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**Patient Name:** 구광서
**Gender:** M
**Sample ID:** N25-333

**Primary Tumor Site:** skin
**Collection Date:** 20251125

## Sample Cancer Type: Melanoma

| Table of Contents | Page |
|---|---|


### Report Highlights
6 Relevant Biomarkers
3 Therapies Available
16 Clinical Trials

## Relevant Melanoma Findings

| Gene | Finding | Gene | Finding |
|---|---|---|---|
| BRAF | None detected | NTRK2 | None detected |
| KIT | None detected | NTRK3 | None detected |
| NRAS | None detected | RET | None detected |
| NTRK1 | None detected | ROS1 | None detected |

| Genomic Alteration | Finding |
|---|---|
| Tumor Mutational Burden | ***10.42 Mut/Mb measured*** |

## Relevant Biomarkers

| Tier | Genomic Alteration | Relevant Therapies (In this cancer type) | Relevant Therapies (In other cancer type) | Clinical Trials |
|---|---|---|---|---|
| IIC | *MET amplification*<br>MET proto-oncogene, receptor tyrosine kinase<br>Locus: chr7:116339789 | None* | capmatinib<br>crizotinib<br>tepotinib | 11 |
| IIC | *ATM deletion*<br>ATM serine/threonine kinase<br>Locus: chr11:108098341 | None* | None* | 5 |
| IIC | *BRCA1 deletion*<br>BRCA1, DNA repair associated<br>Locus: chr17:41197602 | None* | None* | 3 |
| IIC | *CDK12 deletion*<br>cyclin dependent kinase 12<br>Locus: chr17:37618286 | None* | None* | 1 |

*** Public data sources included in relevant therapies: FDA**[1], NCCN, **EMA**[2], ESMO
*** Public data sources included in prognostic and diagnostic significance:** NCCN, ESMO
**Line of therapy:** I: First-line therapy, II+: Other line of therapy
**Tier Reference:** Li et al. *Standards and Guidelines for the Interpretation and Reporting of Sequence Variants in Cancer: A Joint Consensus Recommendation of the Association for Molecular Pathology, American Society of Clinical Oncology, and College of American Pathologists.* J Mol Diagn. 2017 Jan;19(1):4-23.

## Relevant Biomarkers (continued)

| Tier | Genomic Alteration | Relevant Therapies (In this cancer type) | Relevant Therapies (In other cancer type) | Clinical Trials |
|---|---|---|---|---|
| IIC | *CHEK1 deletion*<br>checkpoint kinase 1<br>Locus: chr11:125496639 | None* | None* | 1 |
| IIC | *RAD51D deletion*<br>RAD51 paralog D<br>Locus: chr17:33427950 | None* | None* | 1 |

*** Public data sources included in relevant therapies: FDA**1, NCCN, **EMA**2, ESMO
*** Public data sources included in prognostic and diagnostic significance:** NCCN, ESMO
**Line of therapy:** I: First-line therapy, II+: Other line of therapy
**Tier Reference:** Li et al. *Standards and Guidelines for the Interpretation and Reporting of Sequence Variants in Cancer: A Joint Consensus Recommendation of the Association for Molecular Pathology, American Society of Clinical Oncology, and College of American Pathologists.* J Mol Diagn. 2017 Jan;19(1):4-23.

### Prevalent cancer biomarkers without relevant evidence based on included data sources

*CBL p.(Y371H) c.1111T>C, FGFR4 p.(D127H) c.379G>C, Microsatellite stable, NF1 p.(W221*) c.662G>A, TERT c.-146C>T, TP53 p.(D281N) c.841G>A, HLA-B deletion, HDAC9 p.(Q631*) c.1891C>T, Tumor Mutational Burden*

## Variant Details

### DNA Sequence Variants

| Gene | Amino Acid Change | Coding | Variant ID | Locus | Allele Frequency | Transcript | Variant Effect |
|---|---|---|---|---|---|---|---|
| CBL | p.(Y371H) | c.1111T>C | COSM34052 | chr11:119148891 | 19.26% | NM_005188.4 | missense |
| FGFR4 | p.(D127H) | c.379G>C | . | chr5:176517769 | 53.77% | NM_213647.3 | missense |
| NF1 | p.(W221*) | c.662G>A | . | chr17:29508735 | 17.83% | NM_001042492.3 | nonsense |
| TERT | p.(?) | c.-146C>T | COSM1716559 | chr5:1295250 | 6.00% | NM_198253.3 | unknown |
| TP53 | p.(D281N) | c.841G>A | COSM43596 | chr17:7577097 | 24.46% | NM_000546.6 | missense |
| HDAC9 | p.(Q631*) | c.1891C>T | . | chr7:18767362 | 8.36% | NM_178425.3 | nonsense |
| NRXN1 | p.(P1122S) | c.3364C>T | . | chr2:50692580 | 35.19% | NM_004801.5 | missense |
| PARD3B | p.(Q152H) | c.456G>T | . | chr2:205912365 | 53.70% | NM_152526.6 | missense |
| HLA-B | p.([T118I;L119I]) | c.353_355delCCCinsTCA | . | chr6:31324208 | 100.00% | NM_005514.8 | missense, missense |
| PXDNL | p.(E437Q) | c.1309G>C | . | chr8:52361619 | 18.38% | NM_144651.5 | missense |
| PXDNL | p.(E433Q) | c.1297G>C | . | chr8:52361631 | 18.39% | NM_144651.5 | missense |
| C8orf89 | p.(Q66*) | c.196C>T | . | chr8:74169293 | 44.26% | NM_001243237.1 | nonsense |
| CYP2C9 | p.(S365N) | c.1094G>A | . | chr10:96741072 | 7.59% | NM_000771.4 | missense |
| SYT10 | p.(D479N) | c.1435G>A | . | chr12:33532832 | 14.69% | NM_198992.4 | missense |
| TRHDE | p.(A775T) | c.2323G>A | . | chr12:73012672 | 13.04% | NM_013381.3 | missense |
| PARP4 | p.(?) | c.3285_3285+5delinsAGT | . | chr13:25021149 | 100.00% | NM_006437.4 | unknown |
| ERCC4 | p.(L151F) | c.451C>T | . | chr16:14020480 | 14.45% | NM_005236.3 | missense |
| PRDM7 | p.(?) | c.194-3C>T | . | chr16:90141434 | 9.18% | NM_001098173.2 | unknown |

# Variant Details (continued)

## Copy Number Variations

| Gene | Locus | Copy Number | CNV Ratio |
|---|---|---|---|
| MET | chr7:116339789 | 8.2 | 2.55 |
| ATM | chr11:108098341 | 1 | 0.93 |
| BRCA1 | chr17:41197602 | 1 | 0.95 |
| CDK12 | chr17:37618286 | 1 | 0.92 |
| CHEK1 | chr11:125496639 | 1 | 0.92 |
| RAD51D | chr17:33427950 | 1 | 0.99 |
| HLA-B | chr6:31322252 | 0.42 | 0.6 |

# Biomarker Descriptions

**MET amplification**

*MET proto-oncogene, receptor tyrosine kinase*

Background: The MET gene encodes the MET proto-oncogene, encodes a receptor tyrosine kinase for the hepatocyte growth factor (HGF) protein, which is expressed by mesenchymal cells[47]. MET is expressed as multiple isoforms with transcript variant 1 (NM_001127500.3) encoding a 1408 amino acid protein and transcript variant 2 (NM_000245.4) encoding a 1390 amino acid protein, both of which possess an intact protein kinase domain[47]. Ubiquitin-dependent proteolysis is responsible for regulating the steady-state level of the MET protein via recognition of the tyrosine phosphorylation site Y1003(NM_000245.4), sometimes referred to as Y1021 (NM_001127500.3), in the MET Cbl-binding domain within the juxtamembrane region[133,134,135]. Growth factor signaling leads to MET dimerization and subsequent initiation of downstream effectors, including those involved in the RAS/RAF/MEK/ERK and PI3K/AKT signaling pathways, which regulate cell migration, proliferation, and survival[136,137].

Alterations and prevalence: Somatic mutations in MET are observed in 10% of uterine corpus endometrial carcinoma, 9% of skin cutaneous melanoma, 8% of kidney renal papillary cell carcinoma (PRCC), 4% of lung adenocarcinoma, colorectal adenocarcinoma, bladder urothelial carcinoma, and uterine carcinosarcoma, and 2% of diffuse large B-cell lymphoma, esophageal adenocarcinoma, glioblastoma multiforme, lung squamous cell carcinoma, stomach adenocarcinoma, and sarcoma[16,35]. Recurrent somatic mutations fall into two classes, mutations in the MET kinase domain, which are uncommon, and splice-site mutations affecting exon 14[138]. Recurrent kinase domain mutations are observed in PRCC and include M1250T, H1094Y, and V1070E (NM_000245.4)[16,35,138]. Mutation of the Y1003 phosphorylation site is reported in approximately 2% of MET altered lung cancer[139]. In contrast, splice-site mutations flanking exon 14 are observed in 3-4% of all non-small cell lung cancer (NSCLC)[140]. These mutations include canonical splice site mutations affecting exon 14 and deletions that extend into the splicing motifs within intron 13[139,141]. Such mutations disrupt splicing leading to the formation of an alternative transcript that joins exon 13 directly to exon 15 and skips exon 14 entirely. The MET exon 14 skipping transcript lacks the juxtamembrane domain that contains the recognition motif for ubiquitin-dependent proteolysis and thus leads to a marked increase in the steady-state level of the MET protein[142]. MET exon 14 skipping mutations act as oncogenic drivers in lung cancer mutually exclusive to activating mutations in EGFR and KRAS and other oncogenic fusions such as ALK and ROS1[141,143,144]. MET amplification is observed in 3% of esophageal adenocarcinoma, ovarian serous cystadenocarcinoma, stomach adenocarcinoma, and glioblastoma multiforme, and 2% of lung adenocarcinoma, liver hepatocellular carcinoma, bladder urothelial carcinoma, diffuse large B-cell lymphoma, kidney renal papillary cell carcinoma, skin cutaneous melanoma, sarcoma, and kidney chromophobe[16,35]. Recurrent MET fusions, although infrequent, are observed in adult and pediatric glioblastoma, papillary renal cell carcinoma, lung cancer, liver cancer, thyroid cancer, and melanoma[145,146,147]. MET alterations are believed to be enriched in late-stage cancers where they drive tumor progression and metastasis[148,149,150]. Alterations in MET are rare in pediatric cancers[16,35]. Somatic mutations are observed in less that 1% of embryonal tumors (3 in 332 cases), bone cancer (2 in 327 cases), glioma(1 in 297 cases), leukemia (1 in 354 cases), peripheral nervous system cancers (2 in 1158 cases), and Wilms tumor (1 in 710 cases)[16,35]. Amplification of MET is observed in less than 1% of Wilms tumor (1 in 136 cases) and B-lymphoblastic leukemia/lymphoma (3 in 731 cases)[16,35].

Potential relevance: In 2020, the FDA granted accelerated approval to capmatinib[151] for NSCLC harboring MET exon 14 skipping positive as detected by an FDA-approved test. The kinase inhibitor, tepotinib[152], is also approved (2021) for MET exon 14 skipping mutations in NSCLC. MET exon 14 skipping mutations confer sensitivity to approved kinase inhibitors including crizotinib (2011), which is recommended for MET amplifications and exon 14 skipping mutations[141,143,144,153]. The FDA also granted breakthrough therapy designation (2018) to crizotinib for metastatic non-small cell lung cancer (NSCLC) with MET exon 14 alterations with disease progression on or after platinum-based chemotherapy[154]. MET amplification has been observed to mediate resistance to EGFR

## Biomarker Descriptions (continued)

tyrosine kinase inhibitors (TKIs)[155,156,157,158,159]. The FDA has granted fast track designation (2021) to the MET/CSF1R/SRC small molecule inhibitor, elzovantinib (TPX-0022)[160], for MET amplified advanced or metastatic gastric cancer and gastroesophageal junction adenocarcinoma (GEJ) after prior chemotherapy. Tepotinib has also been recommended for treatment of NSCLC with high-level MET amplification[153]. The MET inhibitor savolitinib is also under investigation, with results from a phase II clinical trial showing increased progression-free survival in patients with advanced PRCC who had MET alterations compared to those with MET-independent PRCC[161]. MET amplification is a diagnostic marker of infant-type hemispheric glioma[162,163].

**ATM deletion**

*ATM serine/threonine kinase*

Background: The ATM gene encodes a serine/threonine kinase that belongs to the phosphatidylinositol-3-kinase related kinases (PIKKs) family of genes that also includes ATR and PRKDC (also known as DNA-PKc)[71]. ATM and ATR act as master regulators of DNA damage response. Specifically, ATM is involved in double-stranded break (DSB) repair while ATR is involved in single-stranded DNA (ssDNA) repair[72]. ATM is recruited to the DNA damage site by the MRE11/RAD50/NBN (MRN) complex that senses DSB[72,73]. Upon activation, ATM phosphorylates several downstream proteins such as the NBN, MDC1, BRCA1, CHK2 and TP53BP1 proteins[74]. ATM is a tumor suppressor gene and loss of function mutations in ATM are implicated in the BRCAness phenotype, which is characterized by a defect in homologous recombination repair (HRR), mimicking BRCA1 or BRCA2 loss[69,75]. Germline mutations in ATM often result in Ataxia-telangiectasia, a hereditary disease also referred to as DNA damage response syndrome that is characterized by chromosomal instability[76].

Alterations and prevalence: Recurrent somatic mutations in ATM are observed in 17% of endometrial carcinoma, 15% of undifferentiated stomach adenocarcinoma, 13% of bladder urothelial carcinoma, 12% of colorectal adenocarcinoma, 9% of melanoma as well as esophagogastric adenocarcinoma and 8% of non-small cell lung cancer[16,35].

Potential relevance: The PARP inhibitor, olaparib[39] is approved (2020) for metastatic castration-resistant prostate cancer (mCRPC) with deleterious or suspected deleterious, germline or somatic mutations in HRR genes that includes ATM. Additionally, talazoparib[41] in combination with enzalutamide is approved (2023) for metastatic castration-resistant prostate cancer (mCRPC) with mutations in HRR genes that includes ATM. Consistent with other genes associated with the BRCAness phenotype, ATM mutations may aid in selecting patients likely to respond to PARP inhibitors[75,77,78]. Specifically, in a phase II trial of metastatic, castration-resistant prostate cancer, four of six patients with germline or somatic ATM mutations demonstrated clinical responses to olaparib[79]. In 2022, the FDA granted fast track designation to the small molecule inhibitor, pidnarulex[46], for BRCA1/2, PALB2, or other homologous recombination deficiency (HRD) mutations in breast and ovarian cancers.

**BRCA1 deletion**

*BRCA1, DNA repair associated*

Background: The breast cancer early onset gene 1 (BRCA1) encodes one of two BRCA proteins (BRCA1 and BRCA2) initially discovered as major hereditary breast cancer genes. Although structurally unrelated, both BRCA1 and BRCA2 exhibit tumor suppressor function and are integrally involved in the homologous recombination repair (HRR) pathway, a pathway critical in the repair of damaged DNA[21,22]. Specifically, BRCA1/2 are required for the repair of chromosomal double strand breaks (DSBs) which are highly unstable and compromise genome integrity[21,22]. Inherited pathogenic mutations in BRCA1/2 are known to confer increased risk in women for breast and ovarian cancer and in men for breast and prostate cancer[23,24,25]. For individuals diagnosed with inherited pathogenic or likely pathogenic BRCA1/2 variants, the cumulative risk of breast cancer by 80 years of age was 69-72% and the cumulative risk of ovarian cancer by 70 years was 20-48%[23,26].

Alterations and prevalence: Inherited BRCA1/2 mutations occur in 1:400 to 1:500 individuals and are observed in 10-15% of ovarian cancer, 5-10% of breast cancer, and 1-4% of prostate cancer[27,28,29,30,31,32,33,34]. Somatic alterations in BRCA1 are observed in 5-10% of uterine corpus endometrial carcinoma, cutaneous melanoma, bladder urothelial carcinoma, diffuse large B-cell lymphoma, and cervical squamous cell carcinoma, 3-4% of lung squamous cell carcinoma, lung adenocarcinoma, stomach adenocarcinoma, ovarian serous cystadenocarcinoma, colorectal adenocarcinoma, and breast invasive carcinoma, and 2% of head and neck squamous cell carcinoma and glioblastoma multiforme[16,35].

Potential relevance: Individuals possessing BRCA1/2 pathogenic germline or somatic mutations are shown to exhibit sensitivity to platinum based chemotherapy as well as treatment with poly (ADP-ribose) polymerase inhibitors (PARPi)[36]. Inhibitors targeting PARP induce synthetic lethality in recombination deficient BRCA1/2 mutant cells[37,38]. Consequently, several PARP inhibitors have been FDA approved for BRCA1/2-mutated cancers. Olaparib[39] (2014) was the first PARPi to be approved by the FDA for BRCA1/2 aberrations. Originally approved for the treatment of germline variants, olaparib is now indicated (2018) for the maintenance treatment of both germline BRCA1/2-mutated (gBRCAm) and somatic BRCA1/2-mutated (sBRCAm) epithelial ovarian, fallopian tube, or primary peritoneal cancers that are responsive to platinum-based chemotherapy. Olaparib is also indicated for the treatment of patients with gBRCAm HER2-negative metastatic breast cancer and metastatic pancreatic adenocarcinoma. Additionally, olaparib[39] is approved

## Biomarker Descriptions (continued)

(2020) for metastatic castration-resistant prostate cancer (mCRPC) with deleterious or suspected deleterious, germline or somatic mutations in HRR genes that includes BRCA1. Rucaparib[40] is also approved (2020) for deleterious gBRCAm or sBRCAm mCRPC and ovarian cancer. Talazoparib[41] (2018) is indicated for the treatment of gBRCAm HER2-negative locally advanced or metastatic breast cancer. Additionally, talazoparib[41] in combination with enzalutamide is approved (2023) for metastatic castration-resistant prostate cancer (mCRPC) with mutations in HRR genes that includes BRCA1. Niraparib[42] (2017) is another PARPi approved for the treatment of epithelial ovarian, fallopian tube, or primary peritoneal cancers with a deleterious or suspected deleterious BRCA mutation. Niraparib in combination with abiraterone acetate[43] received FDA approval (2023) for the treatment of deleterious or suspected deleterious BRCA-mutated (BRCAm) mCRPC. Despite tolerability and efficacy, acquired resistance to PARP inhibition has been clinically reported[44]. One of the most common mechanisms of resistance includes secondary intragenic mutations that restore BRCA1/2 functionality[45]. In addition to PARP inhibitors, other drugs which promote synthetic lethality have been investigated for BRCA mutations. In 2022, the FDA granted fast track designation to the small molecule inhibitor, pidnarulex[46], for BRCA1/2, PALB2, or other homologous recombination deficiency (HRD) mutations in breast and ovarian cancers. Like PARPi, pidnarulex promotes synthetic lethality but through an alternative mechanism which involves stabilization of G-quadruplexes at the replication fork leading to DNA breaks and genomic instability.

**CDK12 deletion**

*cyclin dependent kinase 12*

Background: CDK12 encodes the cyclin-dependent kinase 12 protein and is required for the maintenance of genomic stability[66,67,68]. CDK12 phosphorylates RNA polymerase II and is a regulator of transcription elongation and expression of DNA repair genes[66,67,68,69,70]. Alterations in CDK12 impair the transcription of homologous recombination repair (HRR) genes such as BRCA1, ATR, FANCI, and FANCD2, contributing to a BRCAness phenotype[68,69]. CDK12 is a tumor suppressor gene and loss of function mutations are observed in various solid tumors[70]. However, observations of CDK12 amplification and overexpression in breast cancer indicate that it could also function as an oncogene[70].

Alterations and prevalence: Somatic alterations of CDK12 include mutations and amplification. Missense and truncating mutations in CDK12 are observed in 8% of undifferentiated stomach adenocarcinoma, 7% of bladder urothelial, and 6% endometrial carcinoma[16,47]. CDK12 is amplified in 9% of esophagogastric adenocarcinoma and invasive breast carcinoma, 8% of undifferentiated stomach adenocarcinoma, and 3% of bladder urothelial and endometrial carcinoma[16,47].

Potential relevance: The PARP inhibitor, olaparib[39] is approved (2020) for metastatic castration-resistant prostate cancer (mCRPC) with deleterious or suspected deleterious, germline or somatic mutations in HRR genes that includes CDK12. Additionally, talazoparib[41] in combination with enzalutamide is approved (2023) for mCRPC with mutations in HRR genes that includes CDK12. Consistent with other genes associated with homologous recombination repair, CDK12 loss may aid in selecting patients likely to respond to PARP inhibitors[69,70]. In 2022, the FDA granted fast track designation to the small molecule inhibitor, pidnarulex[46], for BRCA1/2, PALB2, or other homologous recombination deficiency (HRD) mutations in breast and ovarian cancers.

**CHEK1 deletion**

*checkpoint kinase 1*

Background: The CHEK1 gene encodes the checkpoint kinase 1 protein and belongs to a family of serine/threonine checkpoint kinases, that also includes CHEK2[47]. Checkpoint kinases play an important role in S phase and G2/M transition and DNA damage induced cell cycle arrest[55]. CHEK1 is a tumor suppressor and it interacts with proteins involved in transcription regulation, cell-cycle arrest, and DNA repair including homologous recombination repair (HRR)[56,57]. Upon DNA damage, CHEK1 is phosphorylated and activated by DNA damage repair proteins ATM and ATR[56]. Activated CHEK1 subsequently phosphorylates and negatively regulates downstream proteins such as CDC25A thereby slowing or stalling DNA replication[56,58].

Alterations and prevalence: Recurrent somatic alterations of CHEK1 include mutations and copy number loss. Somatic mutations of CHEK1 are observed in 3% of endometrial carcinoma, 2% of non-small cell lung cancer and 1% of cervical squamous carcinoma cases[16,59]. CHEK1 copy number loss occurs in 10% of seminoma, 8% of non-seminomatous germ cell tumor, 5% of ocular melanoma, and 3% of melanoma cases[16,59].

Potential relevance: The PARP inhibitor, olaparib[39] is approved (2020) for metastatic castration-resistant prostate cancer (mCRPC) with deleterious or suspected deleterious, germline or somatic mutations in HRR genes that includes CHEK1. In 2022, the FDA granted fast track designation to the small molecule inhibitor, pidnarulex[46], for BRCA1/2, PALB2, or other homologous recombination deficiency (HRD) mutations in breast and ovarian cancers.

## Biomarker Descriptions (continued)

**RAD51D deletion**

*RAD51 paralog D*

Background: The RAD51D gene encodes the RAD51 paralog D protein, a member of the RAD51 recombinase family that also includes RAD51, RAD51B (RAD51L1), RAD51C (RAD51L2), XRCC2, and XRCC3 paralogs. The RAD51 family proteins are involved in homologous recombination repair (HRR) and DNA repair of double-strand breaks (DSB)[80]. RAD51D associates with other RAD51 paralogs to form RAD51B-RAD51C-RAD51D-XRCC2 (BCDX2) complex[81]. The BCDX2 complex binds single- and double-stranded DNA to hydrolyze ATP[82]. RAD51D is a tumor suppressor gene. Loss of function mutations in RAD51D are implicated in the BRCAness phenotype, which is characterized by a defect in HRR, mimicking BRCA1 or BRCA2 loss[69,75]. Germline point mutations in RAD51D are implicated in non-BRCA2 associated breast, ovarian, and colorectal cancer[83].

Alterations and prevalence: Somatic mutations in RAD51D are rare but have been reported in 1-2% of uterine cancer[16].

Potential relevance: The PARP inhibitor, olaparib[39] is approved (2020) for metastatic castration-resistant prostate cancer (mCRPC) with deleterious or suspected deleterious, germline or somatic mutations in HRR genes that includes RAD51D. Additionally, consistent with other genes associated with the BRCAness phenotype, RAD51D mutations may aid in selecting patients likely to respond to PARP inhibitors[75]. In 2022, the FDA granted fast track designation to the small molecule inhibitor, pidnarulex[46], for BRCA1/2, PALB2, or other homologous recombination deficiency (HRD) mutations in breast and ovarian cancers.

**CBL p.(Y371H) c.1111T>C**

*Cbl proto-oncogene*

Background: The CBL gene encodes the casitas B-lineage lymphoma (CBL) ubiquitin ligase, a member of the ubiquitin ligase (E3) protein family that also includes CBL-b and CBL-c[7]. CBL proteins are characterized by their highly conserved N-terminal tyrosine kinase binding (TKB) domain and RING finger (RF) catalytic domain which are directly involved in the regulation of receptor tyrosine kinase (RTK) signaling[7,8]. Upon recognition of an activated RTK via its TKB domain, CBL mediates the transfer of ubiquitin from the ubiquitin-conjugating enzyme (E2) via its RF domain, consequently targeting the RTK for proteasome degradation. CBL can also function as an adaptor protein via recruitment of signaling molecules to active RTKs[8]. CBL is the target of genetic aberrations, including missense mutations and translocations, which can lead to oncogenic transformation in hematological malignancies as well as solid tumors[8,9,10,11]. Mutations in CBL often result in a loss of E3 ligase activity, thereby preventing proteasome-mediated RTK degradation, which supports the role of CBL as a tumor suppressor gene[9]. However, CBL mutants often maintain their adapter function, contributing to their transforming potential and suggesting a simultaneous oncogenic role for CBL in cancer[8]. Hereditary mutations in CBL lead to constitutive activation of RAS and MAPK pathways resulting in genetic disorders known as RASopathies which can lead to increased cancer risk[4].

Alterations and prevalence: Genetic alterations in CBL were first recognized in acute myeloid leukemia (AML) as a result of an interstitial deletion leading to MLL::CBL fusion[12,13]. However, fusions involving CBL are relatively rare. Aberrations in CBL most often involve missense mutations which commonly cluster in the linker region or RF domain corresponding to exons 8 and 9[8,9]. Such mutations lead to disruption of E3 ligase activity and have been reported in systemic mastocytosis (SM), 1-3% of de novo AML, 10% of secondary AML, 8% of atypical AML, and 10-15% of juvenile myelomonocytic leukemia (JMML) and chronic myelomonocytic leukemia (CMML)[8,14,15,16,17,18,19]. Mutations in CBL have also been reported in 1-6% of melanomas, lung, stomach, colorectal, esophageal, and uterine cancers[11,16].

Potential relevance: Mutations in CBL confer adverse prognosis in SM and have been shown to be independently predictive of inferior survival[15,20].

**FGFR4 p.(D127H) c.379G>C**

*fibroblast growth factor receptor 4*

Background: The FGFR4 gene encodes fibroblast growth receptor 4, a member of the fibroblast growth-factor receptor (FGFR) family that also includes FGFR1, 2, and 3. These proteins are single-transmembrane receptors composed of three extracellular immunoglobulin (Ig)-type domains and an intracellular kinase domain. Upon FGF-mediated stimulation, FGFRs activate several oncogenic signaling pathways, including the RAS/RAF/MEK/ERK, PI3K/AKT/MTOR, PLC/PKC, and JAK/STAT pathways influencing cell proliferation, migration, and survival[164,165,166]. FGFR4 selectively binds the ligand FGF19, wherein FGF19-mediated aberrant signaling has been identified as an oncogenic driver in hepatocellular carcinoma[167,168].

Alterations and prevalence: Aberrations most common to the FGFR family are amplifications, followed by mutations and fusions. The majority of these aberrations result in gain of function[169]. FGFR4 exhibits amplification in up to 15% of clear-cell renal cell carcinomas, with somatic mutations observed in up to 6% of melanomas and uterine cancer[16,35].

## Biomarker Descriptions (continued)

Potential relevance: Currently, no targeted therapies are approved for FGFR4 aberrations. However, FDA-approved multi-kinase inhibitors known to inhibit FGFR family members, including regorafenib (2013), ponatinib (2012), lenvatinib (2015), nintedanib (2014), and pazopanib (2009), have demonstrated anti-tumor activity in select cancer types harboring FGFR alterations[170,171,172,173,174,175,176]. Selective, irreversible FGFR4 inhibitors, including BLU-554, have underwent clinical trial evaluation. In a phase-I clinical study of BLU-554 in patients with FGF19-positive advanced hepatocellular carcinoma, the overall response rate was 17%[177].

**Microsatellite stable**

Background: Microsatellites are short tandem repeats (STR) of 1 to 6 bases of DNA between 5 to 50 repeat units in length. There are approximately 0.5 million STRs that occupy 3% of the human genome[111]. Microsatellite instability (MSI) is defined as a change in the length of a microsatellite in a tumor as compared to normal tissue[112,113]. MSI is closely tied to the status of the mismatch repair (MMR) genes. In humans, the core MMR genes include MLH1, MSH2, MSH6, and PMS2[114]. Mutations and loss of expression in MMR genes, known as defective MMR (dMMR), lead to MSI. In contrast, when MMR genes lack alterations, they are referred to as MMR proficient (pMMR). Consensus criteria were first described in 1998 and defined MSI-high (MSI-H) as instability in two or more of the following five markers: BAT25, BAT26, D5S346, D2S123, and D17S250[115]. Tumors with instability in one of the five markers were defined as MSI-low (MSI-L) whereas, those with instability in zero markers were defined as MS-stable (MSS)[115]. Tumors classified as MSI-L are often phenotypically indistinguishable from MSS tumors and tend to be grouped with MSS[116,117,118,119,120]. MSI-H is a hallmark of Lynch syndrome (LS), also known as hereditary non-polyposis colorectal cancer, which is caused by germline mutations in the MMR genes[113]. LS is associated with an increased risk of developing colorectal cancer, as well as other cancers, including endometrial and stomach cancer[112,113,117,121].

Alterations and prevalence: The MSI-H phenotype is observed in 30% of uterine corpus endothelial carcinoma, 20% of stomach adenocarcinoma, 15-20% of colon adenocarcinoma, and 5-10% of rectal adenocarcinoma[112,113,122,123]. MSI-H is also observed in 5% of adrenal cortical carcinoma and at lower frequencies in other cancers such as esophageal, liver, and ovarian cancers[122,123].

Potential relevance: Anti-PD-1 immune checkpoint inhibitors including pembrolizumab[124] (2014) and nivolumab[125] (2015) are approved for patients with MSI-H or dMMR colorectal cancer who have progressed following chemotherapy. Pembrolizumab[124] is also approved as a single agent, for the treatment of patients with advanced endometrial carcinoma that is MSI-H or dMMR with disease progression on prior therapy who are not candidates for surgery or radiation. Importantly, pembrolizumab is approved for the treatment of MSI-H or dMMR solid tumors that have progressed following treatment, with no alternative option and is the first anti-PD-1 inhibitor to be approved with a tumor agnostic indication[124]. Dostarlimab[126] (2021) is also approved for dMMR recurrent or advanced endometrial carcinoma or solid tumors that have progressed on prior treatment and is recommended as a subsequent therapy option in dMMR/MSI-H advanced or metastatic colon or rectal cancer[118,127]. The cytotoxic T-lymphocyte antigen 4 (CTLA-4) blocking antibody, ipilimumab[128] (2011), is approved alone or in combination with nivolumab in MSI-H or dMMR colorectal cancer that has progressed following treatment with chemotherapy. MSI-H may confer a favorable prognosis in colorectal cancer although outcomes vary depending on stage and tumor location[118,129,130]. Specifically, MSI-H is a strong prognostic indicator of better overall survival (OS) and relapse free survival (RFS) in stage II as compared to stage III colorectal cancer patients[130]. The majority of patients with tumors classified as either MSS or pMMR do not benefit from treatment with single-agent immune checkpoint inhibitors as compared to those with MSI-H tumors[131,132]. However, checkpoint blockade with the addition of chemotherapy or targeted therapies have demonstrated response in MSS or pMMR cancers[131,132].

**NF1 p.(W221*) c.662G>A**

*neurofibromin 1*

Background: The NF1 gene encodes the neurofibromin protein, a tumor suppressor within the Ras-GTPase-activating protein (GAP) family[1]. NF1 regulates cellular levels of activated RAS proteins including KRAS, NRAS, and HRAS, by down regulating the active GTP-bound state to an inactive GDP-bound state[1,2]. Inactivation of NF1 due to missense mutations results in sustained intracellular levels of RAS-GTP and prolonged activation of the RAS/RAF/MAPK and PI3K/AKT/mTOR signaling pathways leading to increased proliferation and survival[1]. Constitutional mutations in NF1 are associated with neurofibromatosis type 1, a RASopathy autosomal dominant tumor syndrome with predisposition to myeloid malignancies such as juvenile myelomonocytic leukemia (JMML) and myeloproliferative neoplasms (MPN)[1,3,4].

Alterations and prevalence: NF1 aberrations include missense mutations, insertions, indels, aberrant splicing, microdeletions, and rearrangements[1]. The majority of NF1 mutated tumors exhibit biallelic inactivation of NF1, supporting the 'two-hit' hypothesis of carcinogenesis[1,5]. Somatic mutations in NF1 have been identified in over 30% of ovarian serous carcinoma, 12-30% of melanoma, 10-20% of chronic myelomonocytic leukemia (CMML), and 7% of acute myeloid leukemia (AML)[1,4].

Potential relevance: Currently, no therapies are approved for NF1 aberrations. Somatic mutation of NF1 is useful as an ancillary diagnostic marker for malignant peripheral nerve sheath tumor (MPNST)[6].

## Biomarker Descriptions (continued)

**TERT c.-146C>T**

*telomerase reverse transcriptase*

Background: The TERT gene encodes telomerase reverse transcriptase, a component of the telomerase core enzyme along with the internal telomerase RNA template (TERC)[84]. TERT is repressed in most differentiated cells, resulting in telomerase silencing[84]. In cancer, telomerase reactivation is known to contribute to cellular immortalization[84,85]. Increased TERT expression results in telomerase activation, allowing for unlimited cancer cell proliferation through telomere stabilization[84]. In addition to its role in telomere maintenance, TERT has RNA-dependent RNA polymerase activity, which, when deregulated, can promote oncogenesis by facilitating mitotic progression and cancer cell stemness[84].

Alterations and prevalence: Somatic mutations are observed in 4% of skin cutaneous melanoma and uterine corpus endometrial carcinoma, 3% of kidney renal papillary cell carcinoma, and 2% of pancreatic adenocarcinoma, stomach adenocarcinoma, and sarcoma[16,35]. Additionally, TERT promoter mutations causing upregulation are observed in many cancer types, especially non-aural cutaneous melanoma (80% of cases), and glioblastoma (70% of cases)[85]. Specifically, TERT promoter mutations at C228T and C250T are recurrent and result in de novo binding sites for ETS transcription factors, leading to enhanced TERT transcription[84]. Amplification of TERT is observed in 15% of lung squamous cell carcinoma, 14% of esophageal adenocarcinoma, 13% of adrenocortical carcinoma and lung adenocarcinoma, and 10% of bladder urothelial carcinoma, 9% of ovarian serous cystadenocarcinoma, 6% of cervical squamous cell carcinoma, 5% of liver hepatocellular carcinoma, sarcoma, skin cutaneous melanoma, stomach adenocarcinoma, head and neck squamous cell carcinoma, 4% of uterine carcinosarcoma, 3% of uterine corpus endometrial carcinoma, breast invasive carcinoma, and 2% of diffuse large B-cell lymphoma[16,35]. TERT is overexpressed in over 85% of tumors and is considered a universal tumor associated antigen[86]. Alterations in TERT are rare in pediatric cancers[16,35]. Somatic mutations are observed in less than 1% of B-lymphoblastic leukemia/lymphoma (2 in 252 cases), glioma (2 in 297 cases), bone cancer (1 in 327 cases), and Wilms tumor (1 in 710 cases)[16,35]. TERT amplification is observed in 1-2% of peripheral nervous system cancers (2 in 91 cases), leukemia (2 in 250 cases), and B-lymphoblastic leukemia/lymphoma (5 in 731 cases)[16,35].

Potential relevance: Currently, no therapies are approved for TERT aberrations. TERT promoter mutations are diagnostic of oligodendroglioma IDH-mutant with 1p/19q co-deletion, while the absence of promoter mutations combined with an IDH mutation is characteristic of astrocytoma[87,88]. Due to its immunogenicity and near-universal expression on cancer cells, TERT has been a focus of immunotherapy research, including peptide, dendritic, and DNA vaccines as well as T-cell therapy[86].

**TP53 p.(D281N) c.841G>A**

*tumor protein p53*

Background: The TP53 gene encodes the tumor suppressor protein p53, which binds to DNA and activates transcription in response to diverse cellular stresses to induce cell cycle arrest, apoptosis, or DNA repair[47]. In unstressed cells, TP53 is kept inactive by targeted degradation via MDM2, a substrate recognition factor for ubiquitin-dependent proteolysis[89]. Alterations in TP53 are required for oncogenesis as they result in loss of protein function and gain of transforming potential[90]. Germline mutations in TP53 are the underlying cause of Li-Fraumeni syndrome, a complex hereditary cancer predisposition disorder associated with early-onset cancers[91,92].

Alterations and prevalence: TP53 is the most frequently mutated gene in the cancer genome with approximately half of all cancers experiencing TP53 mutations. Ovarian, head and neck, esophageal, and lung squamous cancers have particularly high TP53 mutation rates (60-90%)[16,35,93,94,95,96]. Approximately two-thirds of TP53 mutations are missense mutations and several recurrent missense mutations are common, including substitutions at codons R158, R175, Y220, R248, R273, and R282[16,35]. Invariably, recurrent missense mutations in TP53 inactivate its ability to bind DNA and activate transcription of target genes[97,98,99,100]. Alterations in TP53 are also observed in pediatric cancers[16,35]. Somatic mutations are observed in 53% of non-Hodgkin lymphoma, 24% of soft tissue sarcoma, 19% of glioma, 13% of bone cancer, 9% of B-lymphoblastic leukemia/lymphoma, 4% of embryonal tumors, 3% of Wilms tumor and leukemia, 2% of T-lymphoblastic leukemia/lymphoma, and less than 1% of peripheral nervous system cancers (5 in 1158 cases )[16,35]. Biallelic loss of TP53 is observed in 10% of bone cancer, 2% of Wilms tumor, and less than 1% of B-lymphoblastic leukemia/lymphoma (2 in 731 cases) and leukemia (1 in 250 cases)[16,35].

Potential relevance: The small molecule p53 reactivator, PC14586[101] (2020), received a fast track designation by the FDA for advanced tumors harboring a TP53 Y220C mutation. In addition to investigational therapies aimed at restoring wild-type TP53 activity, compounds that induce synthetic lethality are also under clinical evaluation[102,103]. TP53 mutation are a diagnostic marker of SHH-activated, TP53-mutant medulloblastoma[104]. TP53 mutations confer poor prognosis and poor risk in multiple blood cancers including AML, MDS, myeloproliferative neoplasms (MPN), and chronic lymphocytic leukemia (CLL), and acute lymphoblastic leukemia (ALL)[4,105,106,107,108]. In mantle cell lymphoma, TP53 mutations are associated with poor prognosis when treated with conventional therapy including hematopoietic cell transplant[109]. Mono- and bi-allelic mutations in TP53 confer unique characteristics in MDS,

## Biomarker Descriptions (continued)

with multi-hit patients also experiencing associations with complex karyotype, few co-occurring mutations, and high-risk disease presentation as well as predicted death and leukemic transformation independent of the IPSS-R staging system[110].

**HLA-B deletion**

*major histocompatibility complex, class I, B*

Background: The HLA-B gene encodes the major histocompatibility complex, class I, B[47]. MHC (major histocompatibility complex) class I molecules are located on the cell surface of nucleated cells and present antigens from within the cell for recognition by cytotoxic T cells[60]. MHC class I molecules are heterodimers composed of two polypeptide chains, α and B2M[61]. The classical MHC class I genes include HLA-A, HLA-B, and HLA-C and encode the α polypeptide chains, which present short polypeptide chains, of 7 to 11 amino acids, to the immune system to distinguish self from non-self[62,63,64]. Downregulation of MHC class I promotes tumor evasion of the immune system, suggesting a tumor suppressor role for HLA-B[65].

Alterations and prevalence: Somatic mutations in HLA-B are observed in 10% of diffuse large B-cell lymphoma (DLBCL), 5% of cervical squamous cell carcinoma and stomach adenocarcinoma, 4% of head and neck squamous cell carcinoma and colorectal adenocarcinoma, 3% of uterine cancer, and 2% of esophageal adenocarcinoma and skin cutaneous melanoma[16,35]. Biallelic loss of HLA-B is observed in 5% of DLBCL[16,35].

Potential relevance: Currently, no therapies are approved for HLA-B aberrations.

**HDAC9 p.(Q631*) c.1891C>T**

*histone deacetylase 9*

Background: The HDAC9 gene encodes the histone deacetylase 9 protein[47]. HDAC9 is part of the histone deacetylase (HDAC) family consisting of 18 different isoforms categorized into four classes (I-IV)[48]. HDACs, including HDAC9, function by removing acetyl groups on histone lysines resulting in chromatin condensation, transcriptional repression, and regulation of cell proliferation and differentiation[48,49]. HDAC9 functions in neurological function, brain development, and maintains regulatory T-cell homeostasis[48]. HDAC deregulation, including overexpression, is observed in a variety of tumor types, which is proposed to affect the expression of genes involved in cellular regulation and promote tumor development[48,50].

Alterations and prevalence: Somatic mutations in HDAC9 are observed in 16% of skin cutaneous melanoma, 8% of lung adenocarcinoma, 7% of colorectal adenocarcinoma, 6% of uterine corpus endometrial carcinoma and lung squamous cell carcinoma, 4% of esophageal adenocarcinoma, 3% of esophageal adenocarcinoma, head and neck squamous cell carcinoma, cholangiocarcinoma, and stomach adenocarcinoma, and 2% of liver hepatocellular carcinoma, diffuse large B-cell lymphoma, cervical squamous cell carcinoma, bladder urothelial carcinoma, pancreatic adenocarcinoma, and kidney chromophobe[16,35]. Biallelic deletion of HDAC9 is observed in 2% of diffuse large B-cell lymphoma[35]. Alterations in HDAC9 are also observed in pediatric cancers[35]. Somatic mutations in HDAC9 are observed in 2% of T-lymphoblastic leukemia/lymphoma (1 in 41 cases) and less than 1% of embryonal tumors (2 in 332 cases), B-lymphoblastic leukemia/lymphoma (1 in 252 cases), glioma (1 in 297 cases), leukemia (1 in 311 cases), bone cancer (1 in 327 cases), and peripheral nervous system cancers (1 in 1158 cases)[35]. Biallelic deletion of HDAC9 is observed in 1% of peripheral nervous system cancers (1 in 91 cases) and less than 1% of B-lymphoblastic leukemia/lymphoma (3 in 731 cases)[35].

Potential relevance: Currently, no therapies are approved for HDAC9 aberrations. Although not approved for specific HDAC2 alterations, the pan-HDAC inhibitor vorinostat[51] (2006) is approved for the treatment of progressive, persistent, or recurrent cutaneous T-cell lymphoma (CTCL) following treatment with two systemic therapies. The pan-HDAC inhibitor, romidepsin[52] (2009), is approved for the treatment of CTCL and peripheral T-cell lymphoma (PTCL) having received at least one prior systemic therapy. The pan-HDAC inhibitor, belinostat[53] (2014), is approved for the treatment of relapsed or refractory PTCL. The FDA granted fast track designation to the pan-HDAC inhibitor, panobinostat[54] (2024), for the treatment of recurrent glioblastoma.

# Alerts Informed By Public Data Sources

## Current FDA Information

Contraindicated Not recommended Resistance Breakthrough Fast Track

FDA information is current as of 2025-09-17. For the most up-to-date information, search www.fda.gov.

## MET amplification

### elzovantinib

**Cancer type:** Gastric Cancer, Gastroesophageal Junction Adenocarcinoma

**Variant class:** MET amplification

**Supporting Statement:**

The FDA has granted Fast Track designation to the MET/CSF1R/SRC small molecule inhibitor, elzovantinib (TPX-0022), for MET amplified advanced or metastatic gastric cancer, including gastroesophageal junction adenocarcinoma (GEJ) after prior chemotherapy.

**Reference:**

https://www.sec.gov/Archives/edgar/data/1595893/000156459021042621/tptx-ex991_20.htm

# Genes Assayed

## Genes Assayed for the Detection of DNA Sequence Variants

ABL1, ABL2, ACVR1, AKT1, AKT2, AKT3, ALK, AR, ARAF, ATP1A1, AURKA, AURKB, AURKC, AXL, BCL2, BCL2L12, BCL6, BCR, BMP5, BRAF, BTK, CACNA1D, CARD11, CBL, CCND1, CCND2, CCND3, CCNE1, CD79B, CDK4, CDK6, CHD4, CSF1R, CTNNB1, CUL1, CYSLTR2, DDR2, DGCR8, DROSHA, E2F1, EGFR, EIF1AX, EPAS1, ERBB2, ERBB3, ERBB4, ESR1, EZH2, FAM135B, FGF7, FGFR1, FGFR2, FGFR3, FGFR4, FLT3, FLT4, FOXA1, FOXL2, FOXO1, GATA2, GLI1, GNA11, GNAQ, GNAS, HIF1A, HRAS, IDH1, IDH2, IKBKB, IL6ST, IL7R, IRF4, IRS4, KCNJ5, KDR, KIT, KLF4, KLF5, KNSTRN, KRAS, MAGOH, MAP2K1, MAP2K2, MAPK1, MAX, MDM4, MECOM, MED12, MEF2B, MET, MITF, MPL, MTOR, MYC, MYCN, MYD88, MYOD1, NFE2L2, NRAS, NSD2, NT5C2, NTRK1, NTRK2, NTRK3, NUP93, PAX5, PCBP1, PDGFRA, PDGFRB, PIK3C2B, PIK3CA, PIK3CB, PIK3CD, PIK3CG, PIK3R2, PIM1, PLCG1, PPP2R1A, PPP6C, PRKACA, PTPN11, PTPRD, PXDNL, RAC1, RAF1, RARA, RET, RGS7, RHEB, RHOA, RICTOR, RIT1, ROS1, RPL10, SETBP1, SF3B1, SIX1, SIX2, SLCO1B3, SMC1A, SMO, SNCAIP, SOS1, SOX2, SPOP, SRC, SRSF2, STAT3, STAT5B, STAT6, TAF1, TERT, TGFBR1, TOP1, TOP2A, TPMT, TRRAP, TSHR, U2AF1, USP8, WAS, XPO1, ZNF217, ZNF429

## Genes Assayed for the Detection of Copy Number Variations

ABCB1, ABL1, ABL2, ABRAXAS1, ACVR1B, ACVR2A, ADAMTS12, ADAMTS2, AKT1, AKT2, AKT3, ALK, AMER1, APC, AR, ARAF, ARHGAP35, ARID1A, ARID1B, ARID2, ARID5B, ASXL1, ASXL2, ATM, ATR, ATRX, AURKA, AURKC, AXIN1, AXIN2, AXL, B2M, BAP1, BARD1, BCL2, BCL2L12, BCL6, BCOR, BLM, BMPR2, BRAF, BRCA1, BRCA2, BRIP1, CARD11, CASP8, CBFB, CBL, CCND1, CCND2, CCND3, CCNE1, CD274, CD276, CDC73, CDH1, CDH10, CDK12, CDK4, CDK6, CDKN1A, CDKN1B, CDKN2A, CDKN2B, CDKN2C, CHD4, CHEK1, CHEK2, CIC, CREBBP, CSMD3, CTCF, CTLA4, CTNND2, CUL3, CUL4A, CUL4B, CYLD, CYP2C9, DAXX, DDR1, DDR2, DDX3X, DICER1, DNMT3A, DOCK3, DPYD, DSC1, DSC3, EGFR, EIF1AX, ELF3, EMSY, ENO1, EP300, EPCAM, EPHA2, ERAP1, ERAP2, ERBB2, ERBB3, ERBB4, ERCC2, ERCC4, ERRFI1, ESR1, ETV6, EZH2, FAM135B, FANCA, FANCC, FANCD2, FANCE, FANCF, FANCG, FANCI, FANCL, FANCM, FAT1, FBXW7, FGF19, FGF23, FGF3, FGF4, FGF9, FGFR1, FGFR2, FGFR3, FGFR4, FLT3, FLT4, FOXA1, FUBP1, FYN, GATA2, GATA3, GLI3, GNA13, GNAS, GPS2, HDAC2, HDAC9, HLA-A, HLA-B, HNF1A, IDH2, IGF1R, IKBKB, IL7R, INPP4B, JAK1, JAK2, JAK3, KDM5C, KDM6A, KDR, KEAP1, KIT, KLF5, KMT2A, KMT2B, KMT2C, KMT2D, KRAS, LARP4B, LATS1, LATS2, MAGOH, MAP2K1, MAP2K4, MAP2K7, MAP3K1, MAP3K4, MAPK1, MAPK8, MAX, MCL1, MDM2, MDM4, MECOM, MEF2B, MEN1, MET, MGA, MITF, MLH1, MLH3, MPL, MRE11, MSH2, MSH3, MSH6, MTAP, MTOR, MUTYH, MYC, MYCL, MYCN, MYD88, NBN, NCOR1, NF1, NF2, NFE2L2, NOTCH1, NOTCH2, NOTCH3, NOTCH4, NRAS, NTRK1, NTRK3, PALB2, PARP1, PARP2, PARP3, PARP4, PBRM1, PCBP1, PDCD1, PDCD1LG2, PDGFRA, PDGFRB, PDIA3, PGD, PHF6, PIK3C2B, PIK3CA, PIK3CB, PIK3R1, PIK3R2, PIM1, PLCG1, PMS1, PMS2, POLD1, POLE, POT1, PPM1D, PPP2R1A, PPP2R2A, PPP6C, PRDM1, PRDM9, PRKACA, PRKAR1A, PTCH1, PTEN, PTPN11, PTPRT, PXDNL, RAC1, RAD50, RAD51, RAD51B, RAD51C, RAD51D, RAD52, RAD54L, RAF1, RARA, RASA1, RASA2, RB1, RBM10, RECQL4, RET, RHEB, RICTOR, RIT1, RNASEH2A, RNASEH2B, RNF43, ROS1, RPA1, RPS6KB1, RPTOR, RUNX1, SDHA, SDHB, SDHD, SETBP1, SETD2, SF3B1, SLCO1B3, SLX4, SMAD2, SMAD4, SMARCA4, SMARCB1, SMC1A, SMO, SOX9, SPEN, SPOP, SRC, STAG2, STAT3, STAT6, STK11, SUFU, TAP1, TAP2, TBX3, TCF7L2, TERT, TET2, TGFBR2,

## Genes Assayed (continued)

### Genes Assayed for the Detection of Copy Number Variations (continued)

TNFAIP3, TNFRSF14, TOP1, TP53, TP63, TPMT, TPP2, TSC1, TSC2, U2AF1, USP8, USP9X, VHL, WT1, XPO1, XRCC2, XRCC3, YAP1, YES1, ZFHX3, ZMYM3, ZNF217, ZNF429, ZRSR2

### Genes Assayed for the Detection of Fusions

AKT2, ALK, AR, AXL, BRAF, BRCA1, BRCA2, CDKN2A, EGFR, ERBB2, ERBB4, ERG, ESR1, ETV1, ETV4, ETV5, FGFR1, FGFR2, FGFR3, FGR, FLT3, JAK2, KRAS, MDM4, MET, MYB, MYBL1, NF1, NOTCH1, NOTCH4, NRG1, NTRK1, NTRK2, NTRK3, NUTM1, PDGFRA, PDGFRB, PIK3CA, PPARG, PRKACA, PRKACB, PTEN, RAD51B, RAF1, RB1, RELA, RET, ROS1, RSPO2, RSPO3, TERT

### Genes Assayed with Full Exon Coverage

ABRAXAS1, ACVR1B, ACVR2A, ADAMTS12, ADAMTS2, AMER1, APC, ARHGAP35, ARID1A, ARID1B, ARID2, ARID5B, ASXL1, ASXL2, ATM, ATR, ATRX, AXIN1, AXIN2, B2M, BAP1, BARD1, BCOR, BLM, BMPR2, BRCA1, BRCA2, BRIP1, CALR, CASP8, CBFB, CD274, CD276, CDC73, CDH1, CDH10, CDK12, CDKN1A, CDKN1B, CDKN2A, CDKN2B, CDKN2C, CHEK1, CHEK2, CIC, CIITA, CREBBP, CSMD3, CTCF, CTLA4, CUL3, CUL4A, CUL4B, CYLD, CYP2C9, CYP2D6, DAXX, DDX3X, DICER1, DNMT3A, DOCK3, DPYD, DSC1, DSC3, ELF3, ENO1, EP300, EPCAM, EPHA2, ERAP1, ERAP2, ERCC2, ERCC4, ERCC5, ERRFI1, ETV6, FANCA, FANCC, FANCD2, FANCE, FANCF, FANCG, FANCI, FANCL, FANCM, FAS, FAT1, FBXW7, FUBP1, GATA3, GNA13, GPS2, HDAC2, HDAC9, HLA-A, HLA-B, HNF1A, ID3, INPP4B, JAK1, JAK2, JAK3, KDM5C, KDM6A, KEAP1, KLHL13, KMT2A, KMT2B, KMT2C, KMT2D, LARP4B, LATS1, LATS2, MAP2K4, MAP2K7, MAP3K1, MAP3K4, MAPK8, MEN1, MGA, MLH1, MLH3, MRE11, MSH2, MSH3, MSH6, MTAP, MTUS2, MUTYH, NBN, NCOR1, NF1, NF2, NOTCH1, NOTCH2, NOTCH3, NOTCH4, PALB2, PARP1, PARP2, PARP3, PARP4, PBRM1, PDCD1, PDCD1LG2, PDIA3, PGD, PHF6, PIK3R1, PMS1, PMS2, POLD1, POLE, POT1, PPM1D, PPP2R2A, PRDM1, PRDM9, PRKAR1A, PSMB10, PSMB8, PSMB9, PTCH1, PTEN, PTPRT, RAD50, RAD51, RAD51B, RAD51C, RAD51D, RAD52, RAD54L, RASA1, RASA2, RB1, RBM10, RECQL4, RNASEH2A, RNASEH2B, RNASEH2C, RNF43, RPA1, RPL22, RPL5, RUNX1, RUNX1T1, SDHA, SDHB, SDHC, SDHD, SETD2, SLX4, SMAD2, SMAD4, SMARCA4, SMARCB1, SOCS1, SOX9, SPEN, STAG2, STAT1, STK11, SUFU, TAP1, TAP2, TBX3, TCF7L2, TET2, TGFBR2, TMEM132D, TNFAIP3, TNFRSF14, TP53, TP63, TPP2, TSC1, TSC2, UGT1A1, USP9X, VHL, WT1, XRCC2, XRCC3, ZBTB20, ZFHX3, ZMYM3, ZRSR2

## Relevant Therapy Summary

● In this cancer type ○ In other cancer type ◑ In this cancer type and other cancer types ✖ No evidence

### MET amplification

| Relevant Therapy | FDA | NCCN | EMA | ESMO | Clinical Trials* |
|---|---|---|---|---|---|
| capmatinib | ✖ | ○ | ✖ | ✖ | ● (II/III) |
| crizotinib | ✖ | ○ | ✖ | ✖ | ● (II) |
| tepotinib | ✖ | ○ | ✖ | ✖ | ● (II) |
| cabozantinib | ✖ | ✖ | ✖ | ✖ | ● (II) |
| bozitinib | ✖ | ✖ | ✖ | ✖ | ● (I/II) |
| MCLA-129 | ✖ | ✖ | ✖ | ✖ | ● (I/II) |
| ANS-014004 | ✖ | ✖ | ✖ | ✖ | ● (I) |
| ST-1898 | ✖ | ✖ | ✖ | ✖ | ● (I) |
| talazoparib, crizotinib | ✖ | ✖ | ✖ | ✖ | ● (I) |
| TSN-084 | ✖ | ✖ | ✖ | ✖ | ● (I) |

* Most advanced phase (IV, III, II/III, II, I/II, I) is shown and multiple clinical trials may be available.

## Relevant Therapy Summary (continued)

● In this cancer type ○ In other cancer type ◑ In this cancer type and other cancer types ✖ No evidence

### ATM deletion

| Relevant Therapy | FDA | NCCN | EMA | ESMO | Clinical Trials* |
|---|---|---|---|---|---|
| olaparib | ✖ | ✖ | ✖ | ✖ | ● (II) |
| olaparib, pembrolizumab | ✖ | ✖ | ✖ | ✖ | ● (II) |
| pamiparib, tislelizumab | ✖ | ✖ | ✖ | ✖ | ● (II) |
| senaparib, IMP-9064 | ✖ | ✖ | ✖ | ✖ | ● (I/II) |

### BRCA1 deletion

| Relevant Therapy | FDA | NCCN | EMA | ESMO | Clinical Trials* |
|---|---|---|---|---|---|
| olaparib | ✖ | ✖ | ✖ | ✖ | ● (II) |
| olaparib, pembrolizumab | ✖ | ✖ | ✖ | ✖ | ● (II) |
| pamiparib, tislelizumab | ✖ | ✖ | ✖ | ✖ | ● (II) |

### CDK12 deletion

| Relevant Therapy | FDA | NCCN | EMA | ESMO | Clinical Trials* |
|---|---|---|---|---|---|
| pamiparib, tislelizumab | ✖ | ✖ | ✖ | ✖ | ● (II) |

### CHEK1 deletion

| Relevant Therapy | FDA | NCCN | EMA | ESMO | Clinical Trials* |
|---|---|---|---|---|---|
| pamiparib, tislelizumab | ✖ | ✖ | ✖ | ✖ | ● (II) |

### RAD51D deletion

| Relevant Therapy | FDA | NCCN | EMA | ESMO | Clinical Trials* |
|---|---|---|---|---|---|
| pamiparib, tislelizumab | ✖ | ✖ | ✖ | ✖ | ● (II) |

* Most advanced phase (IV, III, II/III, II, I/II, I) is shown and multiple clinical trials may be available.

## HRR Details

| Gene/Genomic Alteration | Finding |
|---|---|
| LOH percentage | ***25.2%*** |
| BRCA1 | ***CNV, CN:1.0*** |
| BRCA1 | ***LOH, 17q21.31(41197602-41276231)x1*** |
| ATM | ***CNV, CN:1.0*** |
| ATM | ***LOH, 11q22.3(108098341-108236285)x1*** |
| CDK12 | ***CNV, CN:1.0*** |
| CDK12 | ***LOH, 17q12(37618286-37687611)x1*** |
| CHEK1 | ***CNV, CN:1.0*** |
| CHEK1 | ***LOH, 11q24.2(125496639-125525271)x1*** |
| RAD51D | ***CNV, CN:1.0*** |
| RAD51D | ***LOH, 17q12(33427950-33446720)x1*** |

Homologous recombination repair (HRR) genes were defined from published evidence in relevant therapies, clinical guidelines, as well as clinical trials, and include - BRCA1, BRCA2, ATM, BARD1, BRIP1, CDK12, CHEK1, CHEK2, FANCL, PALB2, RAD51B, RAD51C, RAD51D, and RAD54L.

Thermo Fisher Scientific's Ion Torrent Oncomine Reporter software was used in generation of this report. Software was developed and designed internally by Thermo Fisher Scientific. The analysis was based on Oncomine Reporter (6.1.1 data version 2025.10(006)). The data presented here are from a curated knowledge base of publicly available information, but may not be exhaustive. FDA information was sourced from www.fda.gov and is current as of 2025-09-17. NCCN information was sourced from www.nccn.org and is current as of 2025-09-02. EMA information was sourced from www.ema.europa.eu and is current as of 2025-09-17. ESMO information was sourced from www.esmo.org and is current as of 2025-09-02. Clinical Trials information is current as of 2025-09-02. For the most up-to-date information regarding a particular trial, search www.clinicaltrials.gov by NCT ID or search local clinical trials authority website by local identifier listed in 'Other identifiers.' Variants are reported according to HGVS nomenclature and classified following AMP/ASCO/CAP guidelines (Li et al. 2017). Based on the data sources selected, variants, therapies, and trials listed in this report are listed in order of potential clinical significance but not for predicted efficacy of the therapies.

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