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Patient Name: 정미영
Gender: F
Sample ID: N25-145

Primary Tumor Site: Breast
Collection Date: 2025.06.24

Sample Cancer Type: Breast Cancer

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Report Highlights
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Relevant Breast Cancer Findings

Gene	Finding
BRCA1	None detected
ERBB2	None detected

Genomic Alteration	Finding
Tumor Mutational Burden	***0.95 Mut/Mb measured***

Relevant Biomarkers

Tier	Genomic Alteration	Relevant Therapies (In this cancer type)	Relevant Therapies (In other cancer type)	Clinical Trials
IA	*AKT1 p.(E17K) c.49G>A* AKT serine/threonine kinase 1 Allele Frequency: 43.27% Locus: chr14:105246551 Transcript: NM_001014431.2	**capivasertib + hormone therapy** [1, 2 / II +]	None*	4
IIC	*ATM deletion* ATM serine/threonine kinase Locus: chr11:108098341	None*	None*	4
IIC	*CCND1 amplification* cyclin D1 Locus: chr11:69455949	None*	None*	4
IIC	*NF2 deletion* neurofibromin 2 Locus: chr22:29999923	None*	None*	2

*** 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* checkpoint kinase 1 Locus: chr11:125496639	None*	None*	1
IIC	*CHEK2 deletion* checkpoint kinase 2 Locus: chr22:29083868	None*	None*	1
IIC	*FGF19 amplification* fibroblast growth factor 19 Locus: chr11:69513948	None*	None*	1
IIC	*LATS1 deletion* large tumor suppressor kinase 1 Locus: chr6:149982844	None*	None*	1
IIC	*PALB2 deletion* partner and localizer of BRCA2 Locus: chr16:23614759	None*	None*	1
IIC	*RB1 deletion* RB transcriptional corepressor 1 Locus: chr13:48877953	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

ARID1B deletion, FGF3 amplification, FGF4 amplification, KMT2A deletion, MRE11 deletion, Microsatellite stable, RNASEH2B deletion, TCF7L2 deletion, ERAP2 deletion, TNFAIP3 deletion, MAP3K4 deletion, SDHD deletion, NQO1 p.(P187S) c.559C>T, RUNX1 deletion, EP300 deletion, Tumor Mutational Burden

Variant Details

DNA Sequence Variants

Gene	Amino Acid Change	Coding	Variant ID	Locus	Allele Frequency	Transcript	Variant Effect
AKT1	p.(E17K)	c.49G>A	COSM33765	chr14:105246551	43.27%	NM_001014431.2	missense
NQO1	p.(P187S)	c.559C>T	.	chr16:69745145	19.16%	NM_000903.3	missense
HLA-A	p.(C125S)	c.373T>A	.	chr6:29911074	22.30%	NM_001242758.1	missense

Copy Number Variations

Gene	Locus	Copy Number	CNV Ratio
ATM	chr11:108098341	1	0.66
CCND1	chr11:69455949	8.99	3.48
NF2	chr22:29999923	1.07	0.67
CHEK1	chr11:125496639	1	0.66

Variant Details (continued)

Copy Number Variations (continued)

Gene	Locus	Copy Number	CNV Ratio
CHEK2	chr22:29083868	1	0.7
FGF19	chr11:69513948	9.97	3.83
LATS1	chr6:149982844	1.1	0.68
PALB2	chr16:23614759	1	0.77
RB1	chr13:48877953	1	0.64
ARID1B	chr6:157099057	1.03	0.66
FGF3	chr11:69625020	9.55	3.68
FGF4	chr11:69588019	8.73	3.39
KMT2A	chr11:118307146	1.06	0.66
MRE11	chr11:94153270	1.04	0.66
RNASEH2B	chr13:51484145	1	0.64
TCF7L2	chr10:114710485	1.04	0.66
ERAP2	chr5:96219500	0.55	0.48
TNFAIP3	chr6:138192315	1.08	0.68
MAP3K4	chr6:161412931	1.11	0.68
SDHD	chr11:111957573	0.75	0.55
RUNX1	chr21:36164357	1.13	0.69
EP300	chr22:41489001	1.1	0.68
EMSY	chr11:76157926	0.97	0.64
CBL	chr11:119103202	0.9	0.61

Biomarker Descriptions

AKT1 p.(E17K) c.49G>A

AKT serine/threonine kinase 1

Background: The AKT1 gene encodes Protein Kinase B, a serine/threonine kinase, that belongs to a family of closely related protein kinases that also includes AKT2 and AKT3. 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. The PI3K/AKT/MTOR pathway is central to the regulation of cancer cell proliferation, survival, and metabolism[133,134].

Alterations and prevalence: AKT1 encodes a proto-oncogene that is the target of recurrent somatic mutations in cancer[135]. The most common recurrent mutation is E17K, which is located in the N-terminal pleckstrin homology (PH) domain. E17K is a gain-of-function activating mutation that constitutively targets AKT1 to the plasma membrane and leads to downstream signaling[136,137]. Other recurrent activating mutations include L52H, Q79K, and D323Y/G/N, which disrupt negative regulatory interactions between the PH domain and the kinase domain[138]. AKT1 mutations in cancer are common in breast and endometrial cancers, where they occur at a prevalence of 2-5%[10]. AKT1 mutations are observed at a prevalence of 1-2% in bladder, colorectal, melanoma, and thyroid cancers[9,10]. AKT1 is overexpressed via gene amplification in ovarian cancer, lung squamous cell cancer, and sarcoma at a prevalence of 2-5%[9,10].

Potential relevance: Currently no therapies are approved for AKT1 aberrations. However, in the phase II NCI-MATCH trial, the pan-AKT inhibitor capivasertib (AZD5363) demonstrated a partial response in 23% (8/35) of AKT1 E17K mutated solid tumor patients[139]. Results from a phase I clinical trial of capivasertib demonstrated partial responses in 9/52 heavily pre-treated patients with AKT1

Biomarker Descriptions (continued)

E17K mutated solid tumors, with a median progression-free survival (PFS) of 5.5 months in ER positive breast cancer, 6.6 months in gynecologic cancers, and 4.2 months in other solid tumors[140]. In the same phase I study, an ovarian cancer patient with an AKT1 Q79K mutation demonstrated stable disease lasting 14 months[140].

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)[91]. 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[92]. ATM is recruited to the DNA damage site by the MRE11/RAD50/NBN (MRN) complex that senses DSB[92,93]. Upon activation, ATM phosphorylates several downstream proteins such as the NBN, MDC1, BRCA1, CHK2 and TP53BP1 proteins[94]. 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[28,29]. 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[95].

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[9,10].

Potential relevance: The PARP inhibitor, olaparib[89] 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[38] 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[28,96,97]. 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[98]. In 2022, the FDA granted fast track designation to the small molecule inhibitor, pidnarulex[90], for BRCA1/2, PALB2, or other homologous recombination deficiency (HRD) mutations in breast and ovarian cancers.

CCND1 amplification

cyclin D1

Background: The CCND1 gene encodes the cyclin D1 protein, a member of the highly conserved D-cyclin family that also includes CCND2 and CCND3[185,186,187]. D-type cyclins are known to regulate cell cycle progression by binding to and activating cyclin dependent kinases (CDKs), specifically CDK4 and CDK6, which leads to the phosphorylation and inactivation of the retinoblastoma (RB1) protein[185,186]. Consequently, RB1 inactivation results in E2F transcription factor activation and cellular G1/S phase transition thereby resulting in cell cycle progression, a common event observed in tumorigenesis[185,186,188]. Aberrations in the D-type cyclins have been observed to promote tumor progression suggesting an oncogenic role for CCND1[187,189].

Alterations and prevalence: Recurrent somatic alterations to CCND1, including mutations, amplifications, and chromosomal translocations, are observed in many cancer types. A common mechanism of these alterations is to increase the expression and nuclear localization of the cyclin D1 protein. Recurrent somatic mutations include missense mutations at codons T286 and P287 and c-terminal truncating mutations that are enriched in about 33% of uterine cancer, and missense mutations at Y44 that are enriched in about 50% of Mantle cell lymphoma (MCL)[9,10,190,191]. These mutations block phosphorylation-dependent nuclear export and proteolysis[192,193,194,195]. CCND1 is recurrently amplified in many cancer types, including up to 35% of esophageal cancer, 20-30% of head and neck cancer, and 10-20% of breast, squamous lung, and bladder cancers[9,10,196]. MCL is genetically characterized by the t(11;14)(q13;q13) translocation, a rearrangement that juxtaposes CCND1 to the immunoglobulin heavy (IgH) chain gene. This rearrangement leads to constitutive expression of cyclin D1 and plays an important role in MCL pathogenesis[197,198].

Potential relevance: Currently, no therapies are approved for CCND1 aberrations. The t(11;14) translocation involving CCND1 can be used to help diagnose some lymphoma subtypes including non-gastric MALT lymphoma, splenic marginal cell lymphoma, and mantle cell lymphoma[199].

NF2 deletion

neurofibromin 2

Background: The NF2 gene encodes the cytoskeletal Merlin (Moesin-ezrin-radixin-like) protein. NF2 is also known as Schwannomin due to its prevalence in neuronal Schwann cells. NF2 is structurally and functionally related to the Ezrin, Radixin, Moesin (ERM) family which is known to control plasma membrane function, thereby influencing cell shape, adhesion, and growth[146,147,148]. NF2 regulates

Biomarker Descriptions (continued)

several cellular pathways including the RAS/RAF/MEK/ERK, PI3K/AKT, and Hippo-YAP pathways, thus impacting cell motility, adhesion, invasion, proliferation, and apoptosis[146,147,148,149]. NF2 functions as a tumor suppressor wherein loss of function mutations are shown to confer a predisposition to tumor development[147,148,150]. Specifically, deleterious germline mutations or deletion of NF2 leading to loss of heterozygosity (LOH) is causal of neurofibromatosis type 2, a tumor prone disorder characterized by early age onset of multiple Schwannomas and meningiomas[147,148,150].

Alterations and prevalence: Somatic mutations in NF2 are predominantly misssense or truncating and are observed in about 23% of mesothelioma, 5% of cholangiocarcinoma and uterine cancer, and about 3% of papillary renal cell carcinoma (pRCC), bladder, and cervical cancers[10]. Biallelic loss of NF2 is also observed in approximately 8% of mesothelioma cases[10].

Potential relevance: Currently, no therapies are approved for NF2 aberrations. However, the FDA granted Fast Track designation (2022) to the novel TEAD inhibitor, IK-930, for unresectable NF2-deficient malignant pleural mesothelioma (MPM)[151].

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[21]. Checkpoint kinases play an important role in S phase and G2/M transition and DNA damage induced cell cycle arrest[84]. 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)[85,86]. Upon DNA damage, CHEK1 is phosphorylated and activated by DNA damage repair proteins ATM and ATR[85]. Activated CHEK1 subsequently phosphorylates and negatively regulates downstream proteins such as CDC25A thereby slowing or stalling DNA replication[85,87].

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[10,88]. 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[10,88].

Potential relevance: The PARP inhibitor, olaparib[89] 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[90], for BRCA1/2, PALB2, or other homologous recombination deficiency (HRD) mutations in breast and ovarian cancers.

CHEK2 deletion

checkpoint kinase 2

Background: The CHEK2 gene encodes the checkpoint kinase-2 serine/threonine kinase, which is a cell-cycle checkpoint regulator. In response to DNA damage, CHEK2 is phosphorylated by ATM and subsequently phosphorylates and negatively regulates CDC25C to prevent entry into mitosis[179]. CHEK2 also stabilizes p53, leading to cell-cycle arrest in G1 phase, and is capable of phosphorylating BRCA1 and promoting DNA repair including homologous recombination repair (HRR)[86,180,181]. Germline mutations in the CHEK2 gene are associated with Li-Fraumeni syndrome and inherited risk of breast cancer[182,183,184].

Alterations and prevalence: Consistent with its role as a tumor suppressor, CHEK2 is enriched for deleterious truncating mutations. Somatic mutations in CHEK2 are common (2-6%) in uterine carcinoma, bladder carcinoma, and lung adenocarcinoma[9,10]. CHEK2 gene deletions are observed in adrenocortical carcinoma, thymoma, and prostate cancer[9,10].

Potential relevance: The PARP inhibitor, olaparib[89] is approved (2020) for metastatic castration-resistant prostate cancer (mCRPC) with deleterious or suspected deleterious, germline or somatic mutations in HRR genes that includes CHEK2. Additionally, talazoparib[38] in combination with enzalutamide is approved (2023) for mCRPC with mutations in HRR genes that includes CHEK2. In 2022, the FDA granted fast track designation to the small molecule inhibitor, pidnarulex[90], for BRCA1/2, PALB2, or other homologous recombination deficiency (HRD) mutations in breast and ovarian cancers.

FGF19 amplification

fibroblast growth factor 19

Background: The FGF19 gene encodes the fibroblast growth factor 19 protein, a member of the FGF protein family composed of twenty-two members[104,105]. With the exception of four non-signaling FGF memebers (FGF11-14), FGF proteins function as ligands and mediate the activation of the fibroblast growth factor receptor (FGFR) family of tyrosine kinases[104,105]. 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 thereby influencing cell proliferation, migration, and survival[106,107,108]. FGF19 is specifically observed to bind

Biomarker Descriptions (continued)

FGFR4 with increased affinity in the presence of the transmembrane protein klotho beta (KLB) which functions as a cofactor in FGF19 mediated FGFR4 activation[141,142]. FGF19-mediated aberrant signaling has been identified as an oncogenic driver in hepatocellular carcinoma[141,143].

Alterations and prevalence: FGF19 amplification is observed in about 35% of esophageal cancer, 23% of head and neck cancer, 10-15% of invasive breast carcinoma, cholangiocarcinoma, squamous lung, and bladder cancers as well as 5-7% of melanoma, liver, ovarian, and stomach cancers[10]. FGF19 overexpression is correlated with the development and tumor progression in hepatocellular carcinoma[144].

Potential relevance: Currently, no therapies are approved for FGF19 aberrations. Selective, irreversible FGFR4 inhibitors, including fisogatinib (BLU-554), are under current clinical trial evaluation. In a phase-I clinical study of fisogatinib in patients with advanced hepatocellular carcinoma, 63% of the 115 patients enrolled were FGF19-positive by IHC[145]. Additionally, in 53 patients with tissue available for evaluation, 96% also exhibited mRNA-expression of FGFR4 and KLB. The total overall response rate observed for fisogatinib in FGF19-positive patients evaluable for response was 17% (11/66)[145].

LATS1 deletion

large tumor suppressor kinase 1

Background: The LATS1 gene encodes the large tumor suppressor kinase 1[21]. LATS1 is a serine/threonine protein kinase and, along with LATS2, is a member of the AGC kinase family comprised of more than 60 members[46,47]. LATS1 and LATS2 are downstream phosphorylation targets of the Hippo pathway, and when activated, mediate the phosphorylation of transcriptional co-activators YAP and TAZ[48]. Phosphorylation of YAP and TAZ results in their cytoplasmic retention and inhibition of nuclear translocation, thereby inhibiting YAP and TAZ mediated transcription of target genes[48]. Mutations in LATS1 and LATS2 are suggested to result in kinase inactivation and loss of function, supporting a tumor suppressor role for LATS1[49].

Alterations and prevalence: Somatic mutations in LATS1 are observed in 9% of uterine corpus endometrial carcinoma, 4% of cervical squamous cell carcinoma, bladder urothelial carcinoma, colorectal adenocarcinoma, lung squamous cell carcinoma, and skin cutaneous melanoma, and 3% of stomach adenocarcinoma and lung adenocarcinoma[9,10]. Biallelic deletion of LATS1 is observed in 8% of uveal melanoma, 6% of diffuse large B-cell lymphoma, and 2% liver hepatocellular carcinoma, ovarian serous cystadenocarcinoma, and thymoma[9,10].

Potential relevance: Currently, no therapies are approved for LATS1 aberrations.

PALB2 deletion

partner and localizer of BRCA2

Background: The PALB2 gene encodes the partner and localizer of BRCA2 protein that binds to and promotes intranuclear localization of the breast cancer 2 early onset (BRCA2) protein[119]. Also known as FANCN, PALB2 belongs to the Fanconi Anemia (FA) complementation group of proteins that also include FANCA, FANCB, FANCC, FANCD1 (BRCA2), FANCD2, FANCE, FANCF, FANCG, FANCI, FANCJ (BRIP1), FANCL, and FANCM. FA genes are tumor suppressors that play a role in interstrand cross-link (ICL) DNA repair through homologous recombination repair (HRR) of double-strand breaks (DSB) and nucleotide excision repair (NER)[120]. Loss of function mutations of genes in the FA family and HRR pathway, including PALB2, can result in the BRCAness phenotype, characterized by a defect in the HRR pathway, mimicking BRCA1 or BRCA2 loss[29,121]. Germline mutations in FA genes lead to Fanconi Anemia, a condition characterized by chromosomal instability and congenital abnormalities including bone marrow failure and cancer predisposition[122,123]. Specifically, biallelic germline mutations resulting in PALB2 loss of function confer a predisposition to pediatric malignancies[124,125]. Additionally, monoallelic germline mutations in PALB2 have been associated with an increased risk of developing breast cancer[124,126].

Alterations and prevalence: Somatic alterations in PALB2 include missense or truncating mutations and are observed in 2-6% of melanoma, uterine, bladder, breast, lung, stomach and colorectal cancers[10].

Potential relevance: The PARP inhibitor, olaparib[89] is approved (2020) for metastatic castration-resistant prostate cancer (mCRPC) with deleterious or suspected deleterious, germline or somatic mutations in HRR genes that includes PALB2. Additionally, talazoparib[38] in combination with enzalutamide is approved (2023) for mCRPC with mutations in HRR genes that includes PALB2. In a phase II trial of patients with metastatic, castration-resistant prostate cancer, one patient exhibiting a somatic PALB2 frameshift mutation exhibited durable response to olaparib for 39 weeks[98,127]. However, olaparib resistance was observed following 9-months of treatment due to the emergence of a secondary deletion which restored the PALB2 reading frame, a resistance mechanism similar to that observed in PARPi treated BRCA mutated patients[127,128]. In 2022, the FDA granted fast track designation to the small molecule inhibitor, pidnarulex[90], for BRCA1/2, PALB2, or other homologous recombination deficiency (HRD) mutations in breast and ovarian cancers. Rucaparib is recommended as a maintenance therapy for germline or somatic PALB2 mutations in metastatic pancreatic cancer[129].

Biomarker Descriptions (continued)

RB1 deletion

RB transcriptional corepressor 1

Background: The RB1 gene encodes the retinoblastoma protein (pRB), and is an early molecular hallmark of cancer. RB1 belongs to the family of pocket proteins that also includes p107 and p130, which play a crucial role in the cell proliferation, apoptosis, and differentiation[76,77]. RB1 is well characterized as a tumor suppressor gene that restrains cell cycle progression from G1 phase to S phase[78]. Specifically, RB1 binds and represses the E2F family of transcription factors that regulate the expression of genes involved in the G1/S cell cycle regulation[76,77,79]. Germline mutations in RB1 are associated with retinoblastoma (a rare childhood tumor) as well as other cancer types such as osteosarcoma, soft tissue sarcoma, and melanoma[80].

Alterations and prevalence: Recurrent somatic alterations in RB1, including mutations and biallelic loss, lead to the inactivation of the RB1 protein. RB1 mutations are observed in urothelial carcinoma (approximately 16%), endometrial cancer (approximately 12%), and sarcomas (approximately 9%)[9]. Similarly, biallelic loss of RB1 is observed in sarcomas (approximately 13%), urothelial carcinoma (approximately 6%), and endometrial cancer (approximately 1%)[9]. Biallelic loss of the RB1 gene is also linked to the activation of chemotherapy-induced acute myeloid leukemia (AML) and acute lymphoblastic leukemia (ALL)[81,82,83].

Potential relevance: Currently, there are no therapies approved for RB1 aberrations.

ARID1B deletion

AT-rich interaction domain 1B

Background: The ARID1B gene encodes the AT-rich interaction domain 1B tumor suppressor protein[21]. ARID1B, also known as BAF250B, belongs to the ARID1 subfamily that also includes ARID1A[21,99]. ARID1A and ARID1B are mutually exclusive subunits of the BAF variant of the SWI/SNF chromatin remodeling complex[99,100].The BAF complex is a multisubunit protein that consists of SMARCB1/IN1, SMARCC1/BAF155, SMARCC2/BAF170, SMARCA4/BRG1 or SMARCA2/BRM, and ARID1A or ARID1B[100]. The BAF complex remodels chromatin at promoter and enhancer elements to alter and regulate gene expression[100,101]. Recurrent inactivating mutations in BAF complex subunits, including ARID1B, lead to transcriptional dysfunction, suggesting ARID2B functions as a tumor suppressor[99].

Alterations and prevalence: Mutations in SWI/SNF complex subunits are the most commonly mutated chromatin modulators in cancer and have been observed in 20% of all tumors[101]. Somatic mutations in ARID1B are observed in 9% of uterine corpus endometrial carcinoma, 8% of cholangiocarcinoma, 7% of skin cutaneous melanoma, and 6% of stomach adenocarcinoma, bladder urothelial carcinoma, and colorectal adenocarcinoma[9,10]. Biallelic loss of ARID1B is observed in 6% of uveal melanoma, 1% of bladder urothelial carcinoma, stomach adenocarcinoma, skin cutaneous melanoma, and colorectal adenocarcinoma[9,10].

Potential relevance: Currently, no therapies are approved for ARID1B aberrations. Mutations in chromatin modifying genes, including ARID1B, are considered to be characteristic genetic features of hepatosplenic T-cell lymphoma (HSTL), as they have been observed in up to 62% of cases[102,103].

FGF3 amplification

fibroblast growth factor 3

Background: The FGF3 gene encodes the fibroblast growth factor 3 protein, a member of the FGF protein family composed of twenty-two members[104,105]. With the exception of four non-signaling FGF memebers (FGF11-14), FGF proteins function as ligands and mediate the activation of the fibroblast growth factor receptor (FGFR) family of tyrosine kinases[104,105]. 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 thereby influencing cell proliferation, migration, and survival[106,107,108]. Specifically, FGF3 has been shown to bind to both FGFR1 and FGFR2[109,110]. Overexpression of FGF3 has been associated with certain tumor types including lung and liver cancers[111,112]. Additionally, constitutive ectopic expression has been suggested to promote tumorigenesis in vitro, supporting an oncogenic role for FGF3[110].

Alterations and prevalence: FGF3 amplification is observed in about 35% of esophageal cancer, 24% of head and neck cancer, 10-15% of invasive breast carcinoma, squamous lung, and bladder cancers as well as 5-10% of cholangiocarcinoma, melanoma, liver, ovarian and stomach cancers[10]. FGF3 overexpression is correlated with non-small cell lung cancer (NSCLC) development as well as tumor metastasis and recurrence in hepatocellular carcinoma[111,112].

Potential relevance: Currently, no therapies are approved for FGF3 aberrations.

Biomarker Descriptions (continued)

FGF4 amplification

fibroblast growth factor 4

Background: The FGF4 gene encodes the fibroblast growth factor 4 protein, a member of the FGF protein family, which is composed of 22 members[21,105]. With the exception of four non-signaling FGF members (FGF11-14), FGF proteins function as ligands and mediate the activation of the fibroblast growth factor receptor (FGFR) family of tyrosine kinases[104,105]. 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, thereby influencing cell proliferation, migration, and survival[106,107,108].

Alterations and prevalence: Amplifications in FGF4 are observed in various tumor types, but most frequently are found in up to 35% of esophageal adenocarcinoma, 24% of head and neck squamous cell carcinoma, 14% of breast invasive carcinoma, 12% of lung squamous cell carcinoma, 11% of cholangiocarcinoma, 10% of bladder urothelial carcinoma, 7% of stomach adenocarcinoma, and 5% of liver hepatocellular carcinoma[9,10]. FGF4 overexpression has been associated with Kaposi sarcoma lesions as well as testicular cancer[152,153].

Potential relevance: Currently, no therapies are approved for FGF4 aberrations.

KMT2A deletion

lysine methyltransferase 2A

Background: The KMT2A gene encodes lysine methyltransferase 2A, a transcriptional coactivator and histone H3 lysine 4 (H3K4) methyltransferase[21,57]. KMT2A, also known as mixed lineage leukemia (MLL), is part of the SET domain protein methyltransferase superfamily[57]. KMT2A influences the epigenetic regulation of several cellular functions, including neurogenesis, hematopoiesis, and osteogenesis[58]. Located at the chromosomal position 11q23, KMT2A is the target of recurrent chromosomal rearrangements observed in several leukemia subtypes, including MLL, acute myeloid leukemia (AML), and acute lymphoblastic leukemia (ALL)[59]. These translocations encode KMT2A fusion proteins that are oncogenic with simultaneous loss of KMT2A H3K4 methyltransferase activity[59]. Loss of methyltransferase activity, along with gain-of-function partner gene activation, contributes to increased HOX gene expression and promotes the transformation of hematopoietic cells into leukemic stem cells[59,60,61,62].

Alterations and prevalence: KMT2A fusions are observed in 3-10% of adult AML cases with the highest frequencies in therapy-related AML (9%) and patients younger than 60 years (5%)[9,10,59,63]. KMT2A rearrangements including t(4;11)(q21;q23)/AFF1::KMT2A, t(9;11)(p22;q23)/MLLT3::KMT2A, t(11;19)(q23;p13.3)/KMT2A::MLLT1, t(10;11)(p12;q23)/MLLT10::KMT2A, and t(6;11)(q27;q23)/AFDN::KMT2A translocations account for about 80% of all KMT2A rearranged leukemias[59]. KMT2A alterations observed in solid tumors include nonsense or frameshift mutations, which result in KMT2A truncation and loss of methyltransferase activity[10,64]. KMT2A alterations are also observed in pediatric cancers[9,10]. In infant acute leukemic cases, KMT2A rearrangement is reported in more than 70% of pediatric patients diagnosed with either AML or ALL and is observed in 5% of T-lymphoblastic leukemia/lymphoma[9,10,59,65,66].

Potential relevance: KMT2A fusions are associated with variable prognosis based on the partner genes involved in the fusion[15,67]. For example, t(6;11)(q27;q23)/AFDN::KMT2A fusions are associated with poor prognosis, whereas t(9;11)(p22;q23)/MLLT3::KMT2A fusions confer a more favorable or intermediate prognosis in AML[68,69,70]. Additionally, 11q23 rearrangements define an unfavorable karyotype in patients diagnosed with primary myelofibrosis (PMF) and may confer intermediate to high risk depending on concurrent cytogenetic abnormalities[71]. KMT2A fusion is also associated with poor risk in adult and pediatric ALL[16,17,72]. Translocations in KMT2A are recognized by the World Health Organization (WHO) as a molecular subtype of B-lymphoblastic leukemia/lymphoma with KMT2A-rearrangement[73]. In 2024, the FDA approved the oral menin inhibitor, revumenib[74], for the treatment of adult and pediatric patients 1 year and older with relapsed or refractory acute leukemia harboring a KMT2A rearrangement. In 2024, the FDA also granted fast track designation to the small molecule inhibitor, DSP-5336, for the treatment of patients with relapsed or refractory AML with KMT2A rearrangements[75].

MRE11 deletion

MRE11 homolog, double strand break repair nuclease

Background: The MRE11 gene encodes the meiotic recombination 11 protein, a nuclear protein that is part of the multisubunit MRE11/RAD50/NBN (MRN) complex, which is necessary for the maintenance of genomic stability[24]. The MRN complex is involved in the repair of double-stranded breaks (DSB) through two mechanisms namely homologous recombination repair (HRR) and non-homologous end joining (NHEJ)[25,26,27]. Dimerization of MRE11 is required for DNA binding of the MRN complex, and it acts as a 3'–5' exonuclease and ssDNA endonuclease upon binding DNA[24]. MRE11 is a tumor suppressor gene and loss of function mutations are implicated in the BRCAness phenotype, characterized by a defect in the HRR pathway mimicking BRCA1 or BRCA2 loss[28,29]. Germline mutations in MRE11 have been identified as candidate susceptibility aberrations in colorectal cancer and a hallmark of ataxia-telangiectasia-like disorder (ALTD), a heritable disease resulting in progressive cerebellar degeneration and cancer predisposition[30,31,32,33].

Biomarker Descriptions (continued)

Alterations and prevalence: Somatic mutations in MRE11 are observed in 6-7% of uterine cancer as well as 2-3% of lung adenocarcinoma and melanoma[10]. Mutations in the T11 polypyrimidine tract of MRE11 intron 5 are associated with aberrant splicing and reduced MRE11 protein expression. The presence of MRE11 splice variants is frequently observed in mismatch repair deficient (dMMR)/microsatellite instability (MSI-H) colorectal and endometrial cancers[34,35,36,37]

Potential relevance: The PARP inhibitor, talazoparib[38] in combination with enzalutamide is approved (2023) for metastatic castration-resistant prostate cancer (mCRPC) with mutations in HRR genes that includes MRE11. Loss of function in HRR genes, including MRE11, may confer sensitivity to DNA damaging agents and PARP inhibitors[28,29]. Specifically, loss of MRE11 protein expression has been observed to predict sensitivity to PARP inhibitors in colorectal, breast, and endometrial cancers in vitro[39,40,41].

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[154]. Microsatellite instability (MSI) is defined as a change in the length of a microsatellite in a tumor as compared to normal tissue[155,156]. 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[157]. 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[158]. 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)[158]. Tumors classified as MSI-L are often phenotypically indistinguishable from MSS tumors and tend to be grouped with MSS[159,160,161,162,163]. 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[156]. LS is associated with an increased risk of developing colorectal cancer, as well as other cancers, including endometrial and stomach cancer[155,156,160,164].

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[155,156,165,166]. 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[165,166].

Potential relevance: Anti-PD-1 immune checkpoint inhibitors including pembrolizumab[167] (2014) and nivolumab[168] (2015) are approved for patients with MSI-H or dMMR colorectal cancer who have progressed following chemotherapy. Pembrolizumab[167] 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[167]. Dostarlimab[169] (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[161,170]. The cytotoxic T-lymphocyte antigen 4 (CTLA-4) blocking antibody, ipilimumab[171] (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[161,172,173]. 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[173]. 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[174,175]. However, checkpoint blockade with the addition of chemotherapy or targeted therapies have demonstrated response in MSS or pMMR cancers[174,175].

RNASEH2B deletion

ribonuclease H2 subunit B

Background: The RNASEH2B gene encodes the ribonuclease H2 subunit B protein[21]. RNASEH2B functions as an auxiliary subunit of RNase H2 holoenzyme along with RNASEH2C and the catalytic subunit RNASEH2A[22,23]. RNase H2 is responsible for the removal of ribonucleotides that have been misincorporated in DNA, and also degrades DNA:RNA hybrids formed during transcription[22]. Specifically, RNase H2 is observed to interact with BRCA1 for DNA:RNA hybrid resolution at double-strand breaks (DSBs) through homologous recombination repair (HRR)[22].

Alterations and prevalence: Somatic mutations in RNASEH2B are observed in 3% of uterine corpus endometrial carcinoma, and 2% of skin cutaneous melanoma[9,10]. RNASEH2B biallelic deletions are observed in 10% of prostate adenocarcinoma, 7% sarcoma, 6% of bladder urothelial carcinoma, and 3% of ovarian serous cystadenocarcinoma[9,10].

Potential relevance: Currently, no therapies are approved for RNASEH2B aberrations.

Biomarker Descriptions (continued)

TCF7L2 deletion

transcription factor 7 like 2

Background: TCF7L2 encodes the transcription factor 7 like 2, a key component of the WNT signaling pathway[21,176]. Through its interaction with β-catenin, TCF7L2 functions as a central transcriptional regulator of the WNT pathway by modulating the expression of several genes involved in epithelial to mesenchymal transdifferentiation (EMT) and cancer progression, including MYC[176,177,178]. TCF7L2 is also responsible for the regulation of cell cycle inhibitors, including CDKN2C and CDKN2D, thereby influencing cell cycle progression[176]. Loss of TCF7L2 function is commonly observed in colorectal cancer due to mutations or copy number loss which has been correlated with increased tumor invasion and metastasis, supporting a tumor suppressor role for TCF7L2[176].

Alterations and prevalence: Somatic mutations of TCF7L2 are observed in 11% colorectal adenocarcinoma, 6% of uterine corpus endometrial carcinoma, 3% of stomach adenocarcinoma, and 2% of skin cutaneous melanoma and uterine carcinosarcoma[9,10]. Biallelic deletion of TCF7L2 is observed in 2% diffuse large B-cell lymphoma, brain lower grade glioma, and colorectal adenocarcinoma, and 1% of bladder urothelial carcinoma, mesothelioma, stomach adenocarcinoma, esophageal adenocarcinoma, liver hepatocellular carcinoma, and skin cutaneous melanoma[9,10].

Potential relevance: Currently, no therapies are approved for TCF7L2 aberrations.

ERAP2 deletion

endoplasmic reticulum aminopeptidase 2

Background: The ERAP2 gene encodes the endoplasmic reticulum aminopeptidase 2 protein. ERAP2, and structurally related ERAP1, are zinc metallopeptidases which play a role in antigen processing within the immune response pathway[50,51]. Upon uptake by an immune cell, antigens are first processed by the proteasome and then transported into the endoplasmic reticulum where ERAP1 and ERAP2 excise peptide N-terminal extensions to generate mature antigen peptides for presentation on MHC class I molecules[50,52]. The polymorphic variability in ERAP2 is hypothesized to affect the severity of cytotoxic responses to transformed cells and potentially influence their chances to gain mutations that evade the immune system and become tumorigenic[50].

Alterations and prevalence: Somatic mutations in ERAP2 are observed in 7% of uterine corpus endometrial carcinoma and skin cutaneous melanoma, and 2% of colorectal adenocarcinoma, uterine carcinosarcoma, head and neck squamous cell carcinoma, and stomach adenocarcinoma[9,10]. Deletions are observed in 2% of ovarian serous cystadenocarcinoma, prostate adenocarcinoma, and 1% of colorectal adenocarcinoma, mesothelioma, esophageal adenocarcinoma, and lung squamous cell carcinoma[9,10].

Potential relevance: Currently, no therapies are approved for ERAP2 aberrations.

TNFAIP3 deletion

TNF alpha induced protein 3

Background: The TNFAIP3 gene encodes the TNF alpha induced protein 3[21]. TNFAIP3, also known as A20, is a ubiquitin modifying protein that possesses deubiquitination, E3 ligase, and ubiquitin binding activity[130]. TNFAIP3 is known to negatively regulate the NF-κB pathway by means of its ubiquitin modifying ability, thus impacting inflammatory and immune responses[130,131]. Specifically, TNFAIP3 is known to function as a cysteine protease with deubiquitination (DUB) capability and possesses seven zinc finger motifs that mediate binding to K63- and M1- polyubiquitin chains, thereby altering protein degradation and other protein-protein interactions[130]. TNFAIP3 deficient cells are observed to promote aberrant NF-κB signaling, deregulation of which is proposed to contribute to lymphoma pathogenesis[130,132].

Alterations and prevalence: Somatic mutations in TNFAIP3 are observed in 12% of diffuse large B-cell lymphoma (DLBCL), 4% of uterine corpus endometrial carcinoma, 3% of skin cutaneous melanoma, and 2% of colorectal adenocarcinoma and bladder urothelial carcinoma[9,10]. Biallelic loss of TNFAIP3 is observed in 30% of human B-cell lymphoma, 12% of DLBCL and 8% of uveal melanoma[9,10,130].

Potential relevance: Currently, no therapies are approved for TNFAIP3 aberrations.

MAP3K4 deletion

mitogen-activated protein kinase kinase kinase 4

Background: The MAP3K4 gene encodes the mitogen-activated protein kinase kinase kinase 4, also known as MEKK4[21]. MAP3K4 is involved in the JNK signaling pathway along with MAP3K12, MAP2K4, MAP2K7, MAPK8, MAPK9, and MAPK10[53]. Activation of MAPK proteins occurs through a kinase signaling cascade[53,54,55]. Specifically, MAP3Ks are responsible for phosphorylation of MAP2K family members[53,54,55]. Once activated, MAP2Ks are responsible for the phosphorylation of various MAPK proteins whose signaling is involved

Biomarker Descriptions (continued)

in several cellular processes including cell proliferation, differentiation, and inflammation[53,54,55]. In intrahepatic cholangiocarcinoma, mutations leading to lack of MAP3K4 activity result in vascular invasion and poor survival, supporting a tumor suppressor role for MAP3K4[56].

Alterations and prevalence: Somatic mutations in MAP3K4 are observed in 10% of uterine corpus endometrial carcinoma, 9% of skin cutaneous melanoma, 7% of uterine carcinosarcoma, and 6% of colorectal adenocarcinoma[9,10]. Biallelic deletions are observed in 6% of uveal melanoma, 3% of ovarian serous cystadenocarcinoma, and 2% of diffuse large B-cell lymphoma (DLBCL)[9,10].

Potential relevance: Currently, no therapies are approved for MAP3K4 aberrations.

SDHD deletion

succinate dehydrogenase complex subunit D

Background: The SDHD gene encodes succinate dehydrogenase complex subunit D of the succinate dehydrogenase (SDH) enzyme complex[21,42]. The SDH enzyme complex, also known as complex II of the mitochondrial respiratory chain, is composed of four subunits encoded by SDHA, SDHB, SDHC, and SDHD[43,44]. SDH is a key mitochondrial enzyme complex that catalyzes the oxidation of succinate to fumarate in the tricarboxylic acid cycle and transfers the electrons to ubiquinone in the electron transport chain[43,44]. SDHD, along with SDHC, anchors SDHA and SDHB to the inner mitochondrial membrane and provides a binding site for ubiquinone[42]. Mutations in SDH genes lead to abnormal stabilization of hypoxia-inducible factors and pseudo-hypoxia, thereby promoting cell proliferation, angiogenesis, and tumorigenesis[42,43,44]. Inherited pathogenic mutations in SDHD have been associated with paragangliomas and gastrointestinal stromal tumors[21,42,45].

Alterations and prevalence: Somatic mutations in SDHD are observed in 1% of mesothelioma, uterine corpus endometrial carcinoma, adrenocortical carcinoma, esophageal adenocarcinoma, colorectal adenocarcinoma, and lung adenocarcinoma[9,10]. Biallelic loss of SDHD is observed in 3% of testicular germ cell tumors, skin cutaneous melanoma, cervical squamous cell carcinoma, and uveal melanoma, and 2% of sarcoma and uterine carcinosarcoma[9,10].

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

RUNX1 deletion

RUNX family transcription factor 1

Background: The RUNX1 gene encodes the runt-related transcription factor (RUNX) 1, part of the RUNX family of transcription factors, which also includes RUNX2 and RUNX3[1]. All RUNX proteins share several conserved regions with similar functionality, including a highly conserved N-terminal ‘runt’ domain responsible for binding DNA, a C-terminal region composed of an activation domain, inhibitory domain, protein-interacting motifs, and a nuclear matrix targeting signal[2]. Each of these proteins interacts with core binding factor beta (CBFβ) to form the core binding factor (CFB) complex[2]. Consequently, RUNX1, RUNX2, and RUNX3 are collectively known as core binding factor alpha (CBFα) since they can each function as the alpha subunit of CBF[3]. Specifically, CBFβ binds to the 'runt' domain of RUNX1, leading to RUNX1 stabilization and increased affinity of the CFB complex for promoters involved in hematopoietic differentiation and cell cycle regulation[4,5]. RUNX1 is frequently mutated in various hematological malignancies[5]. Germline mutations in RUNX1 result in a rare autosomal dominant condition known as familial platelet disorder with predisposition to acute myeloid leukemia (FPD/AML)[6,7]. Somatic mutations and chromosomal translocations in RUNX1 are often observed in myelodysplastic syndrome (MDS), acute myeloid leukemia (AML), acute lymphoblastic leukemia (ALL), and chronic myelomonocytic leukemia (CMML)[5].

Alterations and prevalence: RUNX1 is frequently rearranged in hematological malignancies with over 50 different observed translocations[8]. RUNX1 translocations occur in 4% of all AML[9,10]. A recurrent translocation, t(8;21)(q22;q22), results in RUNX1::RUNX1T1 fusion and is observed in 5-10% of AML[11]. The RUNX1::RUNX1T1 fusion, consists of the runt-homology domain (RHD) of RUNX1 and the majority of RUNX1T1, which promotes oncogenesis by altering transcriptional regulation of RUNX1 target genes[5,11]. Another translocation, t(12;21)(q34;q11), results in ETV6::RUNX1 fusion and is observed in 2% of adult ALL[12]. Somatic mutations in RUNX1 include missense, nonsense, and frameshift mutations resulting in loss of function or dominant negative effects[5]. RUNX1 somatic mutations are observed in approximately 10% of AML, 10-15% of MDS, 5% of uterine corpus endometrial carcinoma, 4% of breast invasive carcinoma, 3% of bladder urothelial carcinoma, and 2% of colorectal adenocarcinoma[5,9,10]. Biallelic deletion of RUNX1 is observed in 7% of esophageal adenocarcinoma and 2% of stomach adenocarcinoma[9,10]. Alterations in RUNX1 are common in pediatric cancers, particularly the ETV6::RUNX1 fusion, which is observed in 20-25% of childhood ALL[12,13]. Overall, RUNX1 fusions are observed in 12% of B-lymphoblastic leukemia/lymphoma[9,10]. Somatic mutations in RUNX1 are observed in 5% of T-lymphoblastic leukemia/lymphoma, and less than 1% of bone cancer (3 in 327 cases), B-lymphoblastic leukemia/lymphoma (1 in 252 cases), glioma (1 in 297 cases), and embryonal tumor (1 in 332 cases)[9,10]. Biallelic deletion of RUNX1 is observed in 5% of leukemia and less than 1% of B-lymphoblastic leukemia/lymphoma (5 in 731 cases)[9,10].

Potential relevance: AML with RUNX1::RUNX1T1 fusions is considered a distinct molecular subtype by the World Health Organization (WHO)[14]. Translocations involving RUNX1, specifically t(8;21)(q22;q22)/RUNX1::RUNX1T1, is associated with favorable risk in AML[15].

Biomarker Descriptions (continued)

The translocation t(12;21)(q34;q11) that results in ETV6::RUNX1 fusion is associated with standard risk in adult ALL and favorable risk in pediatric ALL[16,17,18]. On the other hand, mutations in RUNX1 confer poor prognosis in AML, MDS, and systemic mastocytosis (SM)[15,19,20].

EP300 deletion

E1A binding protein p300

Background: The EP300 gene encodes the E1A binding protein p300[21]. EP300 is a member of the KAT3 family of lysine acetyl transferases, which, along with CREBBP (also known as CBP), interact with over 400 diverse proteins, including Cyclin D1, p53, and BCL6[113,114]. EP300 functions as a transcriptional coactivator and has been observed to activate members of the E2F transcription factor family, thereby regulating expression of genes required for cell cycle G1/S phase transition[115,116]. Along with transcriptional coactivation, EP300 also functions in the formation of the transcription pre-initiation complex[115]. Inherited EP300 mutations result in Rubinstein-Taybi syndrome (RTS), a developmental disorder with an increased susceptibility to solid tumors[117].

Alterations and prevalence: Somatic mutations in EP300 are observed in 15% of bladder urothelial carcinoma, 14% of uterine corpus endometrial carcinoma, 12% of cervical squamous cell carcinoma, 8% of skin cutaneous melanoma, 7% of head and neck squamous cell carcinoma, and 5% of stomach adenocarcinoma, lung squamous cell carcinoma, esophageal adenocarcinoma, and colorectal adenocarcinoma[9,10]. Inactivating EP300 mutations are associated with lack of acetylation activity of EP300, resulting in altered expression of protein targets[118].

Potential relevance: Currently, no therapies are approved for EP300 aberrations.

Alerts Informed By Public Data Sources

Current FDA Information

Contraindicated Not recommended Resistance Breakthrough Fast Track

FDA information is current as of 2025-05-14. For the most up-to-date information, search www.fda.gov.

NF2 deletion

IK-930

Cancer type: Mesothelioma

Variant class: NF2 deletion

Supporting Statement:

The FDA has granted Fast Track designation for IK-930, a novel TEAD inhibitor targeting the Hippo signaling pathway, for unresectable NF2-deficient malignant pleural mesothelioma (MPM).

Reference:

https://ir.ikenaoncology.com//news-releases/news-release-details/ikena-oncology-receives-fda-fast-track-designation-novel-tead

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, 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 (continued)

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

AKT1 p.(E17K) c.49G>A

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
capivasertib + fulvestrant	●	●	●	✖	✖
ipatasertib + chemotherapy	✖	✖	✖	✖	● (II)
HTL-0039732, atezolizumab	✖	✖	✖	✖	● (I/II)
ALTA-2618	✖	✖	✖	✖	● (I)
IPN-60090, capivasertib	✖	✖	✖	✖	● (I)

ATM deletion

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

CCND1 amplification

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
abemaciclib	✖	✖	✖	✖	● (II)
palbociclib	✖	✖	✖	✖	● (II)
PF-07220060, midazolam	✖	✖	✖	✖	● (I/II)
zotatifin, hormone therapy	✖	✖	✖	✖	● (I/II)

NF2 deletion

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
BPI-460372	✖	✖	✖	✖	● (I)
IAG-933	✖	✖	✖	✖	● (I)

CHEK1 deletion

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

CHEK2 deletion

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

FGF19 amplification

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
TYRA-430	✖	✖	✖	✖	● (I)

LATS1 deletion

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
IAG-933	✖	✖	✖	✖	● (I)

PALB2 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.

Relevant Therapy Summary (continued)

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

RB1 deletion

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
ARTS-021	✖	✖	✖	✖	● (I/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	***11.64%***
ATM	***CNV, CN:1.0***
ATM	***LOH, 11q22.3(108098341-108236285)x1***
CHEK1	***CNV, CN:1.0***
CHEK1	***LOH, 11q24.2(125496639-125525271)x1***
CHEK2	***CNV, CN:1.0***
CHEK2	***LOH, 22q12.1(29083868-29130729)x1***
PALB2	***CNV, CN:1.0***
PALB2	***LOH, 16p12.2(23614759-23652528)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 2025.06(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 2025-05-14. NCCN information was sourced from www.nccn.org and is current as of 2025-05-01. EMA information was sourced from www.ema.europa.eu and is current as of 2025-05-14. ESMO information was sourced from www.esmo.org and is current as of 2025-05-01. Clinical Trials information is current as of 2025-05-01. 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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