MOLECULAR GENETIC ANALYSIS REPORT

REPORT SUMMARY AND INTERPRETATION OF FINDINGS

Patient Name-Surname:	:XXXXX	**Protocol No**	:1111
Identification Number	:******	**Sex/Age**	:XX.XX.XXXX/F
Sample Type	: Liquid Biopsy	**Type of Test**	: Focus 77L
Reference Doctor	:XXXXX	**Reference Institution**	:XXXXX
Sample Arrival Date	:XX.XX.XXXX	**Sample Acceptance Date**	:XX.XX.XXXX
Report Date	:XX.XX.XXXX	**Sample Collection Date**	:XX.XX.XXXX
Indication	: Cholangiocarcinoma		

REPORT SUMMARY

Clinically Significant Biomarker : 2
Other Biomarkers : 0
Relevant Therapy : XX
Clinical Trial : XX

IMPORTANT GENETIC FINDINGS RELATED TO CHOLANGİOCARCİNOMA

Gene	Result
IDH1	**p.Arg132Gly (p.R132G)**
ERBB2	**Amplification**
FGFR2	Not Detected
BRAF	Not Detected
MLH1	Not Detected
MSH2	Not Detected
MSH6	Not Detected
PMS2	Not Detected

Gen	Result
KRAS	Not Detected
NRAS	Not Detected
PIK3CA	Not Detected
TP53	Not Detected
BRCA1	Not Detected
BRCA2	Not Detected
RET	Not Detected
NTRK1	Not Detected

Report Summary Findings

2 Clinically Significant Biomarkers Detected (IDH1 p.R132G and ERBB2 amplification)
Treatment Status: There are a total of 9 relevant/approved treatment options associated with the detected genetic alterations that can be evaluated (e.g., ivosidenib, trastuzumab + pertuzumab, trastuzumab deruxtecan, etc.).
Recommendation: There are 6 clinical trials available that may be suitable for the patient's molecular profile; evaluation of these trials and combination options is recommended in advanced-stage treatment management.

MOLECULAR GENETIC ANALYSIS REPORT

Patient Name-Surname:	:XXXXX	**Protocol No**	:1111

SUMMARY TABLE IN THE ORIGINAL REPORT

Variants & other biomarkers	Therapies approved/recommended in current disease	Therapies approved/recommended in other disease
ERBB2 amplification	pertuzumab + trastuzumab, trastuzumab deruxtecan, trastuzumab + tucatinib,zanidatamab	Yes
variant IDH1 p.R132G	ivosidenib	Excluded from report

This report summary was written by reviewing the Focus 77L analysis report finalized on xx.xx.xxxx.

In the study conducted on circulating cell-free tumor DNA from our patient diagnosed with cholangiocarcinoma, the clinically significant IDH1 p.R132G mutation and ERBB2 amplification were detected.

As a result of the Focus 77L study performed on patient XXX, no oncogenic fusion or rearrangement was detected in the FGFR2 gene. Additionally, BRAF and KRAS/NRAS genes were evaluated as wild-type, and no pathogenic fusion was detected in the RET gene.

EXPLANATION:

The alterations detected in the IDH1 and ERBB2 genes are pathogenic/clinically significant. In cholangiocarcinoma cases where a mutation in the IDH1 gene (p.R132G) is detected, treatment with ivosidenib, an isocitrate dehydrogenase 1 (IDH1) enzyme inhibitor, is approved and recommended by guidelines. Furthermore, the ERBB2 (HER2) amplification detected in the liquid biopsy analysis allows for the consideration of HER2-targeted combination therapies (trastuzumab + pertuzumab, trastuzumab deruxtecan, or zanidatamab) or clinical trial options, depending on the clinician's evaluation.

The results provided in this report are written only for the examined genes and regions and do not exclude the presence of mutations in unexamined genes. It is recommended that the results be evaluated together with the patient's clinical findings.

NOTE: The original report is a continuation of this report summary.

MOLEKÜLER GENETİK ANALİZ RAPORU

Patient Name-Surname:	:XXXXX	**Protocol No**	:1111

Analysis Method:

- **Platform / Device** : Roche Navify-Illumina NextSeq 550Dx (Next Generation Sequencing - NGS)
- **Panel Content / Target Region** : Roche AVENIO ctDNA Expanded Panel v2 (77 Genes)
- **Reference Genome** : hg38 / GRCh38
- **Sequencing Depth** : xxxxxx
- **Read Count** : XX million
- **Interpretation Standard** : AMP/ASCO/CAP Somatic Variant Classification Criteria and NCCN Guidelines

Dr. Gülay ÖZGÖN
Medical Geneticist
Expert License No: 68410

1-This document has been signed with a secure electronic signature in accordance with the Electronic Signature Law No. 5070.
2-Analysis results are valid for the example given above.
3-" + " This analysis was done in the External Laboratory.
4-" * " This parameter is accredited by TÜRKAK in line with TS EN ISO 15189 standard.

Document Verification Code: <Rapor GUID>
Document Verification Link: www.nesiller.com - If you do not know your User Code and Password, Please Contact Us.

Patient Name-Surname:	:XXXXX	**Protocol No**	:1111

77L Gene List

Variant Type	Genes Examined in the Panel
Single Nucleotide Variants (SNVs)	*ABL1, AKT1, AKT2, ALK, APC, AR, ARAF, BRAF, BRCA1, BRCA2, CCND1, CCND2, CCND3, CD274, CDK4, CDK6, CDKN2A, CSF1R, CTNNB1, DDR2, DPYD, EGFR, ERBB2, ESR1, EZH2, FBXW7, FGFR1, FGFR2, FGFR3, FLT1, FLT3, FLT4, GATA3, GNA11, GNAQ, GNAS, IDH1, IDH2, JAK2, JAK3, KDR, KEAP1, KIT, KRAS, MAP2K1, MAP2K2, MET, MLH1, MSH2, MSH6, MTOR, NF2, NFE2L2, NRAS, NTRK1, PDCD1LG2, PDGFRA, PDGFRB, PIK3CA, PIK3R1, PMS2, PTCH1, PTEN, RAF1, RB1, RET, RNF43, ROS1, SMAD4, SMO, STK11, TERT (promoter), TP53, TSC1, TSC2, UGT1A1, VHL*
Insertions and Deletions (Indels)	*ALK, APC, BRAF, CTNNB1, EGFR, ERBB2, KIT, MET, PIK3CA, PTEN, TSC1, VHL*
Fusions*	*ALK, FGFR2, FGFR3, NTRK1, RET, ROS1*
Copy Number Variations (CNVs)	*EGFR, ERBB2, MET*

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Case ID	Patient sex **Female**	Disease **Cholangiocarcinoma**	Tumor purity not specified	Ordering physician
Patient MRN	Patient DOB	Sample type **Plasma**	Sample collection date **06/07/2026**	Ordering institution not specified
Patient name	Patient ethnicity not specified	Sample site **Blood**	Sample receipt date not specified	Ordering institution ID not specified

Report summary: **Cholangiocarcinoma**

2 Clinically significant biomarkers **9** Relevant therapies **6** Clinical trials

Variants & other biomarkers	Therapies approved/recommended in current disease	Therapies approved/recommended in other disease
I-B **ERBB2** amplification	**pertuzumab + trastuzumab, trastuzumab deruxtecan, trastuzumab + tucatinib,zanidatamab**	Yes
I-B variant **IDH1** p.R132G	**ivosidenib**	Excluded from report

* With altered response, † With resistance

ERBB2 amplification

Quality Score **0.14**

Tier I-B

ERBB2 amplification (variant group): There are approved and recommended therapies for certain patients with solid tumors, including hepatobiliary cancer, harboring ERBB2 overexpression and/or amplification (outlined in evidence table). Additional studies suggest these patients may respond to anti-ERBB2 antibody-drug conjugates and a bispecific anti-ERBB2 antibody.

Therapies associated with: **Cholangiocarcinoma**

- pertuzumab + trastuzumab
- trastuzumab deruxtecan
- trastuzumab + tucatinib
- zanidatamab

Therapies approved/guidelines-recommended in: **other indications**

- lapatinib
- neratinib
- pertuzumab + trastuzumab
- trastuzumab
- trastuzumab deruxtecan
- trastuzumab emtansine

variant

IDH1 p.R132G

VAF **3.8%** RD **1,022**

Tier I-B

IDH1 (neomorphic) activating mutation (variant group): Patients with solid tumors harboring IDH1 (neomorphic) activating mutations match inclusion criteria for clinical trials, such as trials with inhibitors of IDH1, PARP, PARP and ATR, and glutaminase.

IDH1 codon 132 mutation (variant group): There are approved and/or recommended therapies for certain patients with IDH1 R132-mutant cholangiocarcinoma and other cancers (outlined in evidence table). In a phase III trial, patients with IDH1-mutated cholangiocarcinoma demonstrated significantly longer progression-free survival, overall survival and higher disease control rate when treated with an IDH1 inhibitor compared to placebo. In a phase I trial, IDH-mutant cholangiocarcinoma patients benefitted from an IDH1 inhibitor. In a phase II trial, patients with IDH-mutant cholangiocarcinoma did not respond to a PARP inhibitor in combination with immunotherapy. A retrospective study suggests IDH-mutant cholangiocarcinomas may be immunologically cold. Patients with IDH1-mutant solid tumors or cholangiocarcinoma match inclusion criteria for clinical trials, such as trials with inhibitors of IDH1, PARP, PARP and ATR, and glutaminase.

Therapies associated with: **Cholangiocarcinoma**

- ivosidenib

Clinical trials from MolecularMatch

Selected trials recruiting: **Female, age ≥ 18** within **Turkey**

Variants matched **1**.

Genes matched **1**.

NCT06282575 Phase 3

ERBB2 Amplification

Efficacy and Safety of Zanidatamab With Standard-of-care Therapy Against Standard-of-care Therapy for Advanced HER2-positive Biliary Tract Cancer

NCT06467357 Phase 3

ERBB2 - gene match

Phase 3 Study of T-DXd and Rilvegostomig Versus SoC in Advanced HER2-expressing Biliary Tract Cancer

NCT06764875 Phase 3

ERBB2 - gene match

A Phase Ⅲ Study of Rilvegostomig in Combination With Fluoropyrimidine and Trastuzumab Deruxtecan as the First-line Treatment for HER2-positive Gastric Cancer

NCT06330064 Phase 2

ERBB2 - gene match

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

NCT06532006 Phase 3

ERBB2 - gene match

A Phase Ⅲ Clinical Study of HLX22 in Combination With Trastuzumab and Chemotherapy for the Treatment of Gastroesophageal Junction and Gastric Cancer

NCT06731478 Phase 3

ERBB2 - gene match

Study of TDXd, Chemotherapy, Pembrolizumab, and Trastuzumab in First-Line Metastatic HER2-Positive Gastric or Gastroesophageal Junction Cancer

End of findings section

Addendum

ERBB2 amplification

Tier I-B

Therapy recommendations

Therapy	Approvals & recommendations from
pertuzumab + trastuzumab	ESMO, NCCN for this cancer
trastuzumab deruxtecan	ESMO, FDA, Health Canada, NCCN, Swissmedic for this cancer
trastuzumab + tucatinib	NCCN for this cancer
zanidatamab	EMA, ESMO, FDA, NCCN for this cancer
Associated therapy	Approvals & recommendations from
lapatinib	ANMAT, ANVISA, EMA, ESMO, FDA, HSA, Health Canada, ISPCH, MFDS, NCCN, Swissmedic, TFDA, TGA, TITCK, eviQ for Breast cancer
neratinib	ANMAT, ANVISA, EMA, ESMO, FDA, HSA, Health Canada, MFDS, NCCN, NICE, Swissmedic, TFDA, TGA, TITCK for Breast cancer
pertuzumab + trastuzumab	NCCN for Breast cancer, Colorectal cancer, Head and neck cancer, Oral cavity cancer, Pharynx cancer ESMO for Breast cancer, Colorectal cancer ANMAT, ANVISA, EMA, FDA, HSA, Health Canada, ISPCH, MFDS, NICE, Swissmedic, TFDA, TGA, TITCK, eviQ for Breast cancer
trastuzumab	ESMO for Breast cancer, Gastroesophageal junction adenocarcinoma, Head and neck cancer, Oral cavity cancer, Pharynx cancer, Stomach cancer NCCN for Breast cancer, Esophageal cancer, Gastroesophageal junction adenocarcinoma, Head and neck cancer, Oral cavity cancer, Pharynx cancer, Stomach cancer eviQ, ANMAT, EMA, FDA, HSA, Health Canada, ISPCH, MFDS, NICE, Swissmedic, TFDA, TGA, TITCK for Breast cancer, Gastroesophageal junction adenocarcinoma, Stomach cancer ANVISA, WHO for Breast cancer
trastuzumab deruxtecan	NCCN for Ampulla of Vater adenocarcinoma, Breast cancer, cancer, unknown primary, Cervical cancer, Colorectal cancer, Endometrial carcinoma, Esophageal cancer, Fallopian tube cancer, Gastroesophageal junction adenocarcinoma, Head and neck cancer, Non-small cell lung carcinoma, Oral cavity cancer, Ovarian cancer, Pancreatic cancer, Peritoneal carcinoma, Pharynx cancer, Small intestine cancer, Stomach cancer, Urinary bladder cancer, Uterine cancer, Uterine corpus endometrial carcinoma, Vaginal cancer, Vulva squamous cell carcinoma Swissmedic, FDA, Health Canada for Ampulla of Vater adenocarcinoma, Breast cancer, cancer, unknown primary, Cervical cancer, Colorectal cancer, Endometrial carcinoma, Esophageal cancer, Fallopian tube cancer, Gastroesophageal junction adenocarcinoma, Glioblastoma multiforme, Head and neck cancer, Kidney cancer, Liver cancer, Melanoma, Non-small cell lung carcinoma, Oral cavity cancer, Ovarian cancer, Pancreatic cancer, Peritoneal carcinoma, Pharynx cancer, Prostate cancer, Sarcoma, Small intestine cancer, Stomach cancer, Urinary bladder cancer, Uterine cancer, Uterine corpus endometrial carcinoma, Vaginal cancer, Vulva squamous cell carcinoma ESMO for Breast cancer, Colorectal cancer, Gastroesophageal junction adenocarcinoma, Stomach cancer TITCK, ANVISA, EMA, HSA, MFDS, TFDA, TGA for Breast cancer, Gastroesophageal junction adenocarcinoma, Stomach cancer ANMAT, ISPCH, NICE, eviQ for Breast cancer
trastuzumab emtansine	NCCN, ESMO for Breast cancer, Head and neck cancer, Oral cavity cancer, Pharynx cancer ANMAT, ANVISA, EMA, FDA, HSA, Health Canada, ISPCH, MFDS, NICE, Swissmedic, TFDA, TGA, TITCK, eviQ for Breast cancer
Note: Refer to the full guidelines of NCCN recommendations and NCCN Categories of Evidence and Consensus.	

Gene clinical summary

Oncogenic ERBB2 alterations, such as amplification and activating mutations are implicated in several cancers including breast, lung, and gastric cancer (PMID: 17471238). Several approved monoclonal antibodies, antibody-drug conjugates, and small molecule inhibitors and combination regimens target ERBB2 and other EGFR family members. Emerging therapies include additional tyrosine kinase inhibitors, immunotherapies, and PI3K pathway inhibitors (PMID: 27249772)(PMID: 30951733).

Variant group clinical summary
There are approved and recommended therapies for certain patients with solid tumors, including hepatobiliary cancer, harboring ERBB2 overexpression and/or amplification (outlined in evidence table).

In a phase II basket trial, 23% (9/39) of patients with biliary tract cancer harboring ERBB2 overexpression and/or amplification had a partial response with pertuzumab and trastuzumab in combination, and 28% (11/39) of these patients had stable disease for more than four months (PMID: 34339623). In another phase II trial, one of three ERBB2-amplified cholangiocarcinoma patients responded to trastuzumab and pertuzumab combination therapy and one patient with ERBB2-amplified gallbladder cancer had stable disease (PMID: 38433347). In phase II trials, trastuzumab treatment resulted in objective response rate (ORR) of 55.5% (50/90), and trastuzumab deruxtecan treatment resulted in ORR of 22.0% (9/41), 36.4% (8/22), and 25% (1/4) in patients with ERBB2-amplified/overexpressed biliary tract cancers (PMID: 37944079)(PMID: 37870536)(PMID: 39102634)(PMID: 39088783). In another phase II trial, 46.7% (14/30) of patients with ERBB2-positive biliary tract cancer responded to tucatinib in combination with trastuzumab (PMID: 37751561). In a phase 2b trial, 41.3% (33/80) of patients with ERBB2-amplified biliary tract cancer treated with zanidatamab had an objective response with a median duration of response over 11 months (PMID: 37276871), and two ERBB2-positive gallbladder patients responded to zanidatamab in a phase I trial (PMID: 38358339). In a phase I trial, trastuzumab rezetecan treatment demonstrated efficacy in patients with ERBB2-positive advanced solid tumors, resulting in an objective response rate of 61.6% (154/250) and a 6-month progression-free survival rate of 73.9%, including an objective response in five of eight patients with endometrial cancer (Cancer Res (2023) 83 (8_Supplement): CT175). In phase II trials, 12.5% (5/40) of patients with ERBB2-positive biliary tract cancers responded to trastuzumab emtansine and 20% (8/40) had stable disease (J Clin Oncol 43, 2025, (suppl 4; abstr 584)), and 3 patients with ERBB2 (HER2)-positive cholangiocarcinoma did not respond to trastuzumab emtansine (PMID: 37119523). One patient with extrahepatic cholangiocarcinoma harboring ERBB2 amplification and overexpression responded to trastuzumab emtansine in a case study (PMID: 32923849). In another clinical case study, one patient with cholangiocarcinoma harboring ERBB2 amplification achieved a partial response with lenvatinib and pembrolizumab combination therapy (PMID: 36973682).

In a phase I trial involving patients with solid tumors harboring ERBB2 alterations (mutations, amplification and rearrangements, n=26), treatment with an investigational ERBB2 inhibitor, BI 1810631, resulted in an overall response rate of 37% (7 partial responses, including one patient with cholangiocarcinoma) and a disease control rate of 84% (Eu J Cancer 2022 Vol 174, Supp 1:S1). In another phase I trial, 56.3% (9/16) of patients with ERBB2-amplified or ERBB2-mutated biliary tract cancer responded to an anti-ERBB2 antibody drug conjugate (PMID: 38900984). In a phase I trial, BB-1701 treatment was well tolerated and demonstrated activity in patients with advanced solid tumors with ERBB2 overexpression, resulting in a best overall response rate of 50% (13/26, all partial responses), a disease control rate of 92.3% (24/26), with stable disease in 11 patients (J Clin Oncol 41, 2023 (suppl 16; abstr 3029)).

Gene biological summary
ERBB2 (HER2) is an EGFR receptor tyrosine kinase, which activates PI3K/AKT/MTOR and RAS/RAF/MEK pathways to regulate cell proliferation, differentiation, growth, and apoptosis (PMID: 11350724). ERBB2 lacks a well-characterized ligand and exists in a constitutively "open" conformation, always able to form heteromeric dimers with ligand-bound HER1 (EGFR), HER3, or HER4 (PMID: 12605220)(PMID: 30951733). The most important domains in ERBB2 are the extracellular domain (residues 23-652) and the tyrosine kinase domain (residues 720-987), which contains an autoinhibitory loop (PMID: 18039657) (UniProt.org).

Variant group functional summary
ERBB2 (HER2) amplification indicates an increased number of copies of the ERBB2 gene. These mutations are highly correlated with overexpression of ERBB2 protein (PMID: 28445098) and have been demonstrated to be oncogenic (PMID: 23400474).

IDH1 p.R132G missense variant

Tier I-B

Variant Group	Variant Oncogenicity	Position (GRCh38)	HGVS	Transcript
IDH1 (neomorphic) activating mutation IDH1 codon 132 mutation	Gain of function	Chr:2 Pos:208248389 Change:G>C	c.394C>G p.Arg132Gly	ENST00000345146.6

Therapy recommendations

Therapy	Approvals & recommendations from
ivosidenib	ANMAT, ANVISA, EMA, ESMO, FDA, Health Canada, MFDS, NCCN, NICE, Swissmedic, TGA, eviQ for this cancer
Note: Refer to the full guidelines of NCCN recommendations and NCCN Categories of Evidence and Consensus.	

Gene clinical summary
Alterations in IDH1 are found in cancers, including colorectal, brain, and blood cancer. Missense mutations in the active site result in neomorphic enzymatic activity, converting α-KG to R-2-hydroxyglutarate (2-HG). 2-HG is an oncogenic metabolite that inhibits α-KG-dependent enzymes. Therapies targeting IDH are under investigation or are approved or recommended in IDH1-altered cancers (PMID: 34974243).

Variant group clinical summary
Patients with solid tumors harboring IDH1 (neomorphic) activating mutations match inclusion criteria for clinical trials, such as trials with IDH1, PARP, glutaminase, and ATR inhibitors (clinicaltrials.gov).

There are approved and/or recommended therapies for certain patients with IDH1 R132-mutant cholangiocarcinoma and other cancers (outlined in evidence table).

In a phase III trial, patients with IDH1-mutated cholangiocarcinoma treated with ivosidenib (n=124) demonstrated longer progression-free survival (median PFS: 2.7 vs 1.4 months; HR: 0.37 [95% CI 0.25–0.54] p<0·0001), and higher disease control rate (53% (three partial responses) vs 28%) compared to patients treated with placebo (n=61) (PMID: 32416072) (NCT02989857). In the same trial, IDH1-mutated cholangiocarcinoma patients demonstrated longer overall survival on ivosidenib therapy (median OS: 10.3 vs 7.5 months; HR=0.79 [95% CI 0.56–1.12] p=0.093) compared to placebo, and when adjusted for crossover, median OS was 5.1 months (HR=0.49 [95% CI 0.34-0.70], p less than 0.001) (PMID: 34554208). In a phase I trial, LY3410738 treatment resulted in D-2-HG inhibition in patients with IDH-mutant advanced solid tumors, and led to partial response in 1 and stable disease in 22 of 42 patients with relapsed or refractory cholangiocarcinoma (Cancer Res (2023) 83 (8_Supplement): CT098; NCT04521686).

In a phase II trial, combination treatment with olaparib and durvalumab was well tolerated but failed to demonstrate efficacy in patients with advanced cholangiocarcinoma harboring mutations in IDH1 or IDH2, with no objective responses, a disease control rate of 30% (3/10, 3 stable disease), and a median progression-free survival of 1.97 months (J Clin Oncol 41, 2023 (suppl 16; abstr 4099)). In a retrospective study, no significant difference in overall survival was observed in cholangiocarcinoma patients with mutations in IDH1 (OS=43 months, n=69) or IDH2 (OS=89 months, n=15) compared to IDH wild type (OS=36 months, n=394, p=0.293), however differences in immune markers, such as lower tumor mutational burden, microsatellite instability, and genomic loss of heterozygosity, suggest IDH-mutant cholangiocarcinoma may be immunologically cold (PMID: 38547421).

Patients with IDH1-mutant solid tumors or cholangiocarcinoma match inclusion criteria for clinical trials, such as trials with inhibitors of IDH1, PARP, PARP and ATR, and glutaminase (clinicaltrials.gov).

Gene biological summary
IDH1, a cytoplasmic isocitrate dehydrogenase, catalyzes the conversion of isocitrate to α-ketoglutarate (α-KG) in metabolic pathways (PMID: 23999441). Important domains in IDH1 include two NADP binding domains (residues 75-77 and 310-315) and the substrate binding site (residues 77, 109 and 132) (UniProt).

Variant functional summary
IDH1 R132G lies within the active site of the IDH1 protein (PMID: 19228619). This mutation confers a gain of novel function to IDH1, as indicated by production of 2-hydroxyglutarate (2HG) in patient tissue and in vitro assays (PMID: 28330869) (PMID: 24529257) (PMID: 19935646).

Variant group functional summary
IDH1 (neomorphic) activating mutations confer a gain of novel function to IDH1 by enabling conversion of alpha-ketoglutarate to the onco-metabolite 2HG (R(-)-2-hydroxyglutarate). This results in increased 2HG levels in patient samples and is transforming in cell culture (PMID: 20171147)(PMID: 23071358) (PMID: 23558173)(PMID: 25495392)(PMID: 27621679).

IDH1 codon 132 mutation indicates any mutation in codon 132 of the IDH1 gene. Many of these mutations confer a gain of novel function to IDH1 by enabling conversion of alpha-ketoglutarate to the onco-metabolite 2HG (R(-)-2-hydroxyglutarate). This results in increased 2HG levels in patient samples and is transforming in cell culture (PMID: 20171147)(PMID: 23071358)(PMID: 23558173)(PMID: 25495392)(PMID: 27621679).

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.

STK11 p.P315P	**MTOR** p.S1821T

Electronically Signed by Gülay Özgön | **Dr. Gülay Özgön** Lab Director | *13/07/2026*

Appendix

Gene List (SNVs)

ABL1, AKT1, AKT2, ALK, APC, AR, ARAF, BRAF, BRCA1, BRCA2, CCND1, CCND2, CCND3, CD274>, CDK4, CDK6, CDKN2A, CSF1R, CTNNB1, DDR2, DPYD, EGFR, ERBB2, ESR1, EZH2, FBXW7, FGFR1, FGFR2, FGFR3, FLT1, FLT3, FLT4, GATA3, GNA11, GNAQ, GNAS, IDH1, IDH2, JAK2, JAK3, KDR, KEAP1, KIT, KRAS, MAP2K, MAP2K2, MET, MLH1, MSH2, MSH6, MTOR, NF2, NFE2L2, NRAS, NTRK1, PDCD1LG2, PDGFRA, PDGFRAB, PIK3CA, PIK3R1, PMS2, PTCH1, PTEN, RAF1, RB1, RET, RNF43, ROS1, SMAD4, SMO, STK11, TER promoter, TP53 TSC1, TSC2, UGT1A1, VHL

Gene List (Indels)

ALK, APC, BRAF, CTNNB1, EGFR, ERBB2, KIT, MET, PIK3CA, PTEN, TSC1, VHL

Gene List (Fusions*)

ALK, FGFR2, FGFR3, NTRK1, RET, ROS1 * Füzyon deteksiyonu için seçilmiş intron bölgelerini içerir.

Gene List (CNVs)

EGFR, ERBB2, MET

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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.

Software and content version numbers

navify® Mutation Profiler Version 2.7.2.63cb336, Release date: 20/11/2025

Roche content Version 2.89.0, Release date: 08/08/2025

CIViC Version 01-Aug-2025, Release date: 01/08/2025

ClinVAR Version 20250807, Release date: 07/08/2025

COSMIC Version v102, Release date: 21/05/2025

dbNSFP Version 4.9a, Release date: 08/08/2024

gnomAD Version 2.1.1, Release date: 06/03/2019

TCGA Version 43.0, Release date: 07/05/2025

Mitelman Version 10-July-2025, Release date: 10/07/2025

dbVar Version 30-Oct-2023, Release date: 30/10/2023

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