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Patient Name: 이기성
Gender: M
Sample ID: N25-262

Primary Tumor Site: lung
Collection Date: 2025.10.01

Sample Cancer Type: Lung Cancer

Report Highlights

4 Relevant Biomarkers
9 Therapies Available
18 Clinical Trials

Relevant Lung Cancer Findings

Gene	Finding	Gene	Finding
ALK	None detected	NTRK1	None detected
BRAF	***BRAF p.(G466A) c.1397G>C***	NTRK2	None detected
EGFR	None detected	NTRK3	None detected
ERBB2	None detected	RET	None detected
KRAS	None detected	ROS1	None detected
MET	None detected		

Genomic Alteration	Finding
Tumor Mutational Burden	***17.06 Mut/Mb measured***

Relevant Biomarkers

Tier	Genomic Alteration	Relevant Therapies (In this cancer type)	Relevant Therapies (In other cancer type)	Clinical Trials
IIC	*BRCA2 c.682-1G>A* BRCA2, DNA repair associated Allele Frequency: 2.95% Locus: chr13:32905055 Transcript: NM_000059.4	None*	**abiraterone + niraparib** [1, 2 / II+] **bevacizumab + olaparib** [1, 2 / II+] **olaparib** [1, 2 / II+] **rucaparib** [1 / II+] **talazoparib + hormone therapy** [1 / II+] bevacizumab + niraparib [II+] niraparib [II+] olaparib + hormone therapy [II+] talazoparib [II+]	13
IIC	*BRAF p.(G466A) c.1397G>C* B-Raf proto-oncogene, serine/threonine kinase Allele Frequency: 4.80% Locus: chr7:140481411 Transcript: NM_004333.6	None*	None*	5

*** 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	*ATR p.(G259*) c.775G>T* ATR serine/threonine kinase Allele Frequency: 3.65% Locus: chr3:142281469 Transcript: NM_001184.4	None*	None*	1
IIC	*ATRX deletion* ATRX, chromatin remodeler Locus: chrX:76763769	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

ARID2 p.(Q843) c.2527C>T, CUL4B deletion, Microsatellite stable, UGT1A1 p.(G71R) c.211G>A, HLA-A deletion, NOTCH4 p.(S244Lfs*31) c.731_731delCinsTG, KMT2C p.(S3755*) c.11264C>A, NQO1 p.(P187S) c.559C>T, ZRSR2 deletion, BCOR deletion, USP9X deletion, DDX3X deletion, KDM6A deletion, RBM10 deletion, KDM5C deletion, SMC1A deletion, AMER1 deletion, ZMYM3 deletion, STAG2 deletion, PHF6 deletion, Tumor Mutational Burden*

Variant Details

DNA Sequence Variants

Gene	Amino Acid Change	Coding	Variant ID	Locus	Allele Frequency	Transcript	Variant Effect
BRCA2	p.(?)	c.682-1G>A	.	chr13:32905055	2.95%	NM_000059.4	unknown
BRAF	p.(G466A)	c.1397G>C	COSM452	chr7:140481411	4.80%	NM_004333.6	missense
ATR	p.(G259*)	c.775G>T	.	chr3:142281469	3.65%	NM_001184.4	nonsense
ARID2	p.(Q843*)	c.2527C>T	.	chr12:46244433	3.45%	NM_152641.4	nonsense
UGT1A1	p.(G71R)	c.211G>A	COSM4415616	chr2:234669144	51.78%	NM_000463.3	missense
NOTCH4	p.(S244Lfs*31)	c.731_731delCinsTG	.	chr6:32188823	3.55%	NM_004557.4	frameshift Block Substitution
KMT2C	p.(S3755*)	c.11264C>A	.	chr7:151859398	5.35%	NM_170606.3	nonsense
NQO1	p.(P187S)	c.559C>T	.	chr16:69745145	46.87%	NM_000903.3	missense
COL11A1	p.(A1065S)	c.3193G>T	.	chr1:103412488	3.13%	NM_001854.4	missense
NOTCH2	p.(D1773E)	c.5319T>G	.	chr1:120463012	3.35%	NM_024408.4	missense
ST6GAL2	p.(R322I)	c.965G>T	.	chr2:107450581	6.86%	NM_032528.3	missense
LRP1B	p.(C39W)	c.117C>G	.	chr2:142567936	2.56%	NM_018557.3	missense
KCNH7	p.(P146Q)	c.437C>A	.	chr2:163393461	5.39%	NM_033272.4	missense
FANCD2	p.(L345F)	c.1033_1035delCTCinsTTT	.	chr3:10085211	5.05%	NM_033084.6	missense
C3orf20	p.(D413Y)	c.1237G>T	.	chr3:14755590	4.30%	NM_032137.5	missense
PLCL2	p.(V770L)	c.2308G>C	.	chr3:17053524	2.43%	NM_015184.5	missense

Variant Details (continued)

DNA Sequence Variants (continued)

Gene	Amino Acid Change	Coding	Variant ID	Locus	Allele Frequency	Transcript	Variant Effect
FAT1	p.(H433R)	c.1298A>G	.	chr4:187629684	5.11%	NM_005245.4	missense
MSH3	p.(A57_A62del)	c.162_179delTGCAGC GGCCGCAGCGGC	.	chr5:79950707	64.11%	NM_002439.5	nonframeshift Deletion
CANX	p.(E351*)	c.1051G>T	.	chr5:179147430	2.60%	NM_001024649.2	nonsense
HLA-A	p.(C125S)	c.373T>A	.	chr6:29911074	28.11%	NM_001242758.1	missense
MLN	p.(A20T)	c.58G>A	.	chr6:33768883	9.11%	NM_002418.3	missense
RSPO3	p.(G212*)	c.634G>T	.	chr6:127476583	4.53%	NM_032784.5	nonsense
HDAC9	p.(A787G)	c.2360C>G	.	chr7:18868821	4.40%	NM_178425.3	missense
KEL	p.(E351*)	c.1051G>T	.	chr7:142650917	4.81%	NM_000420.3	nonsense
RAB11FIP1	p.([A651V;L652=])	c.1952_1954delCCCins TCT	.	chr8:37730366	66.60%	NM_001002814.3	missense, synonymous
DCAF4L2	p.(Y394F)	c.1181A>T	.	chr8:88885019	2.35%	NM_152418.4	missense
DCAF4L2	p.(P353T)	c.1057C>A	.	chr8:88885143	3.25%	NM_152418.4	missense
FAM135B	p.(Y1113*)	c.3339C>A	.	chr8:139160872	4.53%	NM_015912.4	nonsense
PTCH1	p.(R13G)	c.37C>G	.	chr9:98270607	65.68%	NM_000264.5	missense
TRIM48	p.(D40Y)	c.118G>T	.	chr11:55032449	3.15%	NM_024114.5	missense
FGF19	p.(E174Q)	c.520G>C	.	chr11:69514161	3.85%	NM_005117.3	missense
FGF3	p.(R144S)	c.430C>A	.	chr11:69625363	3.20%	NM_005247.4	missense
KMT2A	p.(T998A)	c.2992A>G	.	chr11:118344866	6.10%	NM_001197104.2	missense
OR10G8	p.(A9E)	c.26C>A	.	chr11:123900355	3.56%	NM_001004464.2	missense
NELL2	p.(Q385L)	c.1154A>T	.	chr12:45108515	4.25%	NM_001145107.1	missense
PPFIA2	p.(R1204S)	c.3610C>A	.	chr12:81657115	7.83%	NM_003625.5	missense
PPFIA2	p.(L138M)	c.412C>A	.	chr12:81839493	8.17%	NM_003625.5	missense
HNF1A	p.(S256C)	c.767C>G	.	chr12:121432020	11.71%	NM_000545.8	missense
BRCA2	p.(L1904P)	c.5711T>C	.	chr13:32914203	3.20%	NM_000059.4	missense
DIS3	p.(T608S)	c.1822A>T	.	chr13:73342984	3.26%	NM_014953.5	missense
DGLUCY	p.(G123C)	c.367G>T	.	chr14:91636456	4.00%	NM_001102367.2	missense
DICER1	p.(H648Y)	c.1942C>T	.	chr14:95579527	3.85%	NM_030621.4	missense
GABRA5	p.(A334S)	c.1000G>T	.	chr15:27188484	3.36%	NM_001165037.1	missense
USP8	p.(I95T)	c.284T>C	.	chr15:50741631	48.45%	NM_005154.5	missense
AXIN1	p.(A261S)	c.781G>T	.	chr16:396245	2.30%	NM_003502.4	missense
NQO1	p.(A198G)	c.593C>G	.	chr16:69745111	5.66%	NM_000903.3	missense
NF1	p.(R764W)	c.2290A>T	.	chr17:29554274	4.44%	NM_001042492.3	missense
RARA	p.(G289W)	c.865G>T	.	chr17:38510611	11.31%	NM_000964.4	missense

Variant Details (continued)

DNA Sequence Variants (continued)

Gene	Amino Acid Change	Coding	Variant ID	Locus	Allele Frequency	Transcript	Variant Effect
KMT2B	p.(M2630V)	c.7888A>G	.	chr19:36229198	5.95%	NM_014727.3	missense
ARHGAP35	p.(P345L)	c.1034C>T	.	chr19:47422966	5.51%	NM_004491.5	missense
AURKC	p.(A96P)	c.286G>C	.	chr19:57743582	3.21%	NM_001015878.2	missense
USP9X	p.(E734K)	c.2200G>A	.	chrX:41025339	5.26%	NM_001039590.3	missense
KDM5C	p.(G1160V)	c.3479G>T	.	chrX:53223880	9.75%	NM_004187.5	missense

Copy Number Variations

Gene	Locus	Copy Number	CNV Ratio
ATRX	chrX:76763769	0	0.51
CUL4B	chrX:119660593	0.23	0.65
HLA-A	chr6:29910229	0	0.48
ZRSR2	chrX:15808582	0	0.52
BCOR	chrX:39911340	0	0.55
USP9X	chrX:40982869	0	0.55
DDX3X	chrX:41193501	0	0.49
KDM6A	chrX:44732715	0	0.56
RBM10	chrX:47006798	0	0.56
KDM5C	chrX:53221892	0	0.55
SMC1A	chrX:53406966	0	0.55
AMER1	chrX:63409727	0	0.55
ZMYM3	chrX:70460753	0	0.52
STAG2	chrX:123156472	0.05	0.61
PHF6	chrX:133511628	0	0.57
EIF1AX	chrX:20148599	0	0.58
ARAF	chrX:47422311	0	0.57
AR	chrX:66766015	0	0.55

Biomarker Descriptions

BRCA2 c.682-1G>A

BRCA2, DNA repair associated

Background: The breast cancer early onset gene 2 (BRCA2) encodes one of two BRCA proteins (BRCA1 and BRCA2) initially discovered as major hereditary breast cancer genes. Although structurally unrelated, both BRCA1 and BRCA2 exhibit tumor suppressor function and are integrally involved in the homologous recombination repair (HRR) pathway, a pathway critical in the repair of damaged DNA[71,72]. Specifically, BRCA1/2 are required for repair of chromosomal double strand breaks (DSBs) which are highly unstable and compromise genome integrity[71,72]. Inherited pathogenic mutations in BRCA1/2 are known to confer increased risk in women for breast

Biomarker Descriptions (continued)

and ovarian cancer and in men for breast and prostate cancer[73,74,75]. For individuals diagnosed with inherited pathogenic or likely pathogenic BRCA1/2 variants, the cumulative risk of breast cancer by 80 years of age was 69-72% and the cumulative risk of ovarian cancer by 70 years was 20-48%[73,76].

Alterations and prevalence: Inherited BRCA1/2 mutations occur in 1:400 to 1:500 individuals and are observed in 10-15% of ovarian cancer, 5-10% of breast cancer, and 1-4% of prostate cancer[77,78,79,80,81,82,83,84]. Somatic alterations in BRCA2 are observed in 5-15% of uterine corpus endometrial carcinoma, cutaneous melanoma, bladder urothelial carcinoma, stomach adenocarcinoma, colorectal adenocarcinoma, lung squamous cell carcinoma, lung adenocarcinoma, and uterine carcinosarcoma, 3-4% of cervical squamous cell carcinoma, head and neck squamous cell carcinoma, esophageal adenocarcinoma, ovarian serous cystadenocarcinoma, cholangiocarcinoma, breast invasive carcinoma, renal papillary cell carcinoma, and 2% of renal clear cell carcinoma, hepatocellular carcinoma, thymoma, prostate adenocarcinoma, sarcoma, and glioblastoma multiforme[5,6].

Potential relevance: Individuals possessing BRCA1/2 pathogenic germline or somatic mutations are shown to exhibit sensitivity to platinum based chemotherapy as well as treatment with poly (ADP-ribose) polymerase inhibitors (PARPi)[85]. Inhibitors targeting PARP induce synthetic lethality in recombination deficient BRCA1/2 mutant cells[86,87]. Consequently, several PARP inhibitors have been FDA approved for BRCA1/2-mutated cancers. Olaparib[88] (2014) was the first PARPi to be approved by the FDA for BRCA1/2 aberrations. Originally approved for the treatment of germline variants, olaparib is now indicated (2018) for the maintenance treatment of both germline BRCA1/2-mutated (gBRCAm) and somatic BRCA1/2-mutated (sBRCAm) epithelial ovarian, fallopian tube, or primary peritoneal cancers that are responsive to platinum-based chemotherapy. Olaparib is also indicated for the treatment of patients with gBRCAm HER2-negative metastatic breast cancer and metastatic pancreatic adenocarcinoma. Additionally, olaparib[88] is approved (2020) for metastatic castration-resistant prostate cancer (mCRPC) with deleterious or suspected deleterious, germline or somatic mutations in HRR genes that includes BRCA2. Rucaparib[89] is also approved (2020) for deleterious gBRCAm or sBRCAm mCRPC and ovarian cancer. Talazoparib[70] (2018) is indicated for the treatment of gBRCAm HER2-negative locally advanced or metastatic breast cancer. Additionally, talazoparib[70] in combination with enzalutamide is approved (2023) for metastatic castration-resistant prostate cancer (mCRPC) with mutations in HRR genes that includes BRCA2. Niraparib[90] (2017) is another PARPi approved for the treatment of epithelial ovarian, fallopian tube, or primary peritoneal cancers with a deleterious or suspected deleterious BRCA mutation. Niraparib in combination with abiraterone acetate[91] received FDA approval (2023) for the treatment of deleterious or suspected deleterious BRCA-mutated (BRCAm) mCRPC. Despite tolerability and efficacy, acquired resistance to PARP inhibition has been clinically reported[92]. One of the most common mechanisms of resistance includes secondary intragenic mutations that restore BRCA1/2 functionality[93]. In addition to PARP inhibitors, other drugs which promote synthetic lethality have been investigated for BRCA mutations. In 2022, the FDA granted fast track designation to the small molecule inhibitor, pidnarulex[94], for BRCA1/2, PALB2, or other homologous recombination deficiency (HRD) mutations in breast and ovarian cancers. Like PARPi, pidnarulex promotes synthetic lethality but through an alternative mechanism which involves stabilization of G-quadruplexes at the replication fork leading to DNA breaks and genomic instability. In 2024, the FDA granted fast track designation to TNG-348[95], a USP1 inhibitor, for the treatment of BRCA1/2 mutated breast and ovarian cancer.

BRAF p.(G466A) c.1397G>C

B-Raf proto-oncogene, serine/threonine kinase

Background: The BRAF gene encodes the B-Raf proto-oncogene serine/threonine kinase, a member of the RAF family of serine/threonine protein kinases which also includes ARAF and RAF1(CRAF)[147]. BRAF is among the most commonly mutated kinases in cancer. Activation of the MAPK pathway occurs through BRAF mutations and leads to an increase in cell division, dedifferentiation, and survival[148,149]. BRAF mutations are categorized into three distinct functional classes, namely, class 1, 2, and 3, and are defined by the dependency on the RAS pathway[150]. Class 1 and 2 BRAF mutants are RAS-independent in that they signal as active monomers (Class 1) or dimers (Class 2) and become uncoupled from RAS GTPase signaling, resulting in constitutive activation of BRAF[150]. Class 3 mutants are RAS dependent as the kinase domain function is impaired or dead[150,151,152].

Alterations and prevalence: Somatic mutations in BRAF are observed in 59% of thyroid carcinoma, 53% of skin cutaneous melanoma, 12% of colorectal adenocarcinoma, 8% of lung adenocarcinoma, 5% of uterine corpus endometrial carcinoma, and 2-3% of bladder urothelial carcinoma, lung squamous cell carcinoma, stomach adenocarcinoma, cholangiocarcinoma, diffuse large B-cell lymphoma, glioblastoma multiforme, uterine carcinosarcoma, and head and neck squamous cell carcinoma[5,6]. Mutations at V600 belong to class 1 and include V600E, the most recurrent somatic BRAF mutation across diverse cancer types[151,153]. Class 2 mutations include K601E/N/T, L597Q/V, G469A/V/R, G464V/E, and BRAF fusions[151]. Class 3 mutations include D287H, V459L, G466V/E/A, S467L, G469E, and N581S/I[151]. BRAF V600E is universally present in hairy cell leukemia, mature B-cell cancers, and prevalent in histiocytic neoplasms[154,155,156]. Other recurrent BRAF somatic mutations cluster in the glycine-rich phosphate-binding loop at codons 464-469 in exon 11, as well as additional codons flanking V600 in the activation loop[153]. BRAF amplification is observed in 8% of ovarian serous cystadenocarcinoma, 4% of skin cutaneous melanoma, and 2% of sarcoma, uterine carcinosarcoma, and glioblastoma multiforme[5,6]. BRAF fusions are mutually exclusive to BRAF V600 mutations and have been described in melanoma, thyroid cancer, pilocytic astrocytoma, NSCLC, and several other cancer types[157,158,159,160,161]. Part of the oncogenic mechanism of BRAF gene fusions is the removal of the N-terminal auto-inhibitory domain, leading to constitutive kinase activation[152,157,159]. Alterations in BRAF are rare in pediatric cancers, with the most predominant being the V600E mutation and the BRAF::KIAA1549 fusion, both of which are observed in

Biomarker Descriptions (continued)

low-grade gliomas[162]. Somatic mutations are observed in 6% of glioma and less than 1% of bone cancer (2 in 327 cases), Wilms tumor (1 in 710 cases), and peripheral nervous system cancers (1 in 1158 cases)[5,6]. Amplification of BRAF is observed in 1% or less of Wilms tumor (2 in 136 cases) and B-lymphoblastic leukemia/lymphoma (2 in 731 cases)[5,6].

Potential relevance: Vemurafenib[163] (2011) is the first targeted therapy approved for the treatment of patients with unresectable or metastatic melanoma with a BRAF V600E mutation, and it is also approved for BRAF V600E-positive Erdheim-Chester Disease (2017). BRAF class 1 mutations, including V600E, are sensitive to vemurafenib, whereas class 2 and 3 mutations are insensitive[151]. BRAF kinase inhibitors including dabrafenib[164] (2013) and encorafenib[165] (2018) are also approved for the treatment of patients with unresectable or metastatic melanoma with BRAF V600E/K mutations. Encorafenib[165] is approved in combination with cetuximab[166] (2020) for the treatment of BRAF V600E mutated colorectal cancer. Due to the tight coupling of RAF and MEK signaling, several MEK inhibitors have been approved for patients harboring BRAF alterations[151]. The MEK inhibitors, trametinib[167] (2013) and binimetinib[168] (2018), were approved for the treatment of metastatic melanoma with BRAF V600E/K mutations. Combination therapies of BRAF plus MEK inhibitors have been approved in melanoma and NSCLC[169]. The combinations of dabrafenib/trametinib[167](2015) and vemurafenib/cobimetinib[170] (2015) were approved for the treatment of patients with unresectable or metastatic melanoma with a BRAF V600E/K mutation. Subsequently, the combination of dabrafenib and trametinib was approved for metastatic NSCLC (2017), children with low-grade gliomas, and children and adults with solid tumors (2022) harboring a BRAF V600E mutation[164]. The PD-L1 antibody, atezolizumab[171], has also been approved in combination with cobimetinib and vemurafenib for BRAF V600 mutation-positive unresectable or metastatic melanoma. The FDA has granted fast track designation (2023) to ABM-1310[172] for BRAF V600E-mutated glioblastoma (GBM) patients. In 2018, binimetinib[173] was also granted breakthrough designation in combination with cetuximab and encorafenib for BRAF V600E mutant metastatic colorectal cancer. The ERK inhibitor ulixertinib[174] was granted fast track designation in 2020 for the treatment of patients with non-colorectal solid tumors harboring BRAF mutations G469A/V, L485W, or L597Q. The FDA granted fast track designation (2022) to the pan-RAF inhibitor, KIN-2787[175], for the treatment of BRAF class II or III alteration-positive malignant or unresectable melanoma. The FDA also granted fast track designation (2023) to the BRAF inhibitor, plixorafenib (PLX-8394)[176], for BRAF Class I (V600) and Class II (including fusions) altered cancer patients who have already undergone previous treatments. BRAF fusion is a suggested mechanism of resistance to BRAF targeted therapy in melanoma[177]. Additional mechanisms of resistance to BRAF targeted therapy include BRAF amplification, alternative splice transcripts, as well as activation of PI3K signaling and activating mutations in KRAS, NRAS, and MAP2K1/2 (MEK1/2)[178,179,180,181,182,183,184]. Clinical responses to sorafenib and trametinib in limited case studies of patients with BRAF fusions have been reported[161].

ATR p.(G259*) c.775G>T

ATR serine/threonine kinase

Background: The ATR gene encodes a serine/threonine kinase that belongs to the phosphatidylinositol-3-kinase related kinases (PIKKs) family of genes that also includes ATM and PRKDC (also known as DNA-PKc)[63]. ATR and ATM act as master regulators of DNA damage response. Specifically, ATR and it's interacting protein ATRIP are involved in single-stranded DNA (ssDNA) repair while ATM is involved in double-stranded break (DSB) repair[64]. ATR is characterized as a tumor suppressor that plays a key role in maintaining genomic stability[65]. Upon activation, ATR phosphorylates downstream cell cycle and DNA damage signaling proteins such as CHK1, RAD17, RAD9, and BRCA1[66,67]. Germline mutations in ATR confer susceptibility to various cancers[68,69].

Alterations and prevalence: Somatic mutations of ATR are observed in 12% of melanoma, 11% of endometrial carcinoma, 8% of undifferentiated stomach adenocarcinoma and bladder urothelial carcinoma cases[5,6].

Potential relevance: The PARP inhibitor, talazoparib[70] in combination with enzalutamide is approved (2023) for metastatic castration-resistant prostate cancer (mCRPC) with mutations in HRR genes that includes ATR.

ATRX deletion

ATRX, chromatin remodeler

Background: The ATRX gene encodes the ATRX chromatin remodeler and ATPase/helicase domain protein, which belongs to SWI/SNF family of chromatin remodeling proteins[1]. The SWI/SNF proteins are a group of DNA translocases that use ATP hydrolysis to remodel chromatin structure and maintain genomic integrity by controlling transcriptional regulation, DNA repair, and chromosome stability through the regulation of telomere length[34,35,36,37]. ATRX is a tumor suppressor that interacts with the MRE11-RAD50-NBN (MRN) complex, which is involved in double-stranded DNA (dsDNA) break repair[38,39,40].

Alterations and prevalence: Somatic mutations of ATRX are observed in 38% of brain lower grade glioma, 15% of uterine corpus endometrial carcinoma, 14% of sarcoma, 9% of glioblastoma multiforme and skin cutaneous melanoma, 7% of colorectal adenocarcinoma, 6% of lung adenocarcinoma, stomach adenocarcinoma, and cervical squamous cell carcinoma, 5% of bladder urothelial carcinoma and lung squamous cell carcinoma, 4% of adrenocortical carcinoma, head and neck squamous cell carcinoma and uterine carcinosarcoma, and 2% of diffuse large B-cell lymphoma, ovarian serous cystadenocarcinoma, breast invasive carcinoma, pheochromocytoma and paraganglioma, kidney renal clear cell carcinoma, pancreatic adenocarcinoma, liver hepatocellular carcinoma

Biomarker Descriptions (continued)

and kidney chromophobe[5,6]. Biallelic deletion of ATRX is observed in 7% of sarcoma, 3% of kidney chromophobe, and 2% of brain lower grade glioma[5,6]. Although alterations of ATRX in pediatric populations are rare, somatic mutations are observed in 6% of gliomas, 4% of bone cancer, 3% of soft tissue sarcoma, and less than 1% of B-lymphoblastic leukemia/lymphoma (2 in 252 cases), embryonal tumor (3 in 332 cases), and leukemia (2 in 354 cases)[6]. Biallelic deletion of ATRX is observed in 1% of peripheral nervous system tumors (1 in 91 cases) in and less than 1% of B-lymphoblastic leukemia/lymphoma (2 in 731 cases)[6].

Potential relevance: Currently, no therapies are approved for ATRX aberrations. Loss of ATRX protein expression correlates with the presence of ATRX mutations[41,42]. ATRX deficiency along with IDH mutation and TP53 mutation is diagnostic of astrocytoma IDH-mutant as defined by the World Health Organization (WHO)[43,44].

ARID2 p.(Q843*) c.2527C>T

AT-rich interaction domain 2

Background: The ARID2 gene encodes the AT-rich interaction domain 2 protein[1]. ARID2, also known as BAF200, belongs to the ARID superfamily that also includes ARID1A, ARID1B, and ARID5B[131]. ARID2 is an essential member of the PBAF complex, a SWI/SNF chromatin-remodeling complex[131,132]. The PBAF complex is a multisubunit protein complex that consists of ARID2, SMARCA4A/BRG1, BRD7, ACTL6A/BAF53A, PHF10/BAF45A, PBRM1/BAF180, SMARCC2/BAF170, SMARCC1/BAF155, SMARCB1/BAF47, SMARCD1/BAF60A, and SMARCE1/BAF57[132,133]. ARID2 may alter the expression of IFN responsive genes, which suppress cell proliferation[131]. Loss of function mutations in ARID2 may promote cell proliferation, suggesting a tumor suppressor role of ARID2[131].

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[134]. Somatic mutations in ARID2 are observed in 17% of skin cutaneous melanoma, 11% of uterine corpus endometrial carcinoma, 8% of bladder urothelial carcinoma and stomach adenocarcinoma, 7% of colorectal adenocarcinoma, and 5% of liver hepatocellular carcinoma, lung adenocarcinoma, and lung squamous cell carcinoma[5,6]. ARID2 biallelic deletions are observed in 2% of mesothelioma[5,6].

Potential relevance: Currently, no therapies are approved for ARID2 aberrations.

CUL4B deletion

cullin 4B

Background: The CUL4B gene encodes cullin 4B, a member of the cullin family, which includes CUL1, CUL2, CUL3, CUL4a, CUL5, CUL7, and Parc[1,2]. CUL4B belongs to the CUL4 subfamily which also includes CUL4A[3]. CUL4A and CUL4B share greater than 80% sequence identity and functional redundancy[3,4]. Cullin proteins share a conserved cullin homology domain and act as molecular scaffolds for RING E3 ubiquitin ligases to assemble into cullin-RING ligase complexes (CRLs)[2]. CUL4B is part of the CRL4 complex which is responsible for ubiquitination and degradation of a variety of substrates where substrate specificity is dependent on the substrate recognition component of the CRL4 complex[4]. CRL4 substrates include oncoproteins, tumor suppressors, nucleotide excision repair proteins, cell cycle promoters, histone methylation proteins, and tumor-related signaling molecules, thereby impacting various processes critical to tumor development and progression and supporting a complex role of CUL4B in oncogenesis[3,4].

Alterations and prevalence: Somatic mutations in CUL4B are observed in 9% of uterine corpus endometrial carcinoma, 5% of skin cutaneous melanoma, and 2% of bladder urothelial carcinoma, cervical squamous cell carcinoma, colorectal adenocarcinoma, uterine carcinosarcoma, brain lower grade glioma, and lung squamous cell carcinoma[5,6]. Amplification of CUL4B is observed in 2% of diffuse large B-cell lymphoma[5,6]. Biallelic loss of CUL4B is observed in 1% sarcoma and testicular germ cell tumors[5,6].

Potential relevance: Currently, no therapies are approved for CUL4B 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[185]. Microsatellite instability (MSI) is defined as a change in the length of a microsatellite in a tumor as compared to normal tissue[186,187]. 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[188]. 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[189]. 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)[189]. Tumors classified as MSI-L are often phenotypically indistinguishable from MSS tumors and tend to be grouped with MSS[190,191,192,193,194]. 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[187].

Biomarker Descriptions (continued)

LS is associated with an increased risk of developing colorectal cancer, as well as other cancers, including endometrial and stomach cancer[186,187,191,195].

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[186,187,196,197]. 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[196,197].

Potential relevance: Anti-PD-1 immune checkpoint inhibitors including pembrolizumab[198] (2014) and nivolumab[199] (2015) are approved for patients with MSI-H or dMMR colorectal cancer who have progressed following chemotherapy. Pembrolizumab[198] 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[198]. Dostarlimab[200] (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[192,201]. The cytotoxic T-lymphocyte antigen 4 (CTLA-4) blocking antibody, ipilimumab[202] (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[192,203,204]. 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[204]. 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[205,206]. However, checkpoint blockade with the addition of chemotherapy or targeted therapies have demonstrated response in MSS or pMMR cancers[205,206].

UGT1A1 p.(G71R) c.211G>A

UDP glucuronosyltransferase family 1 member A1

Background: The UGT1A1 gene encodes UDP glucuronosyltransferase family 1 member A1, a member of the UDP-glucuronosyltransferase 1A (UGT1A) subfamily of the UGT protein superfamily[1,114]. UGTs are microsomal membrane-bound enzymes that catalyze the glucuronidation of endogenous and xenobiotic compounds and transform the lipophilic molecules into excretable, hydrophilic metabolites[114,115]. UGTs play an important role in drug metabolism, detoxification, and metabolite homeostasis. Differential expression of UGTs can promote cancer development, disease progression, as well as drug resistance[116]. Specifically, elevated expression of UGT1As are associated with resistance to many anti-cancer drugs due to drug inactivation and lower active drug concentrations. However, reduced expression and downregulation of UGT1As are implicated in bladder and hepatocellular tumorigenesis and progression due to toxin accumulation[116,117,118,119]. Furthermore, UGT1A1 polymorphisms, such as UGT1A1*28, UGT1A1*93, and UGT1A1*6, confer an increased risk of severe toxicity to irinotecan-based chemotherapy treatment of solid tumors, due to reduced glucuronidation of the irinotecan metabolite, SN-38[120].

Alterations and prevalence: Biallelic deletion of UGT1A1 has been observed in 6% of sarcoma, 3% of brain lower grade glioma and uveal melanoma, and 2% of thymoma, cervical squamous cell carcinoma, bladder urothelial carcinoma, head and neck squamous cell carcinoma, and esophageal adenocarcinoma[5,6].

Potential relevance: Currently, no therapies are approved for UGT1A1 aberrations.

HLA-A deletion

major histocompatibility complex, class I, A

Background: The HLA-A gene encodes the major histocompatibility complex, class I, A[1]. 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[125]. MHC class I molecules are heterodimers composed of two polypeptide chains, α and B2M[126]. 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[127,128,129]. Downregulation of MHC class I promotes tumor evasion of the immune system, suggesting a tumor suppressor role for HLA-A[130].

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[5,6]. Biallelic loss of HLA-A is observed in 4% of DLBCL[5,6].

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

Biomarker Descriptions (continued)

NOTCH4 p.(S244Lfs*31) c.731_731delCinsTG

notch 4

Background: The NOTCH4 gene encodes the notch receptor 4 protein, a type 1 transmembrane protein and member of the NOTCH family of genes, which also includes NOTCH1, NOTCH2, and NOTCH3. NOTCH proteins contain multiple epidermal growth factor (EGF)-like repeats in their extracellular domain, which are responsible for ligand binding and homodimerization, thereby promoting NOTCH signaling[56]. Following ligand binding, the NOTCH intracellular domain is released, which activates the transcription of several genes involved in regulation of cell proliferation, differentiation, growth, and metabolism[57,58]. In cancer, depending on the tumor type, aberrations in the NOTCH family can be gain of function or loss of function suggesting both oncogenic and tumor suppressor roles for NOTCH family members[59,60,61,62].

Alterations and prevalence: Somatic mutations observed in NOTCH4 are primarily missense or truncating and are found in about 16% of melanoma, 9% of lung adenocarcinoma and uterine cancer, as well as 3-6% of bladder colorectal, squamous lung and stomach cancers[5].

Potential relevance: Currently, no therapies are approved for NOTCH4 aberrations.

KMT2C p.(S3755*) c.11264C>A

lysine methyltransferase 2C

Background: The KMT2C gene encodes the lysine methyltransferase 2C protein, a transcriptional coactivator and histone H3 lysine 4 (H3K4) methyltransferase[1]. KMT2C belongs to the SET domain protein methyltransferase superfamily[121]. KMT2C is capable of di- and tri-methylation of histone 3 lysine 4 (H3K4) at select transcriptional enhancers depending on the cell type[122]. KMT2C is also found to interact with BAP1 to control ubiquitin-mediated gene silencing of H2A by Polycomb group (PcG) complexes[123,124]. Specifically, KMT2C interaction with BAP1 promotes KMT2C histone recruitment/methyltransferase activity and, along with BAP1 deubiquitination of H2A, facilitates transcription of target genes[123,124]. Mutations that occur within the SET domain of KMT2C are frequently observed in cancer and alter the methylation activity and target methylation states, thereby impacting gene regulation[122].

Alterations and prevalence: Somatic mutations in KMT2C are observed in 20% of bladder urothelial carcinoma and uterine corpus endometrial carcinoma, 19% of skin cutaneous melanoma and cervical squamous cell carcinoma, 15% of lung squamous cell carcinoma, 14% of stomach adenocarcinoma and lung adenocarcinoma, and 11% of cholangiocarcinoma[5,6]. Biallelic deletion of KMT2C is observed in 3% of sarcoma, stomach adenocarcinoma, 2% of esophageal adenocarcinoma, acute myeloid leukemia, uterine carcinosarcoma, and head and neck squamous cell carcinoma[5,6].

Potential relevance: Currently, no therapies are approved for KMT2C aberrations.

ZRSR2 deletion

zinc finger CCCH-type, RNA binding motif and serine/arginine rich 2

Background: The ZRSR2 gene encodes the zinc finger CCCH-type, RNA binding motif and serine/arginine-rich 2 protein, a component of the spliceosome. Specifically, ZRSR2 encodes a splicing factor that is involved in the recognition of the 3’ intron splice site[53]. ZRSR2 interacts with components of the pre-spliceosome assembly including SRSF2 and U2AF2/U2AF1 heterodimer[53,54]. Mutations in ZRSR2 can lead to deregulated global and alternative mRNA splicing, nuclear-cytoplasm export, and unspliced mRNA degradation while concurrently altering the expression of multiple genes[53,55].

Alterations and prevalence: ZRSR2 alterations including nonsense and frameshift mutations are observed in 5-10% of myelodysplastic syndromes (MDS) and 4% of uterine cancer. ZRSR2 deletions are observed in 4% of diffuse large B-cell lymphoma (DLBCL), 3% of head and neck and esophageal cancers[6,12].

Potential relevance: Mutation of ZRSR2 is associated with poor prognosis in myelodysplastic syndromes as well as poor/adverse risk in acute myeloid leukemia (AML)[12,22,23].

BCOR deletion

BCL6 corepressor

Background: The BCOR gene encodes the B-cell CLL/lymphoma 6 (BCL6) co-repressor protein, which potentiates transcriptional repression by BCL6[7,8]. BCOR also associates with class I and II histone deacetylases (HDACs), suggesting an alternate mechanism

Biomarker Descriptions (continued)

for BCOR-mediated transcriptional repression independent of BCL6[8]. Genetic alterations in BCOR result in protein dysfunction, which suggests BCOR functions as a tumor suppressor gene[9,10,11].

Alterations and prevalence: Genetic alterations in BCOR include missense, nonsense, and frameshift mutations that result in loss of function and have been observed in up to 5% of myelodysplastic syndromes (MDS), 5-10% of chronic myelomonocytic leukemia (CMML), and 1-5% of acute myeloid leukemia (AML)[5,12,13,14]. Higher mutational frequencies are reported in some solid tumors, including up to 15% of uterine cancer and 5-10% of colorectal cancer, stomach cancer, cholangiocarcinoma, and melanoma[5,6]. Although less common, BCOR fusions and internal tandem duplications (ITDs) have been reported in certain rare cancer types[15,16,17]. Specifically, BCOR::CCNB3 rearrangements define a particular subset of sarcomas with Ewing sarcoma-like morphology known as BCOR::CCNB3 sarcomas (BCS)[18,19]. Alterations in BCOR are also observed in pediatric cancers[5,6]. Somatic mutations are observed in 13% of soft tissue sarcoma, 4% of glioma, 3% of retinoblastoma, 2% of bone cancer, 1% of B-lymphoblastic leukemia/lymphoma (3 in 252 cases), and less than 1% of embryonal tumors (3 in 332 cases), leukemia (2 in 311 cases), and Wilms tumor (2 in 710 cases)[5,6]. Other alterations have been reported in clear cell carcinoma of the kidney, a rare pediatric renal malignant tumor, with one study reporting the presence of BCOR ITDs in more than 90% of cases[15].

Potential relevance: BCOR rearrangement, including inv(X)(p11.4p11.22) resulting in BCOR::CCNB3 fusion, is diagnostic of sarcoma with BCOR genetic alterations, a subset of undifferentiated round cell sarcomas[20,21]. Additionally, translocation t(x;22)(p11;q13) resulting in ZC3H7B::BCOR fusion is a useful ancillary diagnostic marker of high-grade endometrial stromal sarcoma[20]. Somatic mutation in BCOR is one of the possible molecular abnormality requirements for the diagnosis of myelodysplasia-related AML (AML-MR) and is associated with poor prognosis in AML and MDS[12,13,22,23,24]. In FLT3-ITD negative AML patients under 65 with intermediate cytogenetic prognosis, mutations in BCOR confer inferior overall survival (OS) as well as relapse-free survival (RFS) compared to those without BCOR abnormalities (OS = 13.6% vs. 55%; RFS = 14.3% vs. 44.5%)[14]. Additionally, BCOR ITDs and BCOR::EP300 fusion are molecular alterations of significance in pediatric gliomas[25,26].

USP9X deletion

ubiquitin specific peptidase 9 X-linked

Background: The USP9X gene encodes the ubiquitin specific peptidase 9 X-lined protein[1]. USP9X is a deubiquitinating enzyme (DUB) and a member of the ubiquitin-specific protease (USP) subclass of cysteine proteases[45]. DUBs are responsible for protein deubiquitination, thereby counter-regulating post-transcriptional ubiquitin modification of proteins within the cell[45,46]. USP9X has many substrates and is commonly upregulated in several solid tumor types, supporting an oncogenic role for USP9X[46]. Conversely, in some cancer types, USP9X has been observed to function as a tumor suppressor, suggesting its exact role in cancer may be dependent on its subtrates[46]. In breast cancer, USP9X has been shown to stabilize BRCA1 by inhibiting its ubiquitination, thereby influencing the regulation of homologous recombination and repair[46].

Alterations and prevalence: Somatic mutations are observed in 16% of uterine corpus endometrial carcinoma, 11% of skin cutaneous melanoma, 7% of colorectal adenocarcinoma, 6% of cholangiocarcinoma, 5% of stomach adenocarcinoma, lung squamous cell carcinoma, diffuse large B-cell lymphoma (DLBCL), and head and neck squamous cell carcinoma[5,6]. Biallelic deletions are observed in 4% of esophageal adenocarcinoma, 3% of head and neck squamous cell carcinoma, 2% of mesothelioma, uterine carcinosarcoma, and lung squamous cell carcinoma[5,6].

Potential relevance: Currently, no therapies are approved for USP9X aberrations.

DDX3X deletion

DEAD-box helicase 3, X-linked

Background: The DDX3X gene encodes DEAD-box helicase 3 X-linked, a member of the DEAD-box protein family, which is part of the RNA helicase superfamily II[1,135]. DEAD-box helicases contain twelve conserved motifs including a "DEAD" domain which is characterized by a conserved amino acid sequence of Asp-Glu-Ala-Asp (DEAD)[135,136,137,138]. In DEAD-box proteins, the DEAD domain interacts with β- and γ-phosphates of ATP through Mg2+ and is required for ATP hydrolysis[135]. DDX3X is involved in several processes including the unwinding of double-stranded RNA, splicing of pre-mRNA, RNA export, transcription, and translation[139,140,141,142,143,144,145,146]. Deregulation of DDX3X has been shown to impact cancer progression by modulating proliferation, metastasis, and drug resistance[139].

Alterations and prevalence: Somatic mutations in DDX3X are observed in 9% of skin cutaneous melanoma and uterine corpus endometrial carcinoma, 7% of diffuse large B-cell lymphoma, 4% of cervical squamous cell carcinoma, bladder urothelial carcinoma, and stomach adenocarcinoma, and 2% of lung squamous cell carcinoma and head and neck squamous cell carcinoma[5,6]. Biallelic loss of DDX3X is observed in 4% of esophageal adenocarcinoma, 3% of head and neck squamous cell carcinoma, and 2% of mesothelioma and lung squamous cell carcinoma[5,6].

Biomarker Descriptions (continued)

Potential relevance: Currently, no therapies are approved for DDX3X aberrations.

KDM6A deletion

lysine demethylase 6A

Background: The KDM6A gene encodes the lysine demethylase 6A protein[1]. KDM6A is a histone demethylase that belongs to the KDM6 family of histone H3 lysine demethylases that also includes KDM6B and KDM6C[96]. Methylation of histone lysine and arginine residues functions to regulate transcription and the DNA damage response, specifically in the recruitment of DNA repair proteins and transcriptional repression[32]. KDM6A removes methylation of di- and trimethylated histone 3 lysine 27 (H3K27)[31,96]. KDM6A also interacts with various transcription factors as well as KMT2C, KMT2D, and CBP/p300 chromatin-modifying enzymes, and the SWI/SNF chromatin-remodeling complex to facilitate transcriptional regulation[96]. Mutations in KDM6A lead to activation of the histone methyltransferase, EZH2, resulting in transcriptional repression[96]. KDM6A is believed to function as a tumor suppressor by antagonizing EZH2-mediated transcriptional repression and promoting transcriptional regulation[96,97].

Alterations and prevalence: Somatic mutations in KDM6A are observed in 26% of bladder urothelial carcinoma, 7% of uterine corpus endometrial carcinoma, 5% of skin cutaneous melanoma, lung squamous cell carcinoma, and 4% of esophageal adenocarcinoma, kidney renal papillary cell carcinoma, pancreatic adenocarcinoma, cervical squamous cell carcinoma, and head and neck squamous cell carcinoma[5,6]. Biallelic loss of KDM6A is observed in 8% of esophageal adenocarcinoma, 4% of lung squamous cell carcinoma, 3% of head and neck squamous cell carcinoma, bladder urothelial carcinoma, and pancreatic adenocarcinoma[5,6].

Potential relevance: Currently, no therapies are approved for KDM6A aberrations. Pre-clinical data suggest that KDM6A loss of function or inactivating mutations may respond to EZH2 inhibitors[97].

RBM10 deletion

RNA binding motif protein 10

Background: RBM10 encodes RNA binding motif protein 10, a member of the RNA binding proteins (RBP) family[1,27]. RBM10 regulates RNA splicing and post-transcriptional modification of mRNA[27,28]. RBM10 is suggested to function as a tumor suppressor by promoting apoptosis and inhibiting cellular proliferation through regulation of the MDM2 and p53 feedback loops, as well as influencing BAX expression[27]. RBM10 has been observed to promote transformation and proliferation in lung cancer, supporting an oncogenic role for RBM10[29,30].

Alterations and prevalence: Somatic mutations in RBM10 are observed in 7% of lung adenocarcinoma, 6% of uterine corpus endometrial carcinoma, 4% of bladder urothelial carcinoma, 3% of colorectal adenocarcinoma and skin cutaneous melanoma, and 2% of diffuse large B-cell lymphoma, pancreatic adenocarcinoma, adrenocortical carcinoma, cervical squamous cell carcinoma, esophageal adenocarcinoma, stomach adenocarcinoma, and kidney chromophobe[5,6]. Biallelic loss of RBM10 is observed in 3% of esophageal adenocarcinoma and 2% of head and neck squamous cell carcinoma[5,6]. Amplification of RBM10 is observed in 5% of ovarian serous cystadenocarcinoma, 4% of uterine carcinosarcoma, and 2% of sarcoma, uterine corpus endometrial carcinoma, adrenocortical carcinoma, and diffuse large B-cell lymphoma[5,6].

Potential relevance: Currently, no therapies are approved for RBM10 aberrations.

KDM5C deletion

lysine demethylase 5C

Background: The KDM5C gene encodes the lysine demethylase 5C protein, a histone demethylase, also known as JARID1C[1,31]. Methylation of histone lysine and arginine residues functions to regulate transcription and DNA damage response[32]. KDM5C removes methylation of di- and trimethylated histone H3 lysine 4 (H3K4) and is involved in the repression of transcription in response to DNA damage[31,32]. KDM5C alterations result in aberrant H3K4 trimethylation at active replication origins which can lead to stalled DNA replication[33].

Alterations and prevalence: Somatic mutations in KDM5C are observed in 9% of uterine corpus endometrial carcinoma, 5% of kidney renal clear cell carcinoma, stomach adenocarcinoma, skin cutaneous melanoma, 4% of lung adenocarcinoma and uterine carcinosarcoma[5,6]. Biallelic loss of KDM5C is observed in 3% of esophageal adenocarcinoma and 2% of head and neck squamous cell carcinoma[5,6].

Potential relevance: Currently, no therapies are approved for KDM5C aberrations.

Biomarker Descriptions (continued)

SMC1A deletion

structural maintenance of chromosomes 1A

Background: SMC1A encodes the structural maintenance of chromosomes 1A and belongs to structural maintenance of chromosomes (SMCs) family, which consists of SMC1A, SMC1B, SMC2, SMC3, SMC4, SMC5, and SMC6[1,104,105]. As a part of the cohesion-core complex, SMC1A plays a crucial role in chromosome segregation during mitosis and meiosis[104,106]. SMC1A also plays a role in cell cycle regulation, DNA damage repair, gene transcription regulation, and genomic organization[104]. SMC1A aberrations, including overexpression, have been observed in several cancer types and have been proposed to promote tumor formation and epithelial to mesenchymal transition[105,107].

Alterations and prevalence: Somatic mutations in SMC1A are observed in 11% of uterine corpus endometrial carcinoma, 5% of skin cutaneous melanoma and acute myeloid leukemia, 4% of colorectal adenocarcinoma and bladder urothelial carcinoma, 3% cervical squamous cell carcinoma and glioblastoma multiforme, 2% diffuse large B-Cell lymphoma, adrenocortical carcinoma, stomach adenocarcinoma, uterine carcinosarcoma, ovarian serous cystadenocarcinoma and lung adenocarcinoma[5,6]. Amplification of SMC1A is found in 4% of diffuse large B-Cell lymphoma, 3% of sarcoma, and 2% of ovarian serous cystadenocarcinoma, adrenocortical carcinoma, and uterine carcinosarcoma[5,6]. Biallelic loss of SMC1A is found in 3% of esophageal adenocarcinoma and 2% of head and neck squamous cell carcinoma[5,6].

Potential relevance: Currently, no therapies are approved for SMC1A aberrations.

AMER1 deletion

APC membrane recruitment protein 1

Background: The AMER1 gene encodes APC membrane recruitment protein 1[1]. AMER1 works in complex with CTNNB1, APC, AXIN1, and AXIN2 to regulate the WNT pathway[1,108]. The WNT signaling pathway is responsible for regulating several key components during embryogenesis and has been observed to be involved in tumorigenesis[109,110]. Consequently, the WNT signaling pathway is a target for therapeutic response in various cancer types[110]. The AMER1 gene is located on the X chromosome and is commonly inactivated in Wilms tumor, a pediatric kidney cancer[111]. AMER1 has also been observed to influence cell proliferation, tumorigenesis, migration, invasion, and cell cycle arrest[108].

Alterations and prevalence: Somatic mutations of AMER1 are observed in 13% of colorectal adenocarcinoma,10% of uterine corpus endometrial carcinoma, 8% of skin cutaneous melanoma, 7% of lung adenocarcinoma, 4% of stomach adenocarcinoma, and uterine carcinosarcoma, 3% of lung squamous cell carcinoma, cervical squamous cell carcinoma, bladder urothelial carcinoma, and 2% of diffuse large B-cell lymphoma, liver hepatocellular carcinoma, head and neck squamous cell carcinoma, and breast invasive carcinoma[5,6]. Biallelic deletion of AMER1 is observed in 2% of esophageal adenocarcinoma, diffuse large b-cell lymphoma, uterine carcinosarcoma, lung squamous cell carcinoma, and pancreatic adenocarcinoma, and 1% of stomach adenocarcinoma, sarcoma, liver hepatocellular carcinoma, colorectal adenocarcinoma, head and neck squamous cell carcinoma, uterine corpus endometrial carcinoma, and ovarian serous cystadenocarcinoma[5,6].

Potential relevance: Currently, no therapies are approved for AMER1 aberrations.

ZMYM3 deletion

zinc finger MYM-type containing 3

Background: The ZMYM3 gene encodes the zinc finger MYM-type containing 3 protein[1]. While the function is not fully understood, ZMYM3 is capable of binding histones and DNA, and may facilitate the repair of double-strand breaks (DSBs)[112].

Alterations and prevalence: Somatic mutations in ZMYM3 are observed in 12% of uterine corpus endometrial carcinoma, 5% of skin cutaneous melanoma, 4% of colorectal adenocarcinoma, 3% of lung adenocarcinoma, lung squamous cell carcinoma, cervical squamous cell carcinoma, esophageal adenocarcinoma, and bladder urothelial carcinoma[5,6]. In prostate cancer, ZMYM3 mutations have been observed to be enriched in African American men compared to white men with one study demonstrating occurrence in 11.7% vs. 2.7% of patients, respectively[113]. Biallelic deletion of ZMYM3 is observed in 3% of cholangiocarcinoma and 2% of sarcoma and kidney chromophobe[5,6].

Potential relevance: Currently, no therapies are approved for ZMYM3 aberrations.

Biomarker Descriptions (continued)

STAG2 deletion

stromal antigen 2

Background: The STAG2 gene encodes the stromal antigen 2 protein, one of the core proteins in the cohesin complex, which regulates the separation of sister chromatids during cell division[47,48]. Components of the cohesion complex include SMC1A, SMC3, and RAD21, which bind to STAG1/STAG2 paralogs[49,50]. Inactivating mutations in STAG2 contribute to X-linked neurodevelopmental disorders, aneuploidy, and chromosomal instability in cancer[49,51].

Alterations and prevalence: Somatic mutations in STAG2 include nonsense, frameshift, splice site variants[12]. Somatic mutations in STAG2 are observed in various solid tumors including 14% of bladder cancer, 10% of uterine cancer, 3% of stomach cancer, and 4% of lung adenocarcinoma[6]. In addition, mutations in STAG2 are observed in 5-10% of myelodysplastic syndrome(MDS), 3% of acute myeloid leukemia, and 2% of diffuse large B-cell lymphoma[6,12].

Potential relevance: Mutations in STAG2 are associated with poor prognosis and adverse risk in MDS and Acute Myeloid Leukemia[12,22,23]. Truncating mutations in STAG2 lead to a loss of function in bladder cancer and are often identified as an early event associated with low grade and stage tumors[52].

PHF6 deletion

PHD finger protein 6

Background: The PHF6 gene encodes the plant homeodomain (PHD) finger protein 6 which contains four nuclear localization signals and two imperfect PHD zinc finger domains. PHF6 is a tumor suppressor that interacts with the nucleosome remodeling deacetylase (NuRD) complex, which regulates nucleosome positioning and transcription of genes involved in development and cell-cycle progression[98,99].

Alterations and prevalence: The majority of PHF6 aberrations are nonsense, frameshift (70%), or missense (30%) mutations, which result in complete loss of protein expression[98,100,101,102]. Truncating or missense mutations in PHF6 are observed in 38% of adult and 16% of pediatric T-cell acute lymphoblastic leukemia (T-ALL), 20-25% of mixed phenotype acute leukemias (MPAL), and 3% of AML, and 2.6% of hepatocellular carcinoma (HCC)[100,102]. Missense mutations recurrently involve codon C215 and the second zinc finger domain of PHF6[100]. PHF6 mutations are frequently observed in hematologic malignancies from male patients[98,100].

Potential relevance: Somatic mutations in PHF6 are associated with reduced overall survival in AML patients treated with high-dose induction chemotherapy[103].

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.

BRAF p.(G466A) c.1397G>C

exarafenib

Cancer type: Melanoma **Variant class:** BRAF Class III

Supporting Statement:

The FDA has granted Fast Track designation to the pan-RAF inhibitor, KIN-2787, for the treatment of BRAF Class II or III alteration-positive and/or NRAS mutation-positive stage IIb to IV malignant melanoma that is metastatic or unresectable.

Reference:

https://investors.kinnate.com/news-releases/news-release-details/kinnate-biopharma-inc-receives-fast-track-designation-us-food

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

BRCA2 c.682-1G>A

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
olaparib	○	○	○	○	● (II)
bevacizumab + olaparib	○	○	○	○	✖
abiraterone + niraparib	○	○	○	✖	✖
rucaparib	○	○	✖	○	✖
talazoparib + enzalutamide	○	○	✖	✖	✖
niraparib	✖	○	✖	○	● (II)
bevacizumab + niraparib	✖	○	✖	✖	✖
olaparib + abiraterone acetate	✖	○	✖	✖	✖
talazoparib	✖	✖	✖	○	● (II)
niraparib, dostarlimab	✖	✖	✖	✖	● (II)
olaparib, talazoparib, atezolizumab + talazoparib	✖	✖	✖	✖	● (II)
pamiparib, tislelizumab	✖	✖	✖	✖	● (II)
ZEN-3694, talazoparib	✖	✖	✖	✖	● (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

BRCA2 c.682-1G>A (continued)

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
AMXI-5001	✖	✖	✖	✖	● (I/II)
sacituzumab govitecan, berzosertib	✖	✖	✖	✖	● (I/II)
HS-10502	✖	✖	✖	✖	● (I)
niraparib, chemotherapy	✖	✖	✖	✖	● (I)
novobiocin	✖	✖	✖	✖	● (I)
olaparib, chemotherapy	✖	✖	✖	✖	● (I)

BRAF p.(G466A) c.1397G>C

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
exarafenib, binimetinib	✖	✖	✖	✖	● (I)
IK-595	✖	✖	✖	✖	● (I)
JAB-3312	✖	✖	✖	✖	● (I)
PF-07799544, PF-07799933	✖	✖	✖	✖	● (I)
PF-07799933, cetuximab, binimetinib	✖	✖	✖	✖	● (I)

ATR p.(G259*) c.775G>T

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
talazoparib	✖	✖	✖	✖	● (II)

ATRX deletion

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

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

HRR Details

Gene/Genomic Alteration	Finding
LOH percentage	***0.0%***
Not Detected	***Not Applicable***

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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