative	none	Excluded from report
II-C present in combination **MSS**	none	none
other biomarker **Genomic LOH** Undetermined	none	none

* With altered response, † With resistance

EWSR1::CREM (exon 7::exon 5... # Reads **149** AF **15.75%** Reading Frame **In frame** Tier I-A

EWSR1 fusion (variant group): EWSR1 fusions aid in the diagnosis of several sarcomas. Specifically, EWSR1-ERG, EWSR1-ETV1, EWSR1-ETV4, EWSR1-FEV and EWSR1-FLI1 fusions aid in the diagnosis of Ewing sarcoma/peripheral neuroectodermal tumor (WHO, NCCN, ESMO). EWSR1-PATZ1 fusions also aid in the diagnosis of Ewing sarcoma/peripheral neuroectodermal tumor (NCCN). EWSR1-ATF1 and EWSR1-CREB1 fusions aid in the diagnosis of clear cell sarcoma (WHO, NCCN) and angiomatoid fibrous histiocytoma (WHO, NCCN). EWSR1-CREM fusions also aid in the diagnosis of angiomatoid fibrous histiocytoma (WHO). EWSR1-DDIT3 fusions aid in the diagnosis of myxoid/round cell liposarcoma (WHO, NCCN). The presence of EWSR1-DDIT3 fusion excludes a diagnosis of myxoid pleomorphic liposarcoma (WHO). EWSR1-NR4A3 fusions aid in the diagnosis of extraskeletal myxoid chondrosarcoma (WHO, NCCN). EWSR1-WT1 fusions aid in the diagnosis of desmoplastic small round cell tumors (WHO, NCCN). EWSR1-NFATC2 and EWSR1-PATZ1 fusions aid in the diagnosis of round cell sarcoma with EWSR1-non-ETS fusions (WHO). EWSR1-TFCP2 fusions may aid in the diagnosis of spindle cell rhabdomyosarcoma (WHO). EWSR1-CREB3L1 fusions have been observed in a few patients with low-grade fibromyxoid sarcoma. Patients with EWSR1 translocation positive sarcomas match inclusion criteria for clinical trials, such as trials of anti-PD-L1 monoclonal antibodies, CDK inhibitors, bi-functional short hairpin RNA lipoplexes, VEGFR2/3 inhibitors and certain chemotherapy combinations. EWSR1 rearrangements, such as EWSR1-ATF1 and EWSR1-CREM fusions, aid in the diagnosis of hyalinising clear cell carcinoma of the salivary gland (WHO). EWSR1 fusions have also been observed in a few cases of ependymoma.

No approved therapies

2

combination

Microsatellite Stable (MSS), Tumor Mutation Burden (TMB) - Low Tier II-C

In a retrospective clinical study, patients with microsatellite stable (MSS) solid tumors harboring low or intermediate tumor mutational burden (TMB) treated with immune checkpoint inhibitors demonstrated worse clinical benefit rate and median progression free survival compared to patients with MSS, TMB high tumors.

No approved therapies

variant present in combination

Tumor Mutation Burden (TMB) - Low Total TMB (mut/Mb) **1.21** Tier I-B

In a phase II study of patients with solid tumors treated with the combination of PD-1 and CTLA-4 antibodies, tumor mutational burden (TMB) status was not predictive of clinical benefit. In a retrospective analysis of patients with solid tumors treated with immune checkpoint inhibitors, patients with solid tumors harboring intermediate or low TMB demonstrated shorter overall survival compared to patients with TMB high tumors, and TMB was an independent prognostic factor for OS after multivariate analysis. In patients not treated with immune checkpoint inhibitors, patients with TMB low solid tumors had better survival compared to patients with TMB high or intermediate tumors.

No approved therapies

other biomarker

Homologous Recombination Deficiency Signature (HRDsig) - Negative

Score **0.0561**

Tier II-C

A real-world pan-cancer study reports that HRDsig negative status was common in cancers such as thyroid cancer, acute leukemia and myelodysplastic syndrome. There is a therapy recommendation for certain patients with ovarian cancers based on homologous recombination deficiency (HRD) negative status (outlined in evidence table).

Genomic LOH and HRDsig are only read from certain Roche assays that are for research use only and not for use in diagnostics procedures

Therapies excluded from report

variant present in combination

Microsatellite Stable (MSS)

Value **0.0022**

Tier II-C

There are approved and/or recommended therapies for certain patients with endometrial carcinoma based on mismatch repair proficient (pMMR) status. In a retrospective analysis, among patients with solid tumors, microsatellite instability (MSI) status was not significantly associated with overall survival.

No approved therapies

other biomarker

Loss of Heterozygosity (LOH) - Undetermined

Unclassified

Genomic LOH and HRDsig are only read from certain Roche assays that are for research use only and not for use in diagnostics procedures

No approved therapies

Clinical trials from MolecularMatch

Selected trials recruiting: **Female, age ≥ 18 anywhere**

Variants matched **1**.

Genes matched **0**.

NCT06279130 Phase 2, 3

MSS

Pan-tumor Neoadjuvant Basket Study of Immune Check-point Inhibition and Novel Immuno-oncology Combinations

NCT04977453 Phase 1, 2

MSS

GI-101 as a Single Agent or in Combination With Pembrolizumab, Lenvatinib or Local Radiotherapy in Advanced Solid Tumors

NCT05669430 Phase 1, 2

MSS

A Study of GV20-0251 Monotherapy and GV20-0251 in Combination With Pembrolizumab in Participants With Solid Tumor Malignancies

NCT04895709 Phase 1, 2

MSS

A Study of BMS-986340 as Monotherapy and in Combination With Nivolumab or Docetaxel in Participants With Advanced Solid Tumors

NCT03947385 Phase 1, 2

MSS

Study of IDE196 in Patients with Solid Tumors Harboring GNAQ/11 Mutations or PRKC Fusions

NCT07070518 Phase 1, 2

MSS

Study of GV20-0251 in Participants With Solid Tumor Malignancies

NCT06898450 Phase 1, 2

MSS

A Study to Assess the Safety, Tolerability, and Efficacy of NDI-219216 in Patients With Advanced Solid Tumors.

NCT05919264 Phase 1, 2

MSS

FOG-001 in Locally Advanced or Metastatic Solid Tumors

NCT04903873 Phase 1, 2

MSS

A Study to Evaluate Safety, Efficacy, and Pharmacokinetics in Participants With Advanced Solid Tumors

NCT03810339 Phase 2

MSS

Toripalimab as Monotherapy in Participants With POLE or POLD-1 Mutated and Non-MSI-H Advanced Solid Tumors

NCT05691491 Phase 1, 2

MSS

Testing the Combination of the Anti-Cancer Drugs Temozolomide and M1774 to Evaluate Their Safety and Effectiveness

NCT05944237 Phase 1, 2

MSS

HTL0039732 in Participants With Advanced Solid Tumours

NCT06697197 Phase 1, 2

MSS

A Study of BMS-986482 Alone or as Combination Therapy in Participants With Advanced Solid Tumors

NCT06468358 Phase 1, 2

MSS

A Study to Evaluate LB1410 in Combination With LB4330 in Patients With Advanced or Metastatic Solid Tumors

NCT05784688 Phase 1, 2

MSS

Study of TU2218 in Combination With KEYTRUDA®(Pembrolizumab) in Patients With Advanced Solid Tumors

NCT05584670 Phase 1, 2

MSS

A First-in-human, Dose Escalation and Dose Expansion Study of SAR445877 in Adult Participants With Advanced Solid Tumors

NCT05533697 Phase 1, 2

MSS

Study of mRNA-4359 Administered Alone and in Combination With Immune Checkpoint Blockade in Participants With Advanced Solid Tumors

NCT04896697 Phase 1, 2

MSS

Vilastobart (XTX101) Monotherapy and Vilastobart and Atezolizumab Combination Therapy in Advanced Solid Tumors

NCT04284488 Phase 1, 2

MSS

Dose-escalation Study of APG-1387 and Toripalimab in Solid Tumors

NCT06330064 Phase 2

MSS

A Study To Evaluate The Efficacy And Safety Of Ifinatamab Deruxtecan (I-DXd) In Subjects With Recurrent Or Metastatic Solid Tumors (IDeate-PanTumor02)

NCT05684965 Phase 1, 2

MSS

XTX301 in Patients With Advanced Solid Tumors

NCT05268666 Phase 1, 2

MSS

A Study of Orally Administered JBI-802, an LSD1/HDAC6 Inhibitor, in Patients With Advanced Solid Tumors

End of findings section

Addendum

EWSR1::CREM (exon 7::exon 5) fusion

Tier I-A

Gene clinical summary
Alterations in EWSR1 are found in cancers, including Ewing sarcoma (PMID: 21872822), melanoma (PMID: 29625048) and bladder cancer (PMID: 29625048) (PMID: 24320889). EWSR1 fusions with proto-oncogenes result in expression of oncogenic fusion proteins and tumorigenesis (PMID: 28009602) (PMID: 29309308). Therapies targeting EWSR1 or its downstream effectors, including AURK, BET, and PARP inhibitors, are under clinical investigation (PMID: 25869102) (PMID: 27259270) (PMID: 21653923).

Variant group clinical summary
EWSR1 fusions aid in the diagnosis of several sarcomas.

Specifically, EWSR1-ERG (t(21;22)(q22;q12) translocations), EWSR1-ETV1 (t(7;22)(p22;q12) translocations), EWSR1-ETV4 ((t(17;22)(q12;q22), also referred to as EWSR1-E1AF), EWSR1-FEV (t(2;22)(q33;q12) translocations), EWSR1-FLI1 (t(11;22)(q24;q12) translocations) aid in the diagnosis of Ewing sarcoma/peripheral neuroectodermal tumor (WHO, NCCN, ESMO). EWSR1-PATZ1 fusions (inv(22)(q12;q12), also referred to as EWSR1-ZSG) aid in the diagnosis of Ewing sarcoma/peripheral neuroectodermal tumor (NCCN).

EWSR1-ATF1 fusions (t(12;22)(q13;q12) translocations) and EWSR1-CREB1 fusions (t(2;22)(q33;q12) translocations) aid in the diagnosis of clear cell sarcoma (WHO, NCCN) and angiomatoid fibrous histiocytoma (WHO, NCCN). EWSR1-CREM fusions also aid in the diagnosis of angiomatoid fibrous histiocytoma (WHO).

EWSR1-DDIT3 fusions (t(12;22)(q13;q12) translocations) aid in the diagnosis of myxoid/round cell liposarcoma (WHO, NCCN). The presence of EWSR1-DDIT3 fusion excludes a diagnosis of myxoid pleomorphic liposarcoma (WHO).

EWSR1-NR4A3 fusions (t(9;22)(q22;q12) translocations) aid in the diagnosis of extraskeletal myxoid chondrosarcoma (WHO, NCCN).

EWSR1-WT1 fusions (t(11;22)(p(13;q12) translocations) aid in the diagnosis of desmoplastic small round cell tumors (WHO, NCCN).

EWSR1-NFATC2 and EWSR1-PATZ1 fusions aid in the diagnosis of round cell sarcoma with EWSR1-non-ETS fusions (WHO). EWSR1-TFCP2 fusions may aid in the diagnosis of spindle cell rhabdomyosarcoma (WHO).

EWSR1-CREB3L1 fusions have been observed in a few patients with low-grade fibromyxoid sarcoma (PMID: 23588368) (PMID: 24896634).

Patients with EWSR1 translocation positive sarcomas match inclusion criteria for clinical trials, such as trials of anti-PD-L1 monoclonal antibodies, CDK inhibitors, bi-functional short hairpin RNA lipoplexes, VEGFR2/3 inhibitors and certain chemotherapy combinations (clinicaltrials.gov).

EWSR1 rearrangements, such as EWSR1-ATF1 and EWSR1-CREM fusions, also aid in the diagnosis of hyalinizing clear cell carcinoma of the salivary gland (WHO) (PMID: 21484932) (PMID: 29975250) (PMID: 32816231).

EWSR1 fusions (such as EWSR1-PATZ1) have also been observed in a few cases of ependymoma (PMID: 36480780).

Gene biological summary
EWSR1 is a member of the FET family of DNA/RNA-binding proteins involved in transcriptional regulation and RNA processing (PMID: 30053258) (PMID: 21816343) (PMID: 30962207). Important regions in EWSR1 include an EAD region (residues 1-285), 31 X approximate tandem repeats (residues 8-285), and a nuclear localization signal (residues 639-656) (Uniprot).

Variant group functional summary
EWSR1-CREM results from the fusion of EWSR1 and CREM (PMID: 32668333). EWSR1-CREM has been identified in several tumor types including intracranial mesenchymal tumors (PMID: 32668333), paragangioma (PMID: 36083250), clear cell carcinomas (PMID: 34721908), and clear cell sarcomas (PMID: 30219084), and is predicted to result in gain of function based on the effects of other EWSR1 fusions (PMID: 7700648)(PMID: 10523827) (PMID: 10749119)(PMID: 17172842)(PMID: 9591781)(PMID: 15826834)..

Fusions of the N-terminal transcriptional activating domain of EWSR1 with the C-terminal DNA binding domain of a fusion partner result in novel transcription factor activity (PMID: 19936782). Many EWSR1 fusions are transforming in vitro and in vivo (PMID: 7700648)(PMID: 10523827) (PMID: 10749119)(PMID: 17172842)(PMID: 9591781)(PMID: 15826834).

MSS, TMB Low

Tier II-C

Variant combination clinical summary
In a retrospective clinical study, patients with microsatellite stable (MSS) solid tumors harboring low or intermediate tumor mutational burden (TMB) (n=54) treated with immune checkpoint inhibitors (pembrolizumab, nivolumab, atezolizumab, ipilimumab and nivolumab, or nivolumab and bevacizumab) demonstrated worse clinical benefit rate (38%, 17/54 vs 75%) and median progression free survival (4.3 mo vs 26.8 mo) compared to patients with MSS, TMB high tumors (PMID: 31405947).

Variant combination functional summary
MSI stable indicates a lack of microsatellite instability (MSI). Microsatellites are repetitive stretches of DNA that are susceptible to mutation, and MSI is defined as a change in the size of these microsatellites compared to the normal genome. MSI results from a deficient DNA mismatch repair pathway (dMMR) caused by mutations or epigenetic inactivation of genes in the MMR pathway, including MSH2, MSH6, MLH1 and PMS2 (PMID: 35955855) (PMID: 26031544).

TMB low indicates a low tumor mutational burden. TMB is generally defined as the number of somatic mutations per megabase of genome examined. TMB levels correlate with the expression of neoantigens that can be targeted by activated immune cells (PMID: 30792906). The cut-offs for TMB low differ across tumor types and studies. Low levels of TMB have been identified in some tumor types and they are associated with prognosis or therapeutic response (PMID: 30395155) (PMID: 30505715).

TMB Low

Tier I-B

Variant clinical summary
In a phase II study of patients with solid tumors treated with the combination of nivolumab and ipilimumab, the objective response rate of patients with low tumor mutational burden (TMB) (n=70) was 31% compared to 36% in the TMB high patient cohort (n=11) (PMID: 33930312).

In a retrospective analysis of patients with solid tumors treated with immune checkpoint inhibitors (n=103), patients with solid tumors harboring intermediate (n=61) or low (n=33) tumor mutational burden (TMB) demonstrated shorter overall survival compared to patients with TMB high tumors (n=9), and TMB was an independent prognostic factor for OS after multivariate analysis. In patients not treated with immune checkpoint inhibitors (n=387), patients with TMB low solid tumors (n=101) had better survival compared to patients with TMB high (n=21) or intermediate (n=265) tumors (PMID: 32110280).

Another clinical study of patients with solid tumors treated with immune checkpoint inhibitors (n=93) found no association between TMB status and progression-free or overall survival (J Clin Oncol 36, no. 15_suppl).

Variant functional summary
TMB low indicates a low tumor mutational burden. TMB is generally defined as the number of somatic mutations per megabase of genome examined. TMB levels correlate with the expression of neoantigens that can be targeted by activated immune cells (PMID: 30792906). The cut-offs for TMB low differ across tumor types and studies. Low levels of TMB have been identified in some tumor types and they are associated with prognosis or therapeutic response (PMID: 30395155) (PMID: 30505715).

HRDsig Negative

Tier II-C

Variant clinical summary
In a real-world pan-cancer study, HRDsig negative status was common in cancers such as thyroid cancer, acute leukemia and myelodysplastic syndrome (PMID: 37769224).

There is a therapy recommendation for certain patients with ovarian cancers based on homologous recombination deficiency (HRD) negative status (outlined in evidence table).

Variant functional summary
Homologous recombination deficiency (HRD) refers to the inability of a cell to repair DNA damage through the use of homologous recombination repair (HRR) (PMID: 28250960). HRD is defined in several ways, including mutational signatures or genomic scarring that result from HRD or functional assays that measure HRD (PMID: 33004253). HRD negative tumors are considered to have functional HRR pathways.

HRD Signature (HRDsig) score is calculated by an algorithm which was trained on a classifier model utilizing over one hundred copy number features per genome across hundreds of solid cancer samples (PMID: 37769224). The algorithm generates a score ranging from zero (0) to one (1), which shows a bimodal distribution with most pan-cancer results determined to be between 0-0.2 or 0.8-1.

MSS

Tier II-C

Variant clinical summary
There are approved and/or recommended therapies for certain patients with endometrial carcinoma based on mismatch repair proficient (pMMR) status.

In a retrospective analysis, among patients with solid tumors (microsatellite stable (MSS) n=864, microsatellite instability-high (MSI-H) n=241), MSI status was not significantly associated with overall survival (HR=0.79, p=0.2343) (PMID: 27694933).

Variant functional summary
MSI stable indicates a lack of microsatellite instability (MSI). Microsatellites are repetitive stretches of DNA that are susceptible to mutation, and MSI is defined as a change in the size of these microsatellites compared to the normal genome. MSI results from a deficient DNA mismatch repair pathway (dMMR) caused by mutations or epigenetic inactivation of genes in the MMR pathway, including MSH2, MSH6, MLH1 and PMS2 (PMID: 35955855) (PMID: 26031544).

Genomic LOH Undetermined

Unclassified

Variant functional summary
LOH undetermined indicates that the level of genomic loss of heterozygosity cannot be determined. The LOH score is defined as the percent of LOH in the tumor genome. While LOH high tumors have been associated with prognosis and therapeutic response in some tumor types (PMID: 31785864) (PMID: 28916367), LOH low tumors have been associated with decreased therapeutic response.

Variants of unknown significance

The variants listed here are not sufficiently characterized in the current literature and variant databases, and are therefore, currently, of uncertain or unknown clinical significance. They are reported here for future reference in the event they become clinically significant in light of additional supporting evidence.

BRCA2 p.S384F	**NOTCH1** p.R703H	**NOTCH3** p.A1608T	**NOTCH2** p.Q466K
RET p.W942*	**SMARCB1** p.K97R		

Unclassified variants

The variants listed here have not been classified.

HSD3B1 amplification, ATM p.S1601N, BRCA2 p.A1891T, FGFR3 p.R110Q

Electronically Signed by Gülay Özgön | **Dr. Gülay Özgön** Lab Director | Lab Number: GHDM.SM / 34.09 / 01 | *21/11/2025*

Appendix

Gene List - DNA

ABL1 ACVR1B AKT1 AKT2 AKT3 ALK ALOX12B AMER1# (FAM123B or WTX) APC AR ARAF ARFRP1 ARID1A ASXL1 ATM ATR ATRX AURKA AURKB AXIN1 AXL B2M BAP1 BARD1 BCL2 BCL2L1 BCL2L2 BCL6 BCOR BCORL1 BRAF BRCA1 BRCA2 BRD4 BRIP1 BTG1 BTG2 BTK CALR CARD11 CASP8 CBFB CBL CCND1 CCND2 CCND3 CCNE1 CD22 CD274 (PD-L1) CD70 CD79A CD79B CDC73 CDH1 CDK12 CDK4 CDK6 CDK8 CDKN1A CDKN1B CDKN2A CDKN2B CDKN2C CEBPA CHEK1 CHEK2 CIC CREBBP CRKL CSF1R CSF3R CTCF CTNNA1 CTNNB1 CUL3 CUL4A CXCR4 CYP17A1 DAXX DDR1 DDR2 DICER 1 DIS3 DNMT3A DOT1L EED EGFR EMSY (C11orf30) EP300 EPHA3 EPHB1 EPHB4 ERBB2 ERBB3 ERBB4 ERCC4 ERG ERRFI1 ESR1 ETV6 EZH2 FANCA FANCC FANCG FANCL FAS FBXW7 FGF10 FGF12 FGF14 FGF19 FGF23 FGF3 FGF4 FGF6 FGFR1 FGFR2 FGFR3 FGFR4 FH FLCN FLT1 FLT3 FOXL2# FUBP1 GABRA6 GATA3 GATA4 GATA6 GID4 (C17orf39) GNA11 GNA13 GNAQ GNAS GRM3 GSK3B H3-3A (H3F3A) HDAC1 HGF HNF1A HRAS HSD3B1 ID3 IDH1 IDH2 IGF1R IKBKE IKZF1 IKZF2 IKZF3 INPP4B IRF2 IRF4 IRS2 JAK1 JAK2 JAK3 JUN KDM5A KDM5C KDM6A KDR KEAP1 KEL KIT KLHL6 KMT2A (MLL) KMT2D (MLL2) KRAS LTK LYN MAF MAP2K1 (MEK1) MAP2K2 (MEK2) MAP2K4 MAP3K1 MAP3K13 MAPK1 MCL1 MDM2 MDM4 MED12 MEF2B MEN1 MERTK MET MITF MKNK1 MLH1 MPL MRE11 (MRE11A) MSH2 MSH3 MSH6 MST1R MTAP MTOR MUTYH MYC MYCL (MYCL1) MYCN NBN MYD88 NF1 NF2 NFE2L2 NFKBIA NKX2-1 NOTCH1 NOTCH2 NOTCH3 NOTCH4 NPM1 NRAS NSD2 (WHSC1 or MMSET) NSD3 (WHSC1L1) NT5C2 NTRK1 NTRK2 NTRK3 P2RY8# PALB2 PARP1 PARP2 PARP3 PAX5 PBRM1 PDCD1 (PD-1) PDCD1LG2 (PD-L2) PDGFRA PDGFRB PDK1 PIK3C2B PIK3C2G PIK3CA PIK3CB PIK3R1 PIM1 PLCG2 PMS2 POLD1 POLE PPARG PPP2R1A PPP2R2A PRDM1 PRKAR1A PRKCI PRKN (PARK2) PTCH1 PTEN PTPN11 PTPRO QKI RAC1 RAD21 RAD51 RAD51B RAD51C RAD51D RAD52 RAD54L RAF1 RARA RB1 RBM10 REL RET RICTOR RNF43 ROS1 RPTOR RUNX1 SDHA SDHB SDHC SDHD SETD2 SF3B1 SGK1 SMAD2 SMAD4 SMARCA4 SMARCB1 SMO SNCAIP SOCS1# SOX2 SOX9 SPEN SPOP SRC SRSF2 STAG2 STAT3 STK11 SUFU SYK TBX3 TEK TENT5C# (FAM46C) TET2 TGFBR2 TIPARP TNFAIP3 TNFRSF14 TP53 TBX3 TP53BP1 TSC1 TSC2 TYRO3 U2AF1 VEGFA VHL WT1 XPO1 XRCC2 ZEB2 ZNF217 ZNF703 ZRSF2

Gene List - RNA

RARA RSPO2 TERC* BCL2 BRCA1 FGFR2 EGFR ETV6 FGFR1 KIT MYB PDGFRA RET SDC4 TERT (promoter only)** BCR BRCA2 ETV4 EWSR1 FGFR2 KMT2A (MLL) MYC NTRK2 RAF1 ROS1 SLC34A21 TMPRSS2

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Decisions on patient care and treatment must be based on the independent medical judgment of the treating physician, taking into consideration all applicable information concerning the patient's condition, including information not contained in this report such as other potentially clinically significant information. The information available in this report is obtained from third-party sources (such as biomedical literature, medical guidelines, and publicly available data such as drug labels and clinical trials) and is subject to change over time based on future scientific and medical findings. The selection of any, all or none of the potential therapies identified in this report resides entirely within the discretion of the treating physician, and this report makes no promises or guarantees that such potential therapies will be effective in the treatment of any patient.

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Clinical trial matching based on reported biomarkers are provided by MolecularMatch.

Tier definitions

Tier I-A:
Biomarkers that predict response or resistance AND are approved by drug agency or recommended by medical guidelines based on the region specified.

Biomarker that has prognostic or diagnostic clinical significance based on medical guidelines for the specified geographic region.

Tier I-B:
Biomarkers that predict response or resistance to therapies for the tumor type based on well-powered studies (clinical trials) with consensus from experts in the field.

Biomarkers that achieved high-clinical prognostic and diagnostic significance based on well-powered studies.
Tier II-C:
Biomarkers that predict response or resistance based on multiple small-published studies with emerging consensus.

Biomarkers that predict response or resistance to therapies approved by a drug agency or recommended by medical guidelines societies for a different type of tumor.

Biomarkers that serve as inclusion criteria for clinical trials.

Tier II-D:
Biomarkers that show plausible therapeutic significance based on at least one case report. Biomarkers with possible clinical significance based on preclinical studies.

Tier III (VUS):
Variants of unknown significance.

Not observed at a significant allele frequency across the general population or subpopulations or not well-represented in cancer databases.

No published functional evidence of cancer association.

Tier IV:
Observed at significant allele frequencies in the general population or specific subpopulations AND no published evidence of cancer association.

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