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Patient Name: 염태중
Gender: Male
Sample ID: N26-35

Primary Tumor Site: Unknown
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Sample Cancer Type: Unknown Primary Origin

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Report Highlights

7 Relevant Biomarkers
0 Therapies Available
35 Clinical Trials

Relevant Biomarkers

Tier	Genomic Alteration	Relevant Therapies (In this cancer type)	Relevant Therapies (In other cancer type)	Clinical Trials
IIC	*FGFR1 amplification* fibroblast growth factor receptor 1 Locus: chr8:38271452	None*	None*	16
IIC	*CCNE1 amplification* cyclin E1 Locus: chr19:30303647	None*	None*	14
IIC	*KIT amplification* KIT proto-oncogene receptor tyrosine kinase Locus: chr4:55589693	None*	None*	5
IIC	*KDR amplification* kinase insert domain receptor Locus: chr4:55955541	None*	None*	4
IIC	*PDGFRA amplification* platelet derived growth factor receptor alpha Locus: chr4:55131078	None*	None*	2
IIC	*TP53 p.(R273H) c.818G>A* tumor protein p53 Allele Frequency: 40.05% Locus: chr17:7577120 Transcript: NM_000546.6	None*	None*	1
IIC	*TSC2 deletion* tuberous sclerosis 2 Locus: chr16:2098579	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

*AKT2 amplification, BCL6 amplification, MAP2K7 deletion, Microsatellite stable, XRCC3 deletion, TNFRSF14 deletion, PDCD1 deletion, HLA-A deletion, HDAC9 p.(L630Sfs*14) c.1888delC, IKBKB amplification, NQO1 p.(P187S) c.559C>T, ZFHX3 deletion, Tumor Mutational Burden*

Variant Details

DNA Sequence Variants

Gene	Amino Acid Change	Coding	Variant ID	Locus	Allele Frequency	Transcript	Variant Effect
TP53	p.(R273H)	c.818G>A	COSM10660	chr17:7577120	40.05%	NM_000546.6	missense
HDAC9	p.(L630Sfs*14)	c.1888delC	.	chr7:18767354	35.73%	NM_178425.3	frameshift Deletion
NQO1	p.(P187S)	c.559C>T	.	chr16:69745145	50.58%	NM_000903.3	missense
OR2L2	p.(L200F)	c.600G>C	.	chr1:248202169	42.11%	NM_001004686.2	missense
TET2	p.(T1183P)	c.3547A>C	.	chr4:106164037	53.97%	NM_001127208.3	missense
IL7R	p.(P417T)	c.1249C>A	.	chr5:35876457	54.45%	NM_002185.5	missense
MSH3	p.(A61_P63dup)	c.189_190insGCAGCGCCC	.	chr5:79950735	50.75%	NM_002439.5	nonframeshift Insertion
NOTCH1	p.(C164F)	c.491G>T	.	chr9:139417553	50.15%	NM_017617.5	missense
OR4C6	p.(F160L)	c.478T>C	.	chr11:55433120	42.47%	NM_001004704.1	missense
ATM	p.(A1812V)	c.5435C>T	.	chr11:108173695	29.59%	NM_000051.4	missense
SYT10	p.(E32K)	c.94G>A	.	chr12:33592364	29.91%	NM_198992.4	missense
RB1	p.(S469Y)	c.1406C>A	.	chr13:48954205	83.15%	NM_000321.3	missense
PARP2	p.(?)	c.1369-1G>C	.	chr14:20825209	53.88%	NM_005484.4	unknown
TP53	p.(E180_C182dup)	c.538_546dup	.	chr17:7578383	19.46%	NM_000546.6	nonframeshift Insertion

Copy Number Variations

Gene	Locus	Copy Number	CNV Ratio
FGFR1	chr8:38271452	10.95	3.82
CCNE1	chr19:30303647	6.41	2.39
KIT	chr4:55589693	4.95	1.93
KDR	chr4:55955541	4.78	1.88
PDGFRA	chr4:55131078	5.14	1.99
TSC2	chr16:2098579	0.86	0.64
AKT2	chr19:40739751	7.86	2.84
BCL6	chr3:187440209	6.25	2.34
MAP2K7	chr19:7968792	0.56	0.55
XRCC3	chr14:104165043	1.02	0.69
TNFRSF14	chr1:2488070	0.92	0.66

Variant Details (continued)

Copy Number Variations (continued)

Gene	Locus	Copy Number	CNV Ratio
PDCD1	chr2:242793161	0.97	0.68
HLA-A	chr6:29910229	0.67	0.58
IKBKB	chr8:42129602	6.73	2.49
ZFHX3	chr16:72820995	0.98	0.68
TP63	chr3:189456442	6.68	2.48
FGFR3	chr4:1801456	0.6	0.56
FLT4	chr5:180030092	0.97	0.67
AKT1	chr14:105236628	0.68	0.58
KMT2B	chr19:36209128	4.81	1.88

Biomarker Descriptions

FGFR1 amplification

fibroblast growth factor receptor 1

Background: The FGFR1 gene encodes fibroblast growth receptor 1, a member of the fibroblast growth factor receptor (FGFR) family that also includes FGFR2, 3, and 4[25]. These proteins are single transmembrane receptors composed of three extracellular immunoglobulin (Ig)-type domains and an intracellular kinase domain[25]. Upon FGF-mediated stimulation, FGFRs activate several oncogenic signaling pathways, including the RAS/RAF/MEK/ERK, PI3K/AKT/MTOR, PLCγ/PKC, and JAK/STAT pathways influencing cell proliferation, migration, and survival[87,88,89].

Alterations and prevalence: Recurrent somatic alterations common to the FGFR family include gene amplification, mutation, and chromosomal translocations leading to FGFR fusions[90]. Amplification of FGFR1 is observed in 17% of lung squamous cell carcinoma, 11% of breast invasive carcinoma, 8% of bladder urothelial carcinoma, 7% of uterine carcinosarcoma and head and neck squamous cell carcinoma, 6% of esophageal adenocarcinoma, 5% of sarcoma, 4% of colorectal adenocarcinoma and pancreatic adenocarcinoma, 3% of prostate adenocarcinoma, ovarian serous cystadenocarcinoma, and lung adenocarcinoma, and 2% of uterine corpus endometrial carcinoma[12,15,91,92,93]. The most common recurrent mutations, N546K and K656E, are relatively infrequent (<1%); they activate mutations in the kinase domain and are distributed in diverse cancer types[94]. Somatic mutations in FGFR1 are observed in 7% of skin cutaneous melanoma, 6% of uterine corpus endometrial carcinoma, and 3% of stomach adenocarcinoma and colorectal adenocarcinoma[12,15]. FGFR1 translocations giving rise to expressed fusions are common in certain hematological cancers, but are less common in solid tumors[95,96,97]. Alterations in FGFR1 are rare in pediatric cancers[12]. Amplification of FGFR1 is observed in less than 1% of B-lymphoblastic leukemia/lymphoma (2 in 731 cases)[12]. Somatic mutations in FGFR1 are observed in 6% of non-Hodgkin Lymphoma, 3% of soft tissue sarcoma, 2% of glioma, and less than 1% of embryonal tumors (2 in 332 cases), B-lymphoblastic leukemia/lymphoma (1 in 252 cases), Wilms tumor (2 in 710 cases), and peripheral nervous system cancers (1 in 1158 cases)[12].

Potential relevance: The FGFR kinase inhibitor, pemigatinib[98] (2022) is approved for the treatment of adults with relapsed/refractory myeloid/lymphoid neoplasms (MLNs) with FGFR1 rearrangement. FDA has approved multi-kinase inhibitors, including regorafenib, ponatinib, lenvatinib, nintedanib, and pazopanib, that are known to inhibit FGFR family members[99]. These inhibitors have demonstrated anti-tumor activity in select cancer types with FGFR alterations[100,101,102,103,104,105,106]. Rearrangements in FGFR1 are associated with poor risk pediatric and adult acute lymphoblastic leukemia[107,108,109].

CCNE1 amplification

cyclin E1

Background: The CCNE1 gene encodes the cyclin E1 protein, a member of the highly conserved E-cyclin family which also includes CCNE2[43]. CCNE1 facilitates progression from G1 to the S phase of the cell cycle by binding to cyclin dependent kinase 2 (CDK2) which results in phosphorylation and inactivation of the retinoblastoma (RB1) protein[43]. Consequently, RB1 inactivation results in

Biomarker Descriptions (continued)

E2F transcription factor activation and cellular G1/S phase transition resulting in cell cycle progression, a common event observed in tumorigenesis[44,45,46]. Additionally, CCNE1 is often deregulated in a variety of cancer types supporting an oncogenic role for CCNE1[43,47].

Alterations and prevalence: CCNE1 amplification is observed in about 40% of uterine carcinosarcoma, 20% of ovarian cancer, 11% of stomach cancer, 7-8% sarcoma, uterine, and esophageal cancers, 5-6%, adrenocortical carcinoma, squamous lung, and bladder cancers[15]. Additionally, CCNE1 overexpression has been observed in many different tumor types including in 70-80% of Hodgkin's lymphoma.[43,47,48].

Potential relevance: The FDA has granted fast track designation (2024) to the small molecule PKMYT1 inhibitor, lunresertib[49], in combination with camonsertib for the treatment of adult patients with CCNE1 amplified endometrial cancer and platinum resistant ovarian cancer. CCNE1 amplification and overexpression has been associated with poor prognosis in certain cancer types including lung and breast cancers[50,51,52].

KIT amplification

KIT proto-oncogene receptor tyrosine kinase

Background: The KIT gene, also known as CD117, encodes the KIT proto-oncogene receptor tyrosine kinase (c-KIT), a member of the PDGF receptor type III receptor tyrosine kinase family, which includes PDGFRA, PDGFRB, CSF1R, FLT1, FLT3, FLT4 and KDR[1,2]. The KIT locus is positioned on chromosome 4q12, flanked by PDGFRA and KDR, forming a conserved type III receptor tyrosine kinase gene cluster that is frequently co-amplified and co-regulated across multiple tumor types, contributing to coordinated oncogenic signaling and therapeutic co-targeting in cancer[3,4,5]. KIT serves as the receptor for stem cell factor (SCF) and plays a central role in hematopoietic cell development[6]. Ligand binding to KIT results in kinase activation and stimulation of downstream pathways including the RAS/RAF/MEK/ERK and PI3K/AKT/MTOR pathways, promoting cell proliferation and survival[7].

Alterations and prevalence: Recurrent somatic KIT alterations are observed in both solid and hematological cancers and include activating mutations such as single nucleotide variants, small duplications, and complex in-frame insertions or deletions (indels)[8,9]. Mutations in KIT exons 8, 9, 11, and 17 disrupt auto-inhibitory mechanisms and lead to constitutive activity[10]. Gain of function mutations are found in up to 70% of mast cell tumors, 17% of nasal T-cell lymphomas, and 9% of dysgerminoma[11]. Somatic mutations in exon 11 occur in 60-70% of all gastrointestinal stromal tumor (GIST), whereas alterations in exons 8 and 17 are more common in myeloid cancers[10,11,12]. A common kinase domain mutation that causes ligand-independent constitutive activation, D816V, occurs in 80-93% of aggressive forms of mastocytosis[13,14]. Recurrent somatic mutations in KIT are observed in 13% of testicular germ cell tumors, 9% of uterine corpus endometrial carcinoma, 7% of skin cutaneous melanoma, 5% of colorectal adenocarcinoma, 4% of acute myeloid leukemia, 4% of lung squamous cell carcinoma, 3% of bladder urothelial carcinoma, 3% of stomach adenocarcinoma, 3% of liver hepatocellular carcinoma, and 2% of cervical squamous cell carcinoma, esophageal adenocarcinoma. head and neck squamous cell carcinoma, uterine carcinosarcoma, and lung adenocarcinoma[12,15]. KIT amplification is observed in 5% of lung squamous cell carcinoma, 3% of sarcoma, brain lower grade glioma, skin cutaneous melanoma, and 2% of esophageal adenocarcinoma, testicular germ cell tumors, bladder urothelial carcinoma, and lung adenocarcinoma[12,15]. Alterations in KIT are also observed in the pediatric population[12]. Somatic mutations are observed in 6% of leukemia (22 in 354 cases), 2% of T-lymphoblastic leukemia/lymphoma (1 in 41 cases), and less than 1% of bone cancer (3 in 327 cases), glioma (1 in 297 cases), and embryonal tumor (1 in 332 cases)[12]. KIT amplification is observed in 2% of bone cancer (1 in 42 cases) and 1% of peripheral nervous system (1 in 91 cases) and Wilms tumor (1 in 136 cases)[12].

Potential relevance: Imatinib[16] (2001) is approved for KIT positive unresectable or metastatic GIST and adult patients with aggressive systemic mastocytosis (SM) who do not have the D816V c-Kit mutation or whose c-Kit mutational status is unknown. Imatinib is also recommended for activating mutations, including KIT P577_W582delinsPYD and KIT V560D in melanoma and exon 9 and 11 sensitizing mutations in GIST[17,18,19,20]. Mutations in exon 17 have been identified to confer resistance to imatinib and sunitinib[21]. Additionally, detection of activating mutations in KIT is useful as an ancillary technique in the diagnosis of GIST[19]. Patients with acute myeloid leukemia (AML) that harbor KIT activating mutations with t(8;21) and inv(16) have an increased risk of relapse[22]. KIT D816V mutation is associated with the diagnosis of SM and aggressiveness of the disease[23,24].

KDR amplification

kinase insert domain receptor

Background: The KDR gene encodes the kinase insert domain receptor protein, also known as the vascular endothelial growth factor receptor 2 (VEGFR2). KDR is a type 2 transmembrane cell surface receptor tyrosine kinase (RTK) and is a member of a family of cognate RTKs called VEGFRs that also includes VEGFR1 (FLT-1) and VEGFR3[78,79]. KDR binds to ligands VEGF-A, VEGF-C, VEGF-D, and VEGF-E and is the principal mediator of VEGF-induced angiogenic signaling[78,79]. Upon ligand stimulation, KDR undergoes dimerization and trans-autophosphorylation, leading to activation of the RAF-MEK-ERK and PI3K-AKT pathways, promoting endothelial cell proliferation and migration[79,80].

Biomarker Descriptions (continued)

Alterations and prevalence: Somatic mutations in KDR are observed in 14% of melanoma, 8% of lung adenocarcinoma, uterine carcinoma, and diffuse large B-cell lymphoma (DLBCL)[12,15]. Amplifications are observed in 6% of glioblastoma multiforme (GBM)[12,15]. Overexpression of KDR has been observed in various cancer types including mammary, colorectal, non-small cell lung, and urothelial carcinomas[80].

Potential relevance: Currently, no therapies are approved for KDR aberrations. Drugs targeting KDR reduce angiogenesis or lymphangiogenesis and typically competitively bind to the ATP-site of KDR[79]. Drugs that may target KDR include FDA approved inhibitors apatinib, axitinib, nintedanib, sorafenib, sunitinib, ramucirumab, and pazopanib, although there are no known alterations associated with these approved therapies. FDA approved monoclonal antibodies targeting the KDR pathway include bevacizumab that binds to the ligand VEGF-A and prevents the interaction with KDR[79,81].

PDGFRA amplification

platelet derived growth factor receptor alpha

Background: The PDGFRA gene encodes the platelet derived growth factor receptor alpha, a member of the PDGF receptor type III receptor tyrosine kinase family, which includes PDGFRB, CSF1R, FLT1, FLT3, FLT4, KDR, and KIT[1,2]. PDGFRA is a receptor for platelet derived growth factors, which are mitogens for cells of mesenchymal origin[162]. PDGFRA may function as a homodimer or heterodimer with PDGFRB depending on the ligand[163]. The PDGFRA gene is physically adjacent to KIT and KDR on chromosome 4q12, and all 3 tyrosine kinases are often co-amplified in cancer[164]. Ligand binding to PDGFRA results in kinase activation and stimulation of downstream pathways, including the RAS/RAF/MEK/ERK and PI3K/AKT/MTOR pathways, which promotes cell proliferation and survival[165].

Alterations and prevalence: Recurrent somatic PDGFRA alterations are observed in both solid and hematological cancers and include activating mutations, gene amplification, and translocations generating PDGFRA gene fusions. Recurrent PDGFRA activating mutations, including D842V, V561D, N659K, and in-frame deletions in exon 18, are common in 30-40% of KIT negative gastrointestinal stromal tumors (GISTs) and approximately 7% overall[166,167,168,169]. PDGFRA recurrent mutations are also observed in 9% of skin cutaneous melanoma and uterine corpus endometrial carcinoma, 7% of lung adenocarcinoma, 5% of colorectal adenocarcinoma, 4% of lung squamous cell carcinoma, glioblastoma multiforme, and bladder urothelial carcinoma, 3% of stomach adenocarcinoma and head and neck squamous cell carcinoma, and 2% of cervical squamous cell carcinoma, liver hepatocellular carcinoma, brain lower grade glioma, and ovarian serous cystadenocarcinoma[12,15]. PDGFRA amplification is observed in 13% of glioblastoma multiforme, 5% of lung squamous cell carcinoma, 4% of brain lower grade glioma, 3% of sarcoma and skin cutaneous melanoma, and 2% of esophageal adenocarcinoma, testicular germ cell tumors, lung adenocarcinoma, uterine carcinosarcoma, and bladder urothelial carcinoma[12,15]. PDGFRA fusions are observed in gliomas and glioblastomas as well as eosinophilic leukemias, of which the FIP1L1::PDGFRA fusion defines approximately half of patients with hypereosinophilic syndrome[170,171,172]. Alterations of PDGFRA are rare in pediatric cancers[12,15]. Somatic mutations are observed in 2% of glioma, and less than 1% of embryonal tumors (3 in 332 cases), bone cancer (2 in 327 cases), and leukemia (1 in 354 cases)[12,15]. PDGFRA is amplified in 5% of bone cancer and less than 1% of Wilms tumor (1 in 136 cases)[12,15].

Potential relevance: Avapritinib[173] (2020) is a tyrosine kinase inhibitor (TKI) that is approved by the FDA for metastatic or unresectable gastrointestinal stromal tumors (GISTs) harboring PDGFRA exon 18 mutations, including PDGFRA D842V mutation. The FDA has granted fast track designation to crenolanib[174] (2017) for harboring PDGFRA D842V mutation. Imatinib[16] (2001) is a TKI approved for patients diagnosed with chronic eosinophilic leukemia harboring the FIP1L1::PDGFRA fusion. Additionally, imatinib is recommended for the treatment of GISTs harboring PDGFRA exon 18 mutations, with the exception of D842V[19]. Amplification of PDGFRA is a diagnostic marker of H3-wildtype and IDH-wildtype diffuse pediatric-type high-grade glioma[175,176]. PDGFRA rearrangements are associated with poor risk in pediatric acute lymphoblastic leukemia[108,177].

TP53 p.(R273H) c.818G>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[25]. In unstressed cells, TP53 is kept inactive by targeted degradation via MDM2, a substrate recognition factor for ubiquitin-dependent proteolysis[110]. Alterations in TP53 are required for oncogenesis as they result in loss of protein function and gain of transforming potential[111]. Germline mutations in TP53 are the underlying cause of Li-Fraumeni syndrome, a complex hereditary cancer predisposition disorder associated with early-onset cancers[112,113].

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%)[12,15,91,114,115,116]. 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[12,15]. Invariably, recurrent missense

Biomarker Descriptions (continued)

mutations in TP53 inactivate its ability to bind DNA and activate transcription of target genes[117,118,119,120]. Alterations in TP53 are also observed in pediatric cancers[12,15]. 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)[12,15]. 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)[12,15].

Potential relevance: The small molecule p53 reactivator, PC14586[121] (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[122,123]. TP53 mutations are a diagnostic marker of SHH-activated, TP53-mutant medulloblastoma[124]. 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)[107,125,126,127,128]. In mantle cell lymphoma, TP53 mutations are associated with poor prognosis when treated with conventional therapy including hematopoietic cell transplant[84]. Mono- and bi-allelic mutations in TP53 confer unique characteristics in MDS, 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[129].

TSC2 deletion

tuberous sclerosis 2

Background: The TSC2 gene encodes the tuberin protein. TSC2 and TSC1 (also known as hamartin) form a complex through their respective coiled-coil domains[40]. The TSC1-TSC2 complex is a negative regulator of the mTOR signaling pathway that regulates cell growth, cell proliferation, and protein and lipid synthesis[41]. Specifically, the TSC1-TSC2 complex acts as a GTPase activating (GAP) protein that inhibits the G-protein RHEB and keeps it in an inactivated state (RHEB-GDP)[41]. GTP-bound RHEB (RHEB-GTP) is required to activate the mTOR complex 1 (mTORC1)[41]. TSC1 and TSC2 are tumor suppressor genes and loss of function mutations in TSC1 and TSC2 lead to dysregulation of the mTOR pathway[40,42]. Inactivating germline mutations in TSC1 and TSC2 are associated with tuberous sclerosis complex (TSC), an autosomal dominant neurocutaneous and progressive disorder that presents with multiple benign tumors in different organs[40].

Alterations and prevalence: Somatic mutations in TSC2 are observed in 9% of skin cutaneous melanoma, 7% of uterine corpus endometrial carcinoma, and 4% of cervical squamous cell carcinoma, 3% of stomach adenocarcinoma, liver hepatocellular carcinoma, lung squamous cell carcinoma, colorectal cancer, kidney chromophobe, cholangiocarcinoma, and esophageal adenocarcinoma, and 2% of sarcoma, bladder urothelial carcinoma, kidney renal papillary cell carcinoma, and lung adenocarcinoma[12,15]. Alterations in CRLF1 are also observed in pediatric cancers[12]. Somatic mutations in TSC2 are observed in 5% of Hodgkin lymphoma (3 in 61 cases), 2% of bone cancer (7 in 327 cases), 1% of embryonal tumors (4 in 332 cases), and less than 1% of B-lymphoblastic leukemia/lymphoma (2 in 252 cases), glioma (1 in 297 cases), and leukemia (1 in 311 cases)[12]. Biallelic deletion of TSC2 is observed in less than 1% of B-lymphoblastic leukemia/lymphoma (5 in 731 cases)[12].

Potential relevance: Currently, no therapies are approved for TSC2 aberrations.

AKT2 amplification

AKT serine/threonine kinase 2

Background: The AKT2 gene encodes a serine/threonine kinase that belongs to a family of closely related protein kinases that also includes AKT1 and AKT3[25]. Growth factor signaling leads to the activation of phosphatidylinositol 3-kinase (PI3K), recruitment of AKT to the plasma membrane, and subsequent activation of downstream effectors including MTOR[178]. The PI3K/AKT/MTOR pathway is central to the regulation of cancer cell proliferation, survival, and metabolism[178,179]. AKT2 is implicated in cancer cell invasion, survival, and metastasis in various cancers, including acute myeloid leukemia, neuroblastoma, bladder cancer, prostate cancer, and ovarian cancer[180,181,182].

Alterations and prevalence: Recurrent AKT2 activating mutations occur at E17K, L52R, and D324G/H[183]. Somatic mutations in AKT2 are observed in 4% of uterine corpus endometrial carcinoma and 2% of diffuse large B-cell lymphoma, stomach adenocarcinoma, skin cutaneous melanoma, and cervical squamous cell carcinoma[12,15]. AKT2 is amplified in 14% of uterine carcinosarcoma, 7% of pancreatic adenocarcinoma, 6% of ovarian serous cystadenocarcinoma and lung squamous cell carcinoma, 4% of sarcoma, 3% of cervical squamous cell carcinoma and uterine corpus endometrial carcinoma, and 2% of bladder urothelial carcinoma[12,15]. A BCAM::AKT2 fusion has been identified in ovarian cancer[184]. Alterations in AKT2 are also observed in pediatric cancers[12]. Somatic mutations in AKT2 are observed in less than 1% of Wilms tumors (1 in 710 cases). AKT2 amplification is observed in 2% of Wilms tumors (3 in 136 cases)[12].

Biomarker Descriptions (continued)

Potential relevance: Currently, no therapies are approved specifically for AKT2 aberrations. Although the pan-AKT inhibitor capivasertib (AZD5363) targets all AKT isoforms, clinical evidence of supporting its efficacy in AKT2-aberrant cancers remains limited[185].

BCL6 amplification

B-cell CLL/lymphoma 6

Background: The BCL6 gene encodes the B-cell lymphoma 6 (BCL6) transcription repressor, a protein that is responsible for inhibiting the expression of several genes including those involved in the DNA damage response, cell cycle checkpoints, and modulating BCL2 expression[61,62,63]. BCL6 is most commonly expressed in germinal center B-cells and is required for germinal cell formation and affinity maturation during T-cell dependent antibody responses[62]. BCL6 is observed to competitively bind DNA motifs recognized by the oncogenic transcription factor STAT6, thereby repressing STAT6 mediated gene transcription[64,65]. Aberrations in BCL6 often lead to altered target gene transcription, including those involved in cell cycle arrest, differentiation, and apoptosis[61,62].

Alterations and prevalence: BCL6 rearrangement most commonly occurs with immunoglobulin H (IGH) partners and results in the truncation or removal the BCL6 promoter region and juxtaposition of BCL6 downstream of the partner gene promoter[66]. Replacement of the BCL6 promoter resulting from such translocations has been observed to lead to aberrant BCL6 expression[67]. BCL6 rearrangement is a common event in lymphoma and has been observed in up to 40% of diffuse large B-cell lymphoma (DLBCL) and 15% of follicle center lymphomas[62,66]. Somatic mutations in BCL6 are observed in 7% of uterine corpus endometrial carcinoma, 4% of skin cutaneous melanoma, and 3% of stomach adenocarcinoma and colorectal adenocarcinoma, and 2% of uterine carcinosarcoma, lung adenocarcinoma, and sarcoma[12,15]. Mutations in the 5' regulatory sequences of BCL6 are observed in 30-40% of germinal center B-cells and are believed to disrupt BCL6 negative autoregulation[62]. Amplifications are observed in 31% of lung squamous cell carcinoma, 16% of esophageal adenocarcinoma and ovarian serous cystadenocarcinoma, and 14% of head and neck and cervical squamous cell carcinoma, 9% of uterine carcinosarcoma, 6% of uterine corpus endometrial carcinoma, and 2-4% of stomach adenocarcinoma, diffuse large B-cell lymphoma, bladder urothelial carcinoma, breast invasive carcinoma, testicular germ cell tumors, liver hepatocellular carcinoma, and pancreatic adenocarcinoma[12,15]. Alterations in BCL6 are rare in pediatric cancers[12,15]. Somatic mutations in BCL6 are observed in 3% of soft tissue sarcoma, and less than 1% of bone cancer (3 in 327 cases), embryonal tumors (2 in 332 cases), and glioma (1 in 297 cases)[12,15]. Amplification of BCL6 is observed in 1% or less of Wilms tumor (2 in 136 cases) and B-lymphoblastic leukemia/lymphoma (1 in 731 cases)[12,15].

Potential relevance: B-cell lymphoma with BCL6 translocations that co-occur with MYC are referred to as double-hit lymphoma (DHL), while co-occurrence with MYC and BCL2 rearrangements is referred to as triple-hit lymphoma[68]. Such concomitant rearrangements are recognized by the World Health Organization (WHO) as diagnostic entity of diffuse large B-cell lymphoma/high grade B-cell lymphoma (HGBL) with MYC and BCL2 rearrangements[69]. DHL expressing BCL6 rearrangements are most often aggressive with poor prognosis, involve extra nodal sites, and have a germinal center phenotype[70,71].

MAP2K7 deletion

mitogen-activated protein kinase kinase 7

Background: The MAP2K7 gene encodes the mitogen-activated protein kinase kinase 7, also known as MEK7[25]. MAP2K7 is involved in the JNK signaling pathway along with MAP3K4, MAP3K12, MAP2K4, MAPK8, MAPK9, and MAPK10[29,30,31]. Activation of MAPK proteins occurs through a kinase signaling cascade[29,30,32]. Specifically, MAP3Ks are responsible for phosphorylation of MAP2K family members[29,30,32]. Once activated, MAP2Ks are responsible for the phosphorylation of various MAPK proteins whose signaling is involved in several cellular processes including cell proliferation, differentiation, and inflammation[29,30,32].

Alterations and prevalence: Somatic mutations in MAP2K7 are observed in 7% of stomach adenocarcinoma, 4% of colorectal adenocarcinoma, and 2% of skin cutaneous melanoma and uterine corpus endometrial carcinoma[12,15]. Biallelic deletions are observed in 4% of uterine carcinosarcoma, 2% of esophageal adenocarcinoma, and 1% of uveal melanoma[12,15].

Potential relevance: Currently, no therapies are approved for MAP2K7 aberrations.

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[140]. Microsatellite instability (MSI) is defined as a change in the length of a microsatellite in a tumor as compared to normal tissue[141,142]. 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[143]. 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[144]. 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)[144]. Tumors classified as MSI-L are often phenotypically indistinguishable from MSS tumors and tend to be grouped with MSS[145,146,147,148,149]. MSI-H is a hallmark of Lynch

Biomarker Descriptions (continued)

syndrome (LS), also known as hereditary non-polyposis colorectal cancer, which is caused by germline mutations in the MMR genes[142]. LS is associated with an increased risk of developing colorectal cancer, as well as other cancers, including endometrial and stomach cancer[141,142,146,150].

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[141,142,151,152]. 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[151,152].

Potential relevance: Anti-PD-1 immune checkpoint inhibitors including pembrolizumab[153] (2014) and nivolumab[154] (2015) are approved for patients with MSI-H or dMMR colorectal cancer who have progressed following chemotherapy. Pembrolizumab[153] 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[153]. Dostarlimab[155] (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[147,156]. The cytotoxic T-lymphocyte antigen 4 (CTLA-4) blocking antibody, ipilimumab[157] (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[147,158,159]. 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[159]. 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[160,161]. However, checkpoint blockade with the addition of chemotherapy or targeted therapies have demonstrated response in MSS or pMMR cancers[160,161].

XRCC3 deletion

X-ray repair cross complementing 3

Background: The XRCC3 gene encodes the X-ray cross complementing 3 protein, a member of the RAD51 recombinase family that also includes RAD51, RAD51C, RAD51D, and XRCC2 paralogs[25,26]. XRCC3 complexes with RAD51C to form the CX3 complex, which functions in strand exchange and Holliday junction resolution during homologous recombination repair (HRR)[26,27]. XRCC3 may complex with BRCA2, FANCD2, and FANCG to maintain chromosome stability[28].

Alterations and prevalence: Somatic mutations in XRCC3 are observed in 1% of uveal melanoma, colorectal adenocarcinoma, and cervical squamous cell carcinoma[12,15]. Biallelic deletions in XRCC3 are observed in 3% of cholangiocarcinoma and 2% of diffuse large B-cell lymphoma (DLBCL) and bladder urothelial carcinoma[12,15].

Potential relevance: Currently, no therapies are approved for XRCC3 aberrations. Pre-clinical evidence suggests that XRCC3 mutations may demonstrate sensitivity to cisplatin[28].

TNFRSF14 deletion

TNF receptor superfamily member 14

Background: The TNFRSF14 gene encodes TNF receptor superfamily member 14[25]. TNFRSF14, also known as HVEM, belongs to the tumor necrosis factor superfamily of cell surface receptors (TNFRSF), which interact with the tumor necrosis factor superfamily (TNFSF) of cytokines[82]. TNFSF-TNFRSF interactions regulate several signaling pathways, including those involved in immune cell differentiation, survival, and death[82]. TNFRSF14 can be stimulated by several ligands, including the TNFSF14 ligand (also known as LIGHT), BTLA, and CD160[82,83]. Following ligand binding to TNFRSF in T-cells, TNFRSF proteins aggregate at the cell membrane and initiate co-signaling cascades which promotes activation, differentiation, and survival[82]. In lymphoma, binding of TNFRSF14 by TNFSF14 has been observed to enhance Fas-induced apoptosis, suggesting a tumor suppressor role[83].

Alterations and prevalence: Somatic mutations in TNFRSF14 are observed in 5% of diffuse large B-cell lymphoma (DLBCL), and 2% of skin cutaneous melanoma[12,15]. Biallelic loss of TNFRSF14 occurs in 8% of DLBCL and uveal melanoma, 3% of cholangiocarcinoma, and 2% of adrenocortical carcinoma and liver hepatocellular carcinoma[12,15].

Potential relevance: Currently, no therapies are approved for TNFRSF14 aberrations. Somatic mutations in TNFRSF14 are diagnostic for follicular lymphoma[84]. In addition, TNFRSF14 mutations are associated with poor prognosis in follicular lymphoma[85,86].

Biomarker Descriptions (continued)

PDCD1 deletion

programmed cell death 1

Background: The PDCD1 gene encodes programmed cell death 1, also known as PD-1 or CD279[25]. PDCD1 is a type I transmembrane inhibitory receptor and member of the CD28/CTLA-4 family, which is part of the immunoglobulin superfamily[53]. PDCD1 is an immune checkpoint molecule that acts as a gatekeeper of immune responses through a balance of signaling suppression, which is critical in the facilitation of self and non-self cell recognition[54]. PDCD1 is expressed in a variety of hematopoietic cells, immune cells, tumor cells, and tumor specific T-cells[53,55]. The two main immunoregulatory ligands of PDCD1 are CD274 (PD-L1) and PDCD1LG2 (PD-L2), which are type I transmembrane proteins expressed in many cells including antigen presenting cells and tumor cells[53]. PDCD1 and CD274 act as co-inhibitors and regulate immune tolerance of central and peripheral T-cells and reduce the proliferation of CD8+ T-cells by inhibitor signals[53,55].

Alterations and prevalence: Somatic mutations in PDCD1 are observed in 4% of skin cutaneous melanoma, 3% of uterine corpus endometrial carcinoma, and 2% of uterine carcinosarcoma[12,15]. Deletions in PDCD1 are observed in 8% of sarcoma, 5% of brain lower grade glioma, 3% of cervical squamous cell carcinoma, esophageal adenocarcinoma, bladder urothelial carcinoma, and uveal melanoma[12,15].

Potential relevance: Currently, no therapies are approved for PDCD1 aberrations. Immune checkpoint inhibitor therapy uses immunotherapy to block receptor-ligand interactions and enhance immunity activity against tumor cells[56]. Although not approved for specific PDCD1 aberrations, approved checkpoint inhibitors targeting PDCD1 include the monoclonal antibodies pembrolizumab, nivolumab, and cemiplimab[53].

HLA-A deletion

major histocompatibility complex, class I, A

Background: The HLA-A gene encodes the major histocompatibility complex, class I, A[25]. 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[72]. MHC class I molecules are heterodimers composed of two polypeptide chains, α and B2M[73]. 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[74,75,76]. Downregulation of MHC class I promotes tumor evasion of the immune system, suggesting a tumor suppressor role for HLA-A[77].

Alterations and prevalence: Somatic mutations in HLA-A are observed in 7% of diffuse large B-cell lymphoma (DLBCL), 4% of cervical squamous cell carcinoma and head and neck squamous cell carcinoma, 3% of colorectal adenocarcinoma, and 2% of uterine corpus endometrial carcinoma and stomach adenocarcinoma[12,15]. Biallelic loss of HLA-A is observed in 4% of DLBCL[12,15].

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

HDAC9 p.(L630Sfs*14) c.1888delC

histone deacetylase 9

Background: The HDAC9 gene encodes the histone deacetylase 9 protein[25]. HDAC9 is part of the histone deacetylase (HDAC) family consisting of 18 different isoforms categorized into four classes (I-IV)[33]. HDACs, including HDAC9, function by removing acetyl groups on histone lysines resulting in chromatin condensation, transcriptional repression, and regulation of cell proliferation and differentiation[33,34]. HDAC9 functions in neurological function, brain development, and maintains regulatory T-cell homeostasis[33]. 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[33,35].

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[12,15]. Biallelic deletion of HDAC9 is observed in 2% of diffuse large B-cell lymphoma[12]. Alterations in HDAC9 are also observed in pediatric cancers[12]. 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)[12]. 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)[12].

Biomarker Descriptions (continued)

Potential relevance: Currently, no therapies are approved for HDAC9 aberrations. Although not approved for specific HDAC2 alterations, the pan-HDAC inhibitor vorinostat[36] (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[37] (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[38] (2014), is approved for the treatment of relapsed or refractory PTCL. The FDA granted fast track designation to the pan-HDAC inhibitor, panobinostat[39] (2024), for the treatment of recurrent glioblastoma.

IKBKB amplification

inhibitor of nuclear factor kappa B kinase subunit beta

Background: The IKBKB gene encodes the nuclear factor kappa B kinase subunit beta, also known as IKK-B. IKBKB is a serine/threonine kinase, which acts as an enzyme protein subunit of the IKK complex[57]. IKBKB and IKBKA dimerize to form the regulatory subunit of the IKK complex. Along with modulator IKKγ/NEMO, the IKK complex acts as a master regulator of the family of NF-κB transcription factors.[57]. NF-κB signaling is critical in the inflammatory response and is also known to be implicated in other important physiological processes including cell proliferation[58]. In resting cells, NF-κB dimers are sequestered in the cytoplasm by IκB proteins[58]. Upon signal initiation, IκB proteins are phosphorylated by the IKK complex, leading to IκB protein degradation and liberation of NF-κB dimers[58]. Subsequently, released NF-κB dimers undergo nuclear translocation which leads to the expression of various proinflammatory and cell survival genes[59,60].

Alterations and prevalence: Somatic mutations in IKBKB are observed in 6% of uterine carcinoma, 5% of melanoma and diffuse large B-cell lymphoma (DLBCL)[12,15]. Amplifications are observed in 14% of uterine carcinosarcoma, 7% of breast invasive carcinoma and esophageal cancer[12,15]. IKBKB activating mutations are most commonly found at lysine 175 and are observed in 8% of splenic marginal B-cell lymphomas[57].

Potential relevance: Currently, no therapies are approved for IKBKB aberrations.

ZFHX3 deletion

zinc finger homeobox 3

Background: ZFHX3 encodes zinc finger homeobox 3, a large transcription factor composed of several DNA binding domains, including seventeen zinc finger domains and four homeodomains[25,130,131]. Functionally, ZFHX3 is found to be necessary for neuronal and myogenic differentiation[131,132]. ZFHX3 is capable of binding and repressing transcription of α-fetoprotein (AFP), thereby negatively regulating the expression of MYB and cancer cell growth[133,134,135,136,137]. In addition, ZFHX3 has been observed to be altered in several cancer types, supporting a tumor suppressor role for ZFHX3[133,136,138,139].

Alterations and prevalence: Somatic mutations in ZFHX3 are observed in 24% of uterine corpus endometrial carcinoma, 14% of skin cutaneous melanoma, 10% of colorectal adenocarcinoma, 9% of stomach adenocarcinoma, 8% of lung squamous cell carcinoma, 6% of cervical squamous cell carcinoma, 5% of uterine carcinosarcoma, bladder urothelial carcinoma, and lung adenocarcinoma, 3% of head and neck squamous cell carcinoma, adrenocortical carcinoma, cholangiocarcinoma, esophageal adenocarcinoma, and prostate adenocarcinoma, and 2% of diffuse large B-cell lymphoma, glioblastoma multiforme, pancreatic adenocarcinoma, liver hepatocellular carcinoma, thyroid carcinoma, breast invasive carcinoma, ovarian serous cystadenocarcinoma, thymoma, sarcoma, and acute myeloid leukemia[12,15]. Biallelic loss of ZFHX3 is observed in 6% of prostate adenocarcinoma, 4% of uterine carcinosarcoma, 3% of ovarian serous cystadenocarcinoma, and 2% of uterine corpus endometrial carcinoma, breast invasive carcinoma, and esophageal adenocarcinoma[12,15].

Potential relevance: Currently, no therapies are approved for ZFHX3 aberrations.

Alerts Informed By Public Data Sources

Current FDA Information

Contraindicated Not recommended Resistance Breakthrough Fast Track

FDA information is current as of 2025-11-25. For the most up-to-date information, search www.fda.gov.

CCNE1 amplification

camonsertib + lunresertib

Cancer type: Endometrial Carcinoma, Ovarian Cancer

Variant class: CCNE1 amplification

Supporting Statement:

- The FDA has granted Fast Track designation to lunresertib in combination with camonsertib for the treatment of adult patients with CCNE1 amplified, or FBXW7 or PPP2R1A mutated platinum resistant ovarian cancer.
- The FDA has granted Fast Track designation to lunresertib in combination with camonsertib for the treatment of adult patients with CCNE1 amplified, or FBXW7 or PPP2R1A mutated endometrial cancer.

Reference:

https://ir.reparerx.com/news-releases/news-release-details/repare-therapeutics-announces-fast-track-designation-granted-fda

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,

Genes Assayed (continued)

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

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, 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

FGFR1 amplification

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
pemigatinib	✖	✖	✖	✖	◑ (II)
regorafenib	✖	✖	✖	✖	● (II)
sunitinib	✖	✖	✖	✖	● (II)
BBI-355, futibatinib	✖	✖	✖	✖	● (I/II)
dordaviprone, targeted therapy, radiation therapy	✖	✖	✖	✖	○ (II)
hormone therapy, catequentinib	✖	✖	✖	✖	○ (II)
rogaratinib, chemotherapy	✖	✖	✖	✖	○ (II)
sintilimab, pemigatinib	✖	✖	✖	✖	○ (II)
pazopanib, palbociclib	✖	✖	✖	✖	○ (I/II)

* 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

CCNE1 amplification

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
palbociclib	✖	✖	✖	✖	● (II)
APR-1051	✖	✖	✖	✖	● (I/II)
ARTS-021	✖	✖	✖	✖	● (I/II)
ECI-830, hormone therapy, ribociclib	✖	✖	✖	✖	● (I/II)
INX-315, hormone therapy	✖	✖	✖	✖	● (I/II)
WJB-001	✖	✖	✖	✖	● (I/II)
ETX-197, hormone therapy	✖	✖	✖	✖	● (I)
lunresertib, camonsertib, Debio-0123	✖	✖	✖	✖	● (I)
nedisertib, tuvusertib	✖	✖	✖	✖	● (I)
NKT-3964	✖	✖	✖	✖	● (I)
NKT-5097	✖	✖	✖	✖	● (I)
abemaciclib	✖	✖	✖	✖	○ (II)
lunresertib, chemotherapy	✖	✖	✖	✖	○ (II)
trastuzumab deruxtecan, azenosertib	✖	✖	✖	✖	○ (I)

KIT amplification

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
nilotinib, pazopanib	✖	✖	✖	✖	● (II)
regorafenib	✖	✖	✖	✖	● (II)
sunitinib, regorafenib	✖	✖	✖	✖	● (II)
NB003	✖	✖	✖	✖	● (I)
cabozantinib	✖	✖	✖	✖	○ (II)

KDR amplification

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
pazopanib	✖	✖	✖	✖	● (II)
regorafenib	✖	✖	✖	✖	● (II)
sunitinib, regorafenib	✖	✖	✖	✖	● (II)
cabozantinib	✖	✖	✖	✖	○ (II)

* 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

PDGFRA amplification

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
nilotinib, pazopanib	✖	✖	✖	✖	● (II)
dordaviprone, targeted therapy, radiation therapy	✖	✖	✖	✖	○ (II)

TP53 p.(R273H) c.818G>A

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
TP53-EphA-2-CAR-DC, anti-PD-1	✖	✖	✖	✖	● (I)

TSC2 deletion

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
nab-rapamycin (Abraxis), chemotherapy	✖	✖	✖	✖	○ (I)

* 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	***50.72%***
BRCA2	***LOH, 13q13.1(32890491-32972932)x2***
ATM	***SNV, A1812V, AF:0.3***
BARD1	***LOH, 2q35(215593375-215674382)x2***
RAD51B	***LOH, 14q24.1(68290164-69061406)x2***
RAD54L	***LOH, 1p34.1(46714017-46743978)x2***

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 (6.2.4 data version 2025.12(007)). 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 2025-11-25. NCCN information was sourced from www.nccn.org and is current as of 2025-11-03. EMA information was sourced from www.ema.europa.eu and is current as of 2025-11-25. ESMO information was sourced from www.esmo.org and is current as of 2025-11-03. Clinical Trials information is current as of 2025-11-03. 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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