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Patient Name: 신진용
Gender: M
Sample ID: N25-238

Primary Tumor Site: Lung
Collection Date: 2025.09.17.

Sample Cancer Type: Lung Cancer

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Report Highlights

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Relevant Lung Cancer Findings

Gene	Finding	Gene	Finding
ALK	None detected	NTRK1	***NTRK1 amplification***
BRAF	None detected	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	***4.74 Mut/Mb measured***

Relevant Biomarkers

Tier	Genomic Alteration	Relevant Therapies (In this cancer type)	Relevant Therapies (In other cancer type)	Clinical Trials
IIC	*SMARCB1 deletion* SWI/SNF related, matrix associated, actin dependent regulator of chromatin, subfamily b, member 1 Locus: chr22:24129273	None*	cabozantinib pazopanib sunitinib	4
IIC	*MTAP deletion* methylthioadenosine phosphorylase Locus: chr9:21802646	None*	None*	10
IIC	*CDKN2A deletion* cyclin dependent kinase inhibitor 2A Locus: chr9:21968178	None*	None*	3

*** 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	*NF2 deletion* neurofibromin 2 Locus: chr22:29999923	None*	None*	2
IIC	*NTRK1 amplification* neurotrophic receptor tyrosine kinase 1 Locus: chr1:156834550	None*	None*	2
IIC	*ATRX deletion* ATRX, chromatin remodeler Locus: chrX:76763769	None*	None*	1
IIC	*BAP1 deletion* BRCA1 associated protein 1 Locus: chr3:52436290	None*	None*	1
IIC	*CDKN2B deletion* cyclin dependent kinase inhibitor 2B Locus: chr9:22005728	None*	None*	1
IIC	*DDR2 amplification* discoidin domain receptor tyrosine kinase 2 Locus: chr1:162724523	None*	None*	1
IIC	*FANCA deletion* Fanconi anemia complementation group A Locus: chr16:89804984	None*	None*	1
IIC	*FANCM deletion* FA complementation group M Locus: chr14:45605157	None*	None*	1
IIC	*PTEN deletion* phosphatase and tensin homolog Locus: chr10:89623659	None*	None*	1
IIC	*RAD50 deletion* RAD50 double strand break repair protein Locus: chr5:131892978	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

APC deletion, CUL4B deletion, FANCD2 deletion, MAP2K7 deletion, MLH1 deletion, MSH3 deletion, PARP2 deletion, PARP3 deletion, PIK3R1 deletion, RAD51B deletion, TCF7L2 deletion, TP53 p.(R158G) c.472C>G, XRCC3 deletion, RIT1 amplification, TGFBR2 deletion, DOCK3 deletion, MAP3K1 deletion, RASA1 deletion, ERAP1 deletion, ERAP2 deletion, ADAMTS2 deletion, TPMT amplification, HLA-B deletion, JAK2 deletion, LARP4B deletion, GATA3 deletion, MAPK8 deletion, ARID5B deletion, CYP2C9 deletion, SUFU deletion, DICER1 deletion, PDIA3 deletion, CYLD deletion, CBFB deletion, CTCF deletion, CDH1 deletion, NQO1 p.(P187S) c.559C>T, ZFHX3 deletion, PRKACA amplification, 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
TP53	p.(R158G)	c.472C>G	COSM11087	chr17:7578458	95.51%	NM_000546.6	missense
NQO1	p.(P187S)	c.559C>T	.	chr16:69745145	99.50%	NM_000903.3	missense
HLA-B	p.([T118I;L119I])	c.353_355delCCCinsTCA	.	chr6:31324208	100.00%	NM_005514.8	missense, missense
WT1	p.(C161S)	c.482G>C	.	chr11:32456425	17.79%	NM_024426.6	missense
WT1	p.(P100T)	c.298C>A	.	chr11:32456609	35.00%	NM_024426.6	missense
ATM	p.(L3045R)	c.9134T>G	.	chr11:108236198	17.14%	NM_000051.4	missense
AXIN1	p.(K107R)	c.320A>G	.	chr16:396706	8.86%	NM_003502.4	missense
ATF7IP2	p.(Q577*)	c.1729C>T	.	chr16:10575786	48.12%	NM_024997.5	nonsense

Copy Number Variations

Gene	Locus	Copy Number	CNV Ratio
SMARCB1	chr22:24129273	1.16	0.67
MTAP	chr9:21802646	0.73	0.49
CDKN2A	chr9:21968178	0.6	0.44
NF2	chr22:29999923	1.2	0.68
NTRK1	chr1:156834550	7.81	3.33
ATRX	chrX:76763769	0.51	0.41
BAP1	chr3:52436290	1.08	0.63
CDKN2B	chr9:22005728	0.6	0.44
DDR2	chr1:162724523	7.09	3.04
FANCA	chr16:89804984	0.66	0.46
FANCM	chr14:45605157	1.15	0.66
PTEN	chr10:89623659	1.13	0.65
RAD50	chr5:131892978	1.19	0.67
APC	chr5:112043374	1.24	0.7
CUL4B	chrX:119660593	0.61	0.44
FANCD2	chr3:10070306	1.24	0.69
MAP2K7	chr19:7968792	1.2	0.68
MLH1	chr3:37034957	1.18	0.67
MSH3	chr5:79950540	1.19	0.68
PARP2	chr14:20811781	1.1	0.64
PARP3	chr3:51976651	1.13	0.65
PIK3R1	chr5:67522468	1.18	0.67

Variant Details (continued)

Copy Number Variations (continued)

Gene	Locus	Copy Number	CNV Ratio
RAD51B	chr14:68290164	1.15	0.66
TCF7L2	chr10:114710485	1.13	0.65
XRCC3	chr14:104165043	1.09	0.64
RIT1	chr1:155870154	8.14	3.45
TGFBR2	chr3:30648337	1.16	0.67
DOCK3	chr3:51101879	1.04	0.61
MAP3K1	chr5:56111388	1.14	0.66
RASA1	chr5:86564256	1.04	0.61
ERAP1	chr5:96112128	1.14	0.66
ERAP2	chr5:96219500	0.39	0.36
ADAMTS2	chr5:178549645	0.93	0.57
TPMT	chr6:18130879	5.68	2.47
HLA-B	chr6:31322252	0.81	0.53
JAK2	chr9:5021954	0.64	0.46
LARP4B	chr10:858847	1.09	0.64
GATA3	chr10:8097519	0.99	0.59
MAPK8	chr10:49609682	1.05	0.62
ARID5B	chr10:63661463	0.98	0.59
CYP2C9	chr10:96698378	0.94	0.57
SUFU	chr10:104263903	1.18	0.67
DICER1	chr14:95556791	1.2	0.68
PDIA3	chr15:44038719	1.05	0.62
CYLD	chr16:50783549	1.14	0.65
CBFB	chr16:67063242	1.14	0.65
CTCF	chr16:67644720	1.14	0.66
CDH1	chr16:68771249	1.15	0.66
ZFHX3	chr16:72820995	0.56	0.42
PRKACA	chr19:14204349	5.25	2.3
ZRSR2	chrX:15808582	0.54	0.42
BCOR	chrX:39911340	0.61	0.44
USP9X	chrX:40982869	0.51	0.41
DDX3X	chrX:41193501	0.45	0.38
KDM6A	chrX:44732715	0.55	0.42
RBM10	chrX:47006798	0.54	0.41

Variant Details (continued)

Copy Number Variations (continued)

Gene	Locus	Copy Number	CNV Ratio
KDM5C	chrX:53221892	0.57	0.43
SMC1A	chrX:53406966	0.53	0.41
AMER1	chrX:63409727	0.43	0.37
ZMYM3	chrX:70460753	0.51	0.4
STAG2	chrX:123156472	0.57	0.43
PHF6	chrX:133511628	0.51	0.4
RAF1	chr3:12625930	1.14	0.65
MITF	chr3:69788729	1.13	0.65
PDGFRB	chr5:149497160	1.05	0.62
FGFR4	chr5:176517731	1.15	0.66
FLT4	chr5:180030092	1.08	0.63
FAM135B	chr8:139144776	1.21	0.69
CD274	chr9:5456050	0.61	0.45
PDCD1LG2	chr9:5522530	0.61	0.44
RET	chr10:43609070	1.06	0.62
FGFR2	chr10:123239426	1.06	0.63
FOXA1	chr14:38060550	1.06	0.62
MAX	chr14:65472833	1.16	0.67
AKT1	chr14:105236628	1.09	0.63
CD276	chr15:73991923	0.98	0.59
EIF1AX	chrX:20148599	0.63	0.45
ARAF	chrX:47422311	0.59	0.44
AR	chrX:66766015	0.53	0.41
TAF1	chrX:70608133	0.39	0.35

Biomarker Descriptions

SMARCB1 deletion

SWI/SNF related, matrix associated, actin dependent regulator of chromatin, subfamily b, member 1

Background: The SMARCB1 gene encodes SWI/SNF related BAF chromatin remodeling complex subunit B1[1]. SMARCB1, also known as SNF5 or INI1, is a core member of the ATP-dependent, multi-subunit SWI/SNF chromatin-remodeling complex, along with SMARCC1/BAF155, SMARCC2/BAF170, SMARCA4/BRG1, and SMARCA2/BRM[91]. The SWI/SNF complex remodels chromatin at promoter and enhancer elements to alter and regulate gene expression[91,92]. Independent of its functions in chromatin remodeling, SMARCB1 acts as a tumor suppressor and inhibits MYC activation, so loss of function in SMARCB1 enhances MYC activity[93]. Germline mutations in SMARCB1 are associated with rhabdoid tumor predisposition syndrome and familial schwannomatosis[94,95].

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[92]. SMARCB1 is often the only detected mutation in malignant rhabdoid tumors[93].

Biomarker Descriptions (continued)

Somatic mutations in SMARCB1 are observed in 3% of uterine corpus endometrial carcinoma, stomach adenocarcinoma, and kidney chromophobe[5,6]. Alterations in SMARCB1 are also observed in pediatric cancers[5,6]. Somatic mutations in SMARCB1 are observed in 10% of pediatric rhabdoid tumors, 6% of non-Hodgkin lymphoma, 4% of embryonal tumors, and less than 1% of bone cancer (3 in 327 cases), B-lymphoblastic leukemia/lymphoma (1 in 252 cases), and Ewing sarcoma (1 in 354 cases)[5,6]. Biallelic deletion of SMARCB1 is observed in 22% of embryonal tumors and less than 1% of B-lymphoblastic leukemia/lymphoma (4 in 731 cases)[5,6].

Potential relevance: Currently, no therapies are approved for SMARCB1 aberrations. Mutations and deletions of SMARCB1 are considered diagnostic markers of epithelioid sarcoma and SMARCB1-deficient renal medullary carcinoma[96,97].

MTAP deletion

methylthioadenosine phosphorylase

Background: The MTAP gene encodes methylthioadenosine phosphorylase[1]. Methylthioadenosine phosphorylase, a key enzyme in polyamine biosynthesis and methionine salvage pathways, catalyzes the reversible phosphorylation of S-methyl-5'-thioadenosine (MTA) to adenine and 5-methylthioribose-1-phosphate[273,274]. Loss of MTAP function is commonly observed in cancer due to deletion or promotor methylation which results in the loss of MTA phosphorylation and sensitivity of MTAP-deficient cells to purine synthesis inhibitors and to methionine deprivation[274].

Alterations and prevalence: MTAP is flanked by CDKN2A tumor suppressor on chromosome 9p21 and is frequently found to be co-deleted with CDKN2A in numerous solid and hematological cancers[274,275]. Consequently, biallelic loss of MTAP has been observed in 42% of glioblastoma multiforme, 32% of mesothelioma, 26% of bladder urothelial carcinoma, 22% of pancreatic adenocarcinoma, 21% of esophageal adenocarcinoma, 20% of lung squamous cell carcinoma and skin cutaneous melanoma, 15% of diffuse large B-cell lymphoma and head and neck squamous cell carcinoma, 12% of lung adenocarcinoma, 11% of cholangiocarcinoma, 9% of sarcoma, stomach adenocarcinoma and brain lower grade glioma, and 3% of ovarian serous cystadenocarcinoma, breast invasive carcinoma, adrenocortical carcinoma, thymoma and liver hepatocellular carcinoma[5,6]. Somatic mutations in MTAP have been found in 3% of uterine corpus endometrial carcinoma[5,6].

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

CDKN2A deletion

cyclin dependent kinase inhibitor 2A

Background: CDKN2A encodes cyclin dependent kinase inhibitor 2A, a cell cycle regulator that controls G1/S progression[1]. CDKN2A, also known as p16/INK4A, belongs to a family of INK4 cyclin-dependent kinase inhibitors, which also includes CDKN2B (p15/INK4B), CDKN2C (p18/INK4C), and CDKN2D (p19/INK4D)[223]. The INK4 family regulates cell cycle progression by inhibiting CDK4 or CDK6, thereby preventing the phosphorylation of Rb[224,225,226]. CDKN2A encodes two alternative transcript variants, namely p16 and p14ARF, both of which exhibit differential tumor suppressor functions[227]. Specifically, the CDKN2A/p16 transcript inhibits cell cycle kinases CDK4 and CDK6, whereas the CDKN2A/p14ARF transcript stabilizes the tumor suppressor protein p53 to prevent its degradation[1,227,228]. CDKN2A aberrations commonly co-occur with CDKN2B[223]. Loss of CDKN2A/p16 results in downstream inactivation of the Rb and p53 pathways, leading to uncontrolled cell proliferation[229]. Germline mutations of CDKN2A are known to confer a predisposition to melanoma and pancreatic cancer[230,231].

Alterations and prevalence: Somatic alterations in CDKN2A often result in loss of function (LOF) which is attributed to copy number loss, truncating, or missense mutations[232]. Somatic mutations in CDKN2A are observed in 20% of head and neck squamous cell carcinoma and pancreatic adenocarcinoma, 15% of lung squamous cell carcinoma, 13% of skin cutaneous melanoma, 8% of esophageal adenocarcinoma, 7% of bladder urothelial carcinoma, 6% of cholangiocarcinoma, 4% of lung adenocarcinoma and stomach adenocarcinoma, and 2% of liver hepatocellular carcinoma, uterine carcinosarcoma, and cervical squamous cell carcinoma[5,6]. Biallelic deletion of CDKN2A is observed in 56% of glioblastoma multiforme, 45% of mesothelioma, 39% of esophageal adenocarcinoma, 32% of bladder urothelial carcinoma, 31% of skin cutaneous melanoma and head and neck squamous cell carcinoma, 28% of pancreatic adenocarcinoma, 27% of diffuse large B-cell lymphoma, 26% of lung squamous cell carcinoma, 17% of lung adenocarcinoma and cholangiocarcinoma, 15% of sarcoma, 11% of stomach adenocarcinoma and of brain lower grade glioma, 7% of adrenocortical carcinoma, 6% of liver hepatocellular carcinoma, 4% of breast invasive carcinoma, kidney renal papillary cell carcinoma and thymoma, 3% of ovarian serous cystadenocarcinoma and kidney renal clear cell carcinoma, and 2% of uterine carcinosarcoma and kidney chromophobe[5,6]. Alterations in CDKN2A are also observed in pediatric cancers[6]. Biallelic deletion of CDKN2A is observed in 68% of T-lymphoblastic leukemia/lymphoma, 40% of B-lymphoblastic leukemia/lymphoma, 25% of glioma, 19% of bone cancer, and 6% of embryonal tumors[6]. Somatic mutations in CDKN2A are observed in less that 1.5% of bone cancer (5 in 327 cases), B-lymphoblastic leukemia/lymphoma (3 in 252 cases), and leukemia (1 in 354 cases)[6].

Potential relevance: Loss of CDKN2A can be useful in the diagnosis of mesothelioma, and mutations in CDKN2A are ancillary diagnostic markers of malignant peripheral nerve sheath tumors[97,233,234]. Additionally, deletion of CDKN2B is a molecular marker used in staging Grade 4 pediatric IDH-mutant astrocytoma[235]. Currently, no therapies are approved for CDKN2A aberrations. However,

Biomarker Descriptions (continued)

CDKN2A LOF leading to CDK4/6 activation may confer sensitivity to CDK inhibitors such as palbociclib and abemaciclib[236,237,238]. Alternatively, CDKN2A expression and Rb inactivation demonstrate resistance to palbociclib in cases of glioblastoma multiforme[239]. CDKN2A (p16) expression is associated with a favorable prognosis for progression-free survival (PFS) and overall survival (OS) in p16/HPV positive head and neck cancer[240,241,242,243].

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[148,149,150]. NF2 regulates several cellular pathways including the RAS/RAF/MEK/ERK, PI3K/AKT, and Hippo-YAP pathways, thus impacting cell motility, adhesion, invasion, proliferation, and apoptosis[148,149,150,151]. NF2 functions as a tumor suppressor wherein loss of function mutations are shown to confer a predisposition to tumor development[149,150,152]. 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[149,150,152].

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[5]. Biallelic loss of NF2 is also observed in approximately 8% of mesothelioma cases[5].

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)[153].

NTRK1 amplification

neurotrophic receptor tyrosine kinase 1

Background: The NTRK genes encode a family of neurotrophic receptor tyrosine kinases that function as receptors for nerve growth factors[154]. NTRKs are activated by different neurotrophins and are important for the development of the nervous system[154]. The NTRK1, 2 and 3 proteins are also known as tropomyosin-related kinases (TrkA, TrkB, TrkC) because NTRK1 was originally discovered as part of a chimeric fusion gene with tropomyosin-3 isolated from a human colon carcinoma cell line[155]. NTRKs are the target of recurrent chromosomal rearrangements that generate fusion proteins containing the intact tyrosine kinase domain combined with numerous fusion partner genes[156,157]. NTRK fusion kinases are constitutively active and lead to increased signaling through the RAS/RAF/MEK/ERK, PI3K/AKT/MTOR, or PLCγ/PKC pathways, promoting cell growth and proliferation[156,158].

Alterations and prevalence: NTRK fusions are infrequently observed in diverse pediatric and adult cancer types including glioma, glioblastoma, lung adenocarcinoma, colorectal carcinoma, thyroid cancer, and sarcoma[5,156,159,160,161,162,163]. In certain cancer subtypes, including melanoma, infantile fibrosarcoma, papillary thyroid carcinoma, and secretory carcinoma of the breast or salivary gland, NTRK fusions are more prevalent[156,162,163,164,165,166]. NTRK1 is amplified in 11% of cholangiocarcinoma, 10% of liver hepatocellular carcinoma, 8% of breast invasive carcinoma, 7% of lung adenocarcinoma, 4% of sarcoma, bladder urothelial carcinoma, ovarian serous cystadenocarcinoma, uterine corpus endometrial carcinoma, pancreatic adenocarcinoma, pheochromocytoma and paraganglioma, and uterine carcinosarcoma, 3% of adrenocortical carcinoma, lung squamous cell carcinoma, and esophageal adenocarcinoma, and 2% of skin cutaneous melanoma, diffuse large B-cell lymphoma, cervical squamous cell carcinoma, thymoma, and stomach adenocarcinoma[5,6]. Somatic mutations in NTRK1 are observed in 8% of skin cutaneous melanoma, 6% of uterine corpus endometrial carcinoma, 4% of uterine carcinosarcoma, 3% of lung adenocarcinoma and stomach adenocarcinoma, and 2% of lung squamous cell carcinoma, esophageal adenocarcinoma, bladder urothelial carcinoma, pancreatic adenocarcinoma, and colorectal adenocarcinoma[5,6]. Alterations in NTRK1 are rare in pediatric cancers[6]. NTRK1 is amplified in 6% of Wilms tumor and less than 1% of B-lymphoblastic leukemia/lymphoma (5 in 731 cases)[6]. Somatic mutations in NTRK1 are observed in less than 1% of embryonal tumors (2 in 332 cases), leukemia (1 in 311 cases), and peripheral nervous system tumors (1 in 1158 cases)[6].

Potential relevance: The first-generation selective tropomyosin receptor kinase (TRK) inhibitor, larotrectinib[167], is approved (2018) for the treatment of adults and pediatric patients with any solid tumors harboring NTRK gene fusions and is the first approved small molecule inhibitor with a tissue agnostic indication. Entrectinib[168] is another first-generation TRK inhibitor approved (2019) for adults and pediatric patients with NTRK fusion-positive solid tumors as well as for adult patients with ROS1-positive non-small cell lung cancer (NSCLC). However, acquired resistance to first-generation NTRK inhibition is often mediated by the acquisition of solvent-front and gatekeeper mutations in the kinase domain[169]. Consequently, the second generation TRK inhibitor, repotrectinib[170], is approved by the FDA (2024) for the treatment of adult and pediatric patients with solid tumors that have an NTRK gene fusion. NTRK fusion is diagnostic of NTRK-rearranged spindle cell carcinoma as defined by the World Health Organization (WHO)[171].

Biomarker Descriptions (continued)

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[183,184,185,186]. ATRX is a tumor suppressor that interacts with the MRE11-RAD50-NBN (MRN) complex, which is involved in double-stranded DNA (dsDNA) break repair[187,188,189].

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 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[190,191]. ATRX deficiency along with IDH mutation and TP53 mutation is diagnostic of astrocytoma IDH-mutant as defined by the World Health Organization (WHO)[192,193].

BAP1 deletion

BRCA1 associated protein 1

Background: The BAP1 gene encodes the BRCA1 associated protein 1 that belongs to the ubiquitin C-terminal hydrolase subfamily of deubiquitinating enzymes[1]. BAP1 is a tumor suppressor deubiquitinase that is involved in chromatin modification, transcription, and cell cycle regulation[246]. BAP1 deubiquitylation targets include HCF-1, which modulates chromatin structure[246]. Germline mutations in BAP1 are associated with BAP1-tumor predisposition syndrome (BAP1-TPDS), a heritable condition which confers an elevated risk of developing uveal melanoma, malignant mesothelioma, and renal cell carcinoma[247,248,249,250,251,252].

Alterations and prevalence: Recurrent somatic mutations in BAP1 are observed in 21% of mesothelioma, 19% of cholangiocarcinoma, 16% of uveal melanoma, and 7% of kidney renal clear cell carcinoma[5,6]. BAP1 biallelic deletions are observed in 11% of mesothelioma[5,6].

Potential relevance: Currently, no therapies are approved for BAP1 aberrations.

CDKN2B deletion

cyclin dependent kinase inhibitor 2B

Background: CDKN2B encodes cyclin dependent kinase inhibitor 2B, a cell cycle regulator that controls G1/S progression[1,223]. CDKN2B, also known as p15/INK4B, belongs to a family of INK4 cyclin-dependent kinase inhibitors, which also includes CDKN2A (p16/INK4A), CDKN2C (p18/INK4C), and CDKN2D (p19/INK4D)[223]. The INK4 family regulates cell cycle progression by inhibiting CDK4 or CDK6, thereby preventing the phosphorylation of Rb[224,225,226]. CDKN2B is a tumor suppressor and aberrations in this gene commonly co-occur with CDKN2A[223]. Germline mutations in CDKN2B are linked to pancreatic cancer predisposition and familial renal cell carcinoma[1,244,245].

Alterations and prevalence: CDKN2B copy number loss is a frequently occurring somatic aberration that is observed in 55% of glioblastoma multiforme, 43% of mesothelioma, 35% of esophageal adenocarcinoma, 31% of bladder urothelial carcinoma, 29% of skin cutaneous melanoma, 28% of head and neck squamous cell carcinoma, 27% of pancreatic adenocarcinoma, 26% of lung squamous cell carcinoma, 25% of diffuse large B -cell lymphoma, 16% of lung adenocarcinoma, 15% of sarcoma, 14% of cholangiocarcinoma, 11% of stomach adenocarcinoma and brain lower grade glioma, 5% of liver hepatocellular carcinoma, 4% of adrenocortical carcinoma, breast invasive carcinoma, thymoma, and kidney renal papillary cell carcinoma, 3% of kidney renal clear cell carcinoma and ovarian serous cystadenocarcinoma, and 2% of uterine carcinosarcoma and kidney chromophobe[5,6]. Somatic mutations in CDKN2B are observed in 2% of uterine carcinosarcoma[5,6]. CDKN2B copy number loss is also observed in pediatric cancers, including 64% of childhood T-lymphoblastic leukemia/lymphoma, 37% of pediatric B-lymphoblastic leukemia/lymphoma, 25% of pediatric gliomas, 14%

Biomarker Descriptions (continued)

of pediatric bone cancers, 6% of embryonal tumors, and 2% of peripheral nervous system cancers[5,6]. Somatic mutations in CDKN2B are observed in less than 1% of bone cancer (1 in 327 cases)[5,6].

Potential relevance: Currently, no therapies are approved for CDKN2B aberrations. Homozygous deletion of CDKN2B is a molecular marker used in staging grade 4 pediatric IDH-mutant astrocytoma[235].

DDR2 amplification

discoidin domain receptor tyrosine kinase 2

Background: The DDR2 gene encodes the discoidin domain receptor tyrosine kinase 2 protein. In comparison to receptor tyrosine kinases (RTKs) such as EGFR and FGFR that display rapid and transient activation, DDR2 exhibits delayed and continued receptor activation[137]. DDR2 binds to collagen and can impact cell adhesion and migration through extracellular matrix (ECM) remodeling[138,139]. DDR2 activation stimulates oncogenic signaling including the RAS/RAF/MEK/ERK and PI3K/AKT/MTOR pathways thereby promoting cell proliferation and metastasis[139].

Alterations and prevalence: Somatic mutations are observed in up to 7% of uterine cancer, and up to 4% of melanoma, non-small lung cell carcinoma, stomach cancer, and colorectal cancer[5,140,141]. DDR2 mutations have been found along the kinase and discoidin domains but do not appear to occur in hotspot fashion and are not mutually exclusive with other driver mutations[6,139,142]. Amplification of DDR2 is found to occur in up to 15% of bladder cancer and 10-14% of cholangiocarcinoma, breast, lung adenocarcinoma, and liver cancers[5,6,143,144].

Potential relevance: Currently, no therapies are approved for DDR2 aberrations. Various pre-clinical studies have demonstrated the efficacy of dasatinib (an approved multi-targeted tyrosine kinase inhibitor) in DDR2 mutated cancers[142,145,146]. However, clinical data is limited. In an early phase clinical trial, one squamous cell carcinoma patient with a DDR2 S768R mutation and without an EGFR mutation demonstrated a radiographic response to treatment with dasatinib and erlotinib[147].

FANCA deletion

Fanconi anemia complementation group A

Background: The FANCA gene encodes the FA complementation group A protein, a member of the Fanconi Anemia (FA) family, which also includes FANCB, FANCC, FANCD1 (BRCA2), FANCD2, FANCE, FANCF, FANCG, FANCI, FANCJ (BRIP1), FANCL, FANCM, and FANCN (PALB2)[1]. FA genes are tumor suppressors that are responsible for the maintenance of replication fork stability, DNA damage repair through the removal of interstrand cross-links (ICL), and subsequent initiation of the homologous recombination repair (HRR) pathway[37,38]. In response to DNA damage, FANCA, FANCB, FANCC, FANCE, FANCF, FANCG, FANCL, and FANCM assemble to form the FA core complex which is responsible for the monoubiquitination of the FANCI-FANCD2 (ID2) complex[37]. Monoubiquitination of the ID2 complex promotes co-localization with BRCA1/2, which is critical in BRCA mediated DNA repair[39,40]. Loss of function mutations in the FA family and HRR pathway, including FANCA, can result in the BRCAness phenotype, characterized by a defect in the HRR pathway, mimicking BRCA1 or BRCA2 loss[41,42]. 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[43,44]. Of those diagnosed with FA, mutations in FANCA are the most common and confer predisposition to myelodysplastic syndrome, acute myeloid leukemia, and solid tumors[38,44,73,74,75].

Alterations and prevalence: Somatic mutations in FANCA are observed in 4-8% of uterine, colorectal, and bladder cancers and about 6% of melanoma[5]. Biallelic loss is also reported in 2-5% of uveal melanoma, invasive breast carcinoma, ovarian cancer, and prostate cancer[5].

Potential relevance: The PARP inhibitor, talazoparib[71] in combination with enzalutamide is approved (2023) for metastatic castration-resistant prostate cancer (mCRPC) with mutations in HRR genes that includes FANCA. Consistent with other genes that contribute to the BRCAness phenotype, mutations in FANCA are shown to confer enhanced sensitivity in vitro to DNA damaging agents, including cisplatin, as well as PARP inhibitors such as olaparib[59,76]. FANCA copy number loss along with reduced expression has also been associated with genetic instability in sporadic acute myeloid leukemia (AML)[75].

FANCM deletion

FA complementation group M

Background: The FANCM gene encodes the FA complementation group M protein, a member of the Fanconi Anemia (FA) family, which also includes FANCA, FANCB, FANCC, FANCD1 (BRCA2), FANCD2, FANCE, FANCF, FANCG, FANCI, FANCJ (BRIP1), FANCL, and FANCN (PALB2)[1]. FA genes are tumor suppressors that are responsible for the maintenance of replication fork stability, DNA damage repair through the removal of interstrand cross-links (ICL), and subsequent initiation of the homologous recombination repair (HRR) pathway[37,38]. In response to DNA damage, FANCA, FANCB, FANCC, FANCE, FANCF, FANCG, FANCL, and FANCM assemble to form the

Biomarker Descriptions (continued)

FA core complex which is responsible for the monoubiquitination of the FANCI-FANCD2 (ID2) complex[37]. Monoubiquitination of the ID2 complex promotes co-localization with BRCA1/2, which is critical in BRCA mediated DNA repair[39,40]. Loss of function mutations in the FA family and HRR pathway can result in the BRCAness phenotype, characterized by a defect in the HRR pathway, mimicking BRCA1 or BRCA2 loss[41,42]. 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[43,44].

Alterations and prevalence: Somatic mutations in FANCM are observed in 11% of uterine corpus endometrial carcinoma, 8% of skin cutaneous melanoma, 7% of lung adenocarcinoma, 6% of stomach adenocarcinoma, 5% colorectal adenocarcinoma, uterine carcinosarcoma, and bladder urothelial carcinoma[5,6].

Potential relevance: Currently, no therapies are approved for FANCM aberrations. Consistent with other genes that contribute to the BRCAness phenotype, mutations in FANCM are shown to confer enhanced sensitivity in vitro to PARP inhibitors such as olaparib[45].

PTEN deletion

phosphatase and tensin homolog

Background: The PTEN gene encodes the phosphatase and tensin homolog, a tumor suppressor protein with lipid and protein phosphatase activities[316]. PTEN antagonizes PI3K/AKT signaling by catalyzing the dephosphorylation of phosphatidylinositol (3,4,5)-trisphosphate (PIP3) to PIP2 at the cell membrane, which inhibits the activation of AKT[317,318]. In addition, PTEN has been proposed to influence RAD51 loading at double strand breaks during homologous recombination repair (HRR) and regulate the G2/M checkpoint by influencing CHEK1 localization through AKT inhibition, thereby regulating HRR efficiency[319]. Germline mutations in PTEN are linked to hamartoma tumor syndromes, including Cowden disease, which are defined by uncontrolled cell growth and benign or malignant tumor formation[320]. PTEN germline mutations are also associated with inherited cancer risk in several cancer types[321].

Alterations and prevalence: PTEN is frequently altered in cancer by inactivating loss-of-function mutations and by gene deletion. PTEN mutations are frequently observed in 50%-60% of uterine cancer[5,6]. Nearly half of somatic mutations in PTEN are stop-gain or frame-shift mutations that result in truncation of the protein reading frame. Recurrent missense or stop-gain mutations at codons R130, R173, and R233 result in loss of phosphatase activity and inhibition of wild-type PTEN[318,322,323,324,325]. PTEN gene deletion is observed in 15% of prostate cancer, 9% of squamous lung cancer, 9% of glioblastoma, and 1-5% of melanoma, sarcoma, and ovarian cancer[5,6].

Potential relevance: Due to the role of PTEN in HRR, poly(ADP-ribose) polymerase inhibitors (PARPi) are being explored as a potential therapeutic strategy in PTEN deficient tumors[326,327]. In 2022, the FDA granted fast track designation to the small molecule inhibitor, pidnarulex[136], for BRCA1/2, PALB2, or other homologous recombination deficiency (HRD) mutations in breast and ovarian cancers. In 2023, the FDA approved the kinase inhibitor, capivasertib[328] in combination with fulvestrant for locally advanced or metastatic hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative breast cancer with one or more PIK3CA/AKT1/PTEN-alterations following progression after endocrine treatment.

RAD50 deletion

RAD50 double strand break repair protein

Background: The RAD50 gene encodes the RAD50 double-strand break repair protein and belongs to the adenosine triphosphate (ATP) binding cassette (ABC) transporter family of ATPases[356,357]. RAD50 is an important structural maintenance of chromosome (SMC) protein and mutations in this gene are associated with genomic instability[357,358]. RAD50 is a tumor suppressor gene and part of the multisubunit MRE11/RAD50/NBN (MRN) complex[358,359]. The MRN complex is involved in the repair of double-stranded breaks (DSB) through homologous recombination repair (HRR) and non-homologous end joining (NHEJ)[358,359]. RAD50 contains long coiled-coil regions that link the ATPase domain, as well as a zinc hook domain that interacts with MRE11 and bridges DNA ends together during the DNA damage response[358,360]. RAD50 is a tumor suppressor gene. Loss of function mutations in RAD50 are implicated in the BRCAness phenotype, characterized by a defect in HRR, mimicking BRCA1 or BRCA2 loss[41,133]. The presence of germline mutations in RAD50 is associated with unfavorable recurrence free-survival in BRCA1/2 negative breast cancer patients, although there is no association with increased risk of breast cancer[361].

Alterations and prevalence: Somatic mutations in RAD50 are observed in up to 8% of uterine cancer, 5% of melanoma, and 4% of colorectal cancer[5,6]. Lack of MRN complex proteins are observed in 41% (55/134) of epithelial ovarian cancer patients[362].

Potential relevance: Currently, no therapies are approved for RAD50 aberrations. RAD50 expression is a predictor of clinical outcomes in patients who receive postoperative radiotherapy[363]. Specifically, tissue microarray (TMA) analysis of tumors from 127 NSCLC patients demonstrated that patients with low RAD50 expression had better clinical outcomes including overall survival (OS), distant-metastasis free survival (DMFS), disease-free survival (DFS), and local-regional recurrence-free survival (LRRFS) in comparison to patients with high RAD50 expression[363]. Another study identified RAD50 copy number deletion as a candidate marker for survival and response to PARP inhibitors in BRCA wild-type ovarian cancer with the BRCAness phenotype[364].

Biomarker Descriptions (continued)

APC deletion

APC, WNT signaling pathway regulator

Background: The APC gene encodes the adenomatous polyposis coli tumor suppressor protein that plays a crucial role in regulating the β-catenin/WNT signaling pathway which is involved in cell migration, adhesion, proliferation, and differentiation[172]. APC is an antagonist of WNT signaling as it targets β-catenin for proteasomal degradation[173,174]. Germline mutations in APC are predominantly inactivating and result in an autosomal dominant predisposition for familial adenomatous polyposis (FAP) which is characterized by numerous polyps in the intestine[172,175]. Acquiring a somatic mutation in APC is considered to be an early and possibly initiating event in colorectal cancer[176].

Alterations and prevalence: Somatic mutations in APC are observed in up to 65% of colorectal cancer, and in up to 15% of stomach adenocarcinoma and uterine corpus endometrial carcinoma[5,6,141]. In colorectal cancer, ~60% of somatic APC mutations have been reported to occur in a mutation cluster region (MCR) resulting in C-terminal protein truncation and APC inactivation[177,178].

Potential relevance: Currently, no therapies are approved for APC 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.

FANCD2 deletion

Fanconi anemia complementation group D2

Background: The FANCD2 gene encodes the FA complementation group D2 protein, a member of the Fanconi Anemia (FA) family, which also includes FANCA, FANCB, FANCC, FANCD1 (BRCA2), FANCE, FANCF, FANCG, FANCI, FANCJ (BRIP1), FANCL, FANCM and FANCN (PALB2)[1]. FA genes are tumor suppressors that are responsible for the maintenance of replication fork stability, DNA damage repair through the removal of interstrand cross-links (ICL), and subsequent initiation of the homologous recombination repair (HRR) pathway[37,38]. In response to DNA damage, FANCA, FANCB, FANCC, FANCE, FANCF, FANCG, FANCL, and FANCM assemble to form the FA core complex which is responsible for the monoubiquitination of the FANCI-FANCD2 (ID2) complex[37]. Monoubiquitination of the ID2 complex promotes co-localization with BRCA1/2, which is critical in BRCA mediated DNA repair[39,40]. Loss of function mutations in the FA family and HRR pathway, including FANCD2, can result in the BRCAness phenotype, characterized by a defect in the HRR pathway, mimicking BRCA1 or BRCA2 loss[41,42]. 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[43,44].

Alterations and prevalence: Somatic mutations in FANCD2 are observed in 4-8% of diffuse large B-cell lymphoma (DLBCL), melanoma, bladder, and uterine cancer[5].

Potential relevance: Currently, no therapies are approved for FANCD2 aberrations. Consistent with other genes that contribute to the BRCAness phenotype, FANCD2 deficiency or loss of function has been shown to confer enhanced sensitivity to PARP inhibitors in vitro[59,60,61].

Biomarker Descriptions (continued)

MAP2K7 deletion

mitogen-activated protein kinase kinase 7

Background: The MAP2K7 gene encodes the mitogen-activated protein kinase kinase 7, also known as MEK7[1]. MAP2K7 is involved in the JNK signaling pathway along with MAP3K4, MAP3K12, MAP2K4, MAPK8, MAPK9, and MAPK10[259,260,261]. Activation of MAPK proteins occurs through a kinase signaling cascade[259,260,262]. Specifically, MAP3Ks are responsible for phosphorylation of MAP2K family members[259,260,262]. Once activated, MAP2Ks are responsible for the phosphorylation of various MAPK proteins whose signaling is involved in several cellular processes including cell proliferation, differentiation, and inflammation[259,260,262].

Alterations and prevalence: Somatic mutations in MAP2K7 are observed in 7% of stomach adenocarcinoma, 4% of colorectal adenocarcinoma, and 2% of skin cutaneous melanoma and uterine corpus endometrial carcinoma[5,6]. Biallelic deletions are observed in 4% of uterine carcinosarcoma, 2% of esophageal adenocarcinoma, and 1% of uveal melanoma[5,6].

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

MLH1 deletion

mutL homolog 1

Background: The MLH1 gene encodes the mutL homolog 1 protein[1]. MLH1 is a tumor suppressor gene that heterodimerizes with PMS2 to form the MutLα complex, PMS1 to form the MutLβ complex, and MLH3 to form the MutLγ complex[52]. The MutLα complex functions as an endonuclease that is specifically involved in the mismatch repair (MMR) process and mutations in MLH1 result in the inactivation of MutLα and degradation of PMS2[52,111]. Loss of MLH1 protein expression and MLH1 promoter hypermethylation correlates with mutations in these genes and are used to pre-screen colorectal cancer or endometrial hyperplasia[112,113]. MLH1, along with MSH6, MSH2, and PMS2 form the core components of the MMR pathway[52]. The MMR pathway is critical to the repair of mismatch errors which typically occur during DNA replication[52]. Deficiency in MMR (dMMR) is characterized by mutations and loss of expression in these genes[114]. dMMR is associated with microsatellite instability (MSI), which is defined as a change in the length of a microsatellite in a tumor as compared to normal tissue[115,116,117]. MSI-high (MSI-H) is a hallmark of Lynch Syndrome (LS), also known as hereditary non-polyposis colorectal cancer, which is caused by germline mutations in MMR genes[115,118]. LS is associated with an increased risk of developing colorectal cancer, as well as other cancers, including endometrial and stomach cancer[116,118,119,120]. Specifically, MLH1 mutations are associated with an increased risk of ovarian and pancreatic cancer[121,122,123,124].

Alterations and prevalence: Somatic mutations in MLH1 are observed in 6% of uterine corpus endometrial carcinoma, 4% of colorectal adenocarcinoma, and 2-3% of bladder urothelial carcinoma, stomach adenocarcinoma, and melanoma[5,6]. Alterations in MLH1 are observed in pediatric cancers[5,6]. Somatic mutations are observed in 1% of bone cancer and less than 1% of B-lymphoblastic leukemia/lymphoma (2 in 252 cases), embryonal tumor (2 in 332 cases), and leukemia (2 in 311 cases)[5,6].

Potential relevance: The PARP inhibitor, talazoparib[71] in combination with enzalutamide is approved (2023) for metastatic castration-resistant prostate cancer (mCRPC) with mutations in HRR genes that includes MLH1. Additionally, pembrolizumab (2014) is an anti-PD-1 immune checkpoint inhibitor that is approved for patients with MSI-H or dMMR solid tumors that have progressed on prior therapies[125]. Nivolumab (2015), an anti-PD-1 immune checkpoint inhibitor, is approved alone or in combination with the cytotoxic T-lymphocyte antigen 4 (CTLA-4) blocking antibody, ipilimumab (2011), for patients with dMMR colorectal cancer that have progressed on prior treatment[126,127]. MLH1 mutations are consistent with high grade in pediatric diffuse gliomas[128,129].

MSH3 deletion

mutS homolog 3

Background: The MSH3 gene encodes the mutS homolog 3 protein[1]. MSH3 heterodimerizes with MSH2 to form the MutSβ complex, an ATPase which functions in mismatch repair (MMR) by recognizing mismatches and initiating repair[52,53]. MSH3 is capable of interacting with proliferating cellular nuclear antigen (PCNA), which may facilitate MutSβ localization to DNA mispairs[52,53]. Mutations in MSH3 have been observed to be associated with microsatellite instability (MSI) in colon cancer[54].

Alterations and prevalence: Somatic mutations in MSH3 are observed in 9% of uterine corpus endometrial carcinoma, 4% of stomach adenocarcinoma, and 3% of skin cutaneous melanoma[5,6]. Biallelic deletion of MSH3 are observed in 3% of ovarian serous cystadenocarcinoma and 2% of prostate adenocarcinoma[5,6].

Potential relevance: Currently, no therapies are approved for MSH3 aberrations.

Biomarker Descriptions (continued)

PARP2 deletion

poly(ADP-ribose) polymerase 2

Background: The PARP2 gene encodes the poly(ADP-ribose) polymerase 2 protein[1]. PARP2 belongs to the large PARP protein family that also includes PARP1, PARP3, and PARP4[62]. PARP enzymes are responsible for the transfer of ADP-ribose, known as poly(ADP-ribosyl)ation or PARylation, to a variety of protein targets resulting in the recruitment of proteins involved in DNA repair, DNA synthesis, nucleic acid metabolism, and regulation of chromatin structure[62,63]. PARP enzymes are involved in several DNA repair pathways[62,63]. PARP2 interacts with PARP1 to assist in repair of single-strand breaks through base excision repair (BER)[62,64]. PARP2 has also been observed to promote homologous recombination repair (HRR) of double-strand breaks (DSBs) over non-homologous end joining (NHEJ) by limiting the accumulation of TP53BP1 and preventing TP53BP1 from blocking HRR resection of DNA[64,65]. PARylation of histones H1, H2A, and H2B by PARP2 promotes an open chromatin conformation, which allows DNA repair machinery access to sites of DNA damage[66].

Alterations and prevalence: Somatic mutations in PARP2 are observed in 4% of uterine corpus endometrial carcinoma, and uterine carcinosarcoma, and 2% of stomach adenocarcinoma, and skin cutaneous melanoma[5,6].

Potential relevance: Currently, no therapies are approved for PARP2 aberrations. However, PARP inhibition is known to induce synthetic lethality in certain cancer types that are HRR deficient (HRD) due to mutations in the HRR pathway. This is achieved from PARP inhibitors (PARPi) by promoting the accumulation of DNA damage in cells with HRD, consequently resulting in cell death[67,68]. Although not indicated for specific alterations in PARP2, several PARPis including olaparib, rucaparib, talazoparib, and niraparib have been approved in various cancer types with HRD. Olaparib[69] (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[69] is approved (2020) for metastatic castration-resistant prostate cancer (mCRPC) with deleterious or suspected deleterious germline or somatic mutations in HRR genes that includes BRCA1. Rucaparib[70] (2016) was the first PARPi approved for the treatment of patients with either gBRCAm or sBRCAm epithelial ovarian, fallopian tube, or primary peritoneal cancers and is also approved (2020) for deleterious gBRCAm or sBRCAm mCRPC. Talazoparib[71] (2018) is indicated for the treatment of gBRCAm HER2-negative locally advanced or metastatic breast cancer. Niraparib[72] (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.

PARP3 deletion

poly(ADP-ribose) polymerase family member 3

Background: The PARP3 gene encodes the poly(ADP-ribose) polymerase 3 protein[1]. PARP3 belongs to the large PARP protein family that also includes PARP1, PARP2, and PARP4[62]. PARP enzymes are responsible for the transfer of ADP-ribose, known as poly(ADP-ribosyl)ation or PARylation, to a variety of protein targets resulting in the recruitment of proteins involved in DNA repair, DNA synthesis, nucleic acid metabolism, and regulation of chromatin structure[62,63]. PARP enzymes are involved in several DNA repair pathways[62,63]. Although the functional role of PARP3 is not well understood, PARP3 may serve a role in double-strand break (DSB) repair by facilitating selection for either non-homologous end joining (NHEJ) or homologous recombination repair (HRR)[77,78]. Specifically, PARP3 is proposed to accelerate DSB repair by NHEJ by targeting APLF to chromosomal DSBs[77].

Alterations and prevalence: Somatic mutations in PARP3 are observed in 4% of uterine corpus endometrial carcinoma, and 2% of skin cutaneous melanoma, lung adenocarcinoma, and stomach adenocarcinoma[5,6]. Biallelic deletions in PARP3 are observed in 4% of diffuse large B-cell lymphoma (DLBCL), 3% of kidney renal clear cell carcinoma, 2% of esophageal adenocarcinoma and sarcoma[5,6].

Potential relevance: Currently, no therapies are approved for PARP3 aberrations. However, PARP inhibition is known to induce synthetic lethality in certain cancer types that are HRR deficient (HRD) due to mutations in the HRR pathway. This is achieved from PARP inhibitors (PARPi) by promoting the accumulation of DNA damage in cells with HRD, consequently resulting in cell death[67,68]. Although not indicated for specific alterations in PARP3, several PARPis including olaparib, rucaparib, talazoparib, and niraparib have been approved in various cancer types with HRD. Olaparib[69] (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[69] is approved (2020) for metastatic castration-resistant prostate cancer (mCRPC) with deleterious or suspected deleterious germline or somatic mutations in HRR genes that includes BRCA1. Rucaparib[70] (2016) was the first PARPi approved for the treatment of patients with either gBRCAm or sBRCAm epithelial ovarian, fallopian tube, or primary peritoneal cancers and is also approved (2020) for deleterious gBRCAm or sBRCAm mCRPC. Talazoparib[71] (2018) is indicated for the treatment of gBRCAm HER2-negative locally advanced or

Biomarker Descriptions (continued)

metastatic breast cancer. Niraparib[72] (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.

PIK3R1 deletion

phosphoinositide-3-kinase regulatory subunit 1

Background: The PIK3R1 gene encodes the phosphoinositide-3-kinase regulatory subunit 1 of the class I phosphatidylinositol 3-kinase (PI3K) enzyme[1]. PI3K is a heterodimer that contains a p85 regulatory subunit and a p110 catalytic subunit[253]. Specifically, PIK3R1 encodes the p85α protein, one of five p85 isoforms[253]. p85α is responsible for the binding, stabilization, and inhibition of the p110 catalytic subunit, thereby regulating PI3K activity[253]. PI3K catalyzes the conversion of phosphatidylinositol (4,5)-bisphosphate (PIP2) into phosphatidylinositol (3,4,5)-trisphosphate (PIP3) while the phosphatase and tensin homolog (PTEN) catalyzes the reverse reaction[254,255]. The reversible phosphorylation of inositol lipids regulates diverse aspects of cell growth and metabolism[254,255,256,257]. p85 is also capable of binding PTEN thereby preventing ubiquitination and increasing PTEN stability[258]. Loss of function mutations in PIK3R1 results in the inability of p85 to bind p110 or PTEN resulting in aberrant activation of the PI3K/AKT/MTOR pathway, a common driver event in several cancer types which supports a tumor suppressor role for PIK3R1[253].

Alterations and prevalence: Somatic mutations in PIK3R1 are predominantly truncating or missense and are observed in about 31% of uterine cancer, 10% of uterine carcinosarcoma and glioblastoma, 6% of colorectal cancer, and 3-4% of melanoma, low grade glioma (LGG), stomach, and cervical cancers[5]. Additionally, biallelic loss of PIK3R1 is observed in 3-4% of ovarian and prostate cancers[5].

Potential relevance: Currently, no therapies are approved for PIK3R1 aberrations.

RAD51B deletion

RAD51 paralog B

Background: The RAD51B gene encodes the RAD51 paralog B protein, a member of the RAD51 recombinase family that also includes RAD51, RAD51C (RAD51L2), RAD51D (RAD51L3), XRCC2, and XRCC3 paralogs. The RAD51 family of proteins are involved in homologous recombination repair (HRR) and DNA repair of double-strand breaks (DSB)[130]. RAD51B associates with other RAD51 paralogs to form RAD51B-RAD51C-RAD51D-XRCC2 (BCDX2) complex[131]. The BCDX2 complex binds single- and double-stranded DNA to hydrolyze ATP[132]. RAD51B is a tumor suppressor gene. Loss of function mutations in RAD51B are implicated in the BRCAness phenotype, which is characterized by a defect in HRR mimicking BRCA1 or BRCA2 loss[41,133]. Biallelic expression of RAD51B is required for chromosomal integrity and haploinsufficiency leads to aberrant HRR resulting in centrosome fragmentation, aneuploidy, and mild hypersensitivity to DNA-damaging agents[134]. Genetic variation within the RAD51B locus on 14q24.1 is significantly associated with familial breast cancer risk[135].

Alterations and prevalence: Somatic mutations in RAD51B are observed in up to 3% of uterine cancer[5,6]. Loss of function mutations in RAD51B are rare, but variation within the RAD51B locus is significantly associated with familial breast cancer risk[135].

Potential relevance: The PARP inhibitor, olaparib[69] is approved (2020) for metastatic castration-resistant prostate cancer (mCRPC) with deleterious or suspected deleterious, germline or somatic mutations in HRR genes that includes RAD51B. In 2022, the FDA granted fast track designation to the small molecule inhibitor, pidnarulex[136], for BRCA1/2, PALB2, or other homologous recombination deficiency (HRD) mutations in breast and ovarian cancers.

TCF7L2 deletion

transcription factor 7 like 2

Background: TCF7L2 encodes the transcription factor 7 like 2, a key component of the WNT signaling pathway[1,313]. 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[313,314,315]. TCF7L2 is also responsible for the regulation of cell cycle inhibitors, including CDKN2C and CDKN2D, thereby influencing cell cycle progression[313]. 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[313].

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[5,6]. 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[5,6].

Biomarker Descriptions (continued)

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

TP53 p.(R158G) c.472C>G

tumor protein p53

Background: The TP53 gene encodes the tumor suppressor protein p53, which binds to DNA and activates transcription in response to diverse cellular stresses to induce cell cycle arrest, apoptosis, or DNA repair[1]. In unstressed cells, TP53 is kept inactive by targeted degradation via MDM2, a substrate recognition factor for ubiquitin-dependent proteolysis[372]. Alterations in TP53 are required for oncogenesis as they result in loss of protein function and gain of transforming potential[373]. Germline mutations in TP53 are the underlying cause of Li-Fraumeni syndrome, a complex hereditary cancer predisposition disorder associated with early-onset cancers[374,375].

Alterations and prevalence: TP53 is the most frequently mutated gene in the cancer genome with approximately half of all cancers experiencing TP53 mutations. Ovarian, head and neck, esophageal, and lung squamous cancers have particularly high TP53 mutation rates (60-90%)[5,6,140,376,377,378]. Approximately two-thirds of TP53 mutations are missense mutations and several recurrent missense mutations are common, including substitutions at codons R158, R175, Y220, R248, R273, and R282[5,6]. Invariably, recurrent missense mutations in TP53 inactivate its ability to bind DNA and activate transcription of target genes[379,380,381,382]. Alterations in TP53 are also observed in pediatric cancers[5,6]. Somatic mutations are observed in 53% of non-Hodgkin lymphoma, 24% of soft tissue sarcoma, 19% of glioma, 13% of bone cancer, 9% of B-lymphoblastic leukemia/lymphoma, 4% of embryonal tumors, 3% of Wilms tumor and leukemia, 2% of T-lymphoblastic leukemia/lymphoma, and less than 1% of peripheral nervous system cancers (5 in 1158 cases)[5,6]. Biallelic loss of TP53 is observed in 10% of bone cancer, 2% of Wilms tumor, and less than 1% of B-lymphoblastic leukemia/lymphoma (2 in 731 cases) and leukemia (1 in 250 cases)[5,6].

Potential relevance: The small molecule p53 reactivator, PC14586[383] (2020), received a fast track designation by the FDA for advanced tumors harboring a TP53 Y220C mutation. The FDA has granted fast track designation to the p53 reactivator, eprenetapopt[384], (2019) and breakthrough designation[385] (2020) in combination with azacitidine or azacitidine and venetoclax for acute myeloid leukemia patients (AML) and myelodysplastic syndrome (MDS) harboring a TP53 mutation, respectively. In addition to investigational therapies aimed at restoring wild-type TP53 activity, compounds that induce synthetic lethality are also under clinical evaluation[386,387]. TP53 mutation are a diagnostic marker of SHH-activated, TP53-mutant medulloblastoma[192]. TP53 mutations confer poor prognosis and poor risk in multiple blood cancers including AML, MDS, myeloproliferative neoplasms (MPN), and chronic lymphocytic leukemia (CLL), and acute lymphoblastic leukemia (ALL)[28,31,207,208,209,388]. In mantle cell lymphoma, TP53 mutations are associated with poor prognosis when treated with conventional therapy including hematopoietic cell transplant[389]. Mono- and bi-allelic mutations in TP53 confer unique characteristics in MDS, with multi-hit patients also experiencing associations with complex karyotype, few co-occurring mutations, and high-risk disease presentation as well as predicted death and leukemic transformation independent of the IPSS-R staging system[390].

XRCC3 deletion

X-ray repair cross complementing 3

Background: The XRCC3 gene encodes the X-ray cross complementing 3 protein, a member of the RAD51 recombinase family that also includes RAD51, RAD51C, RAD51D, and XRCC2 paralogs[1,194]. XRCC3 complexes with RAD51C to form the CX3 complex, which functions in strand exchange and Holliday junction resolution during homologous recombination repair (HRR)[194,195]. XRCC3 may complex with BRCA2, FANCD2, and FANCG to maintain chromosome stability[196].

Alterations and prevalence: Somatic mutations in XRCC3 are observed in 1% of uveal melanoma, colorectal adenocarcinoma, and cervical squamous cell carcinoma[5,6]. Biallelic deletions in XRCC3 are observed in 3% of cholangiocarcinoma and 2% of diffuse large B-cell lymphoma (DLBCL) and bladder urothelial carcinoma[5,6].

Potential relevance: Currently, no therapies are approved for XRCC3 aberrations. Pre-clinical evidence suggests that XRCC3 mutations may demonstrate sensitivity to cisplatin[196].

RIT1 amplification

Ras like without CAAX 1

Background: The RIT1 gene encodes the ras-like without CAAX1 protein[1]. RIT1 is a member of the Ras family, possessing intrinsic GTP hydrolysis activity[98]. Specifically, RIT1 is ubiquitously expressed and plays a role in neuron survival following oxidative stress and dendritic cell retraction[98,99,100]. RIT1 mutations have been shown to activate PI3K and MEK signaling pathways and likely promotes tumorigenesis[101]. Hereditary mutations in RIT1 lead to constitutive activation of RAS and MAPK pathways resulting in Noonan syndrome, a type of RASopathy[101,102].

Biomarker Descriptions (continued)

Alterations and prevalence: Somatic mutations in RIT1 are observed in 3% of cholangiocarcinoma, 2% of uterine corpus endometrial carcinoma and lung adenocarcinoma, and 1% of cervical squamous cell carcinoma, skin cutaneous melanoma, and acute myeloid leukemia (AML)[5,6]. Amplifications in RIT1 are observed in 14% of uterine carcinosarcoma, 11% of liver hepatocellular and cholangiocarcinoma, 8% of lung adenocarcinoma, breast invasive carcinoma, uterine corpus endometrial carcinoma, and 6% of ovarian serous cystadenocarcinoma[5,6].

Potential relevance: Currently, no therapies are approved for RIT1 aberrations.

TGFBR2 deletion

transforming growth factor beta receptor 2

Background: TGFBR2 encodes transforming growth factor beta receptor 2[1]. Along with TGFBR1 and TGFBR3, TGFBR2 is a member of the TGF-beta receptor family[47]. Both TGFBR1 and TGFBR2 function as serine/threonine and tyrosine kinases, whereas TGFBR3 does not possess any kinase activity[47]. TGFBR1 heterodimerizes with TGFBR2 and activates ligand binding of TGF-beta cytokines namely TGFB1, TGFB2, and TGFB3[47]. Heterodimerization with TGFBR2 enables TGFBR1 to phosphorylate downstream SMAD2/3, which leads to activation of SMAD4[48]. This process regulates various signaling pathways implicated in cancer initiation and progression, including epithelial to mesenchymal transition (EMT) and apoptosis[49,50,51].

Alterations and prevalence: Somatic mutations in TGFBR2 are observed in 5% of esophageal adenocarcinoma, and head and neck squamous cell carcinoma, 4% of pancreatic adenocarcinoma, stomach adenocarcinoma, uterine corpus endometrial carcinoma, colorectal adenocarcinoma, and cholangiocarcinoma[5,6]. Biallelic deletion of TGFRB2 is observed in 3% of kidney renal clear cell carcinoma and 2% of stomach adenocarcinoma and head and neck squamous cell carcinoma[5,6].

Potential relevance: Currently, no therapies are approved for TGFBR2 aberrations.

DOCK3 deletion

dedicator of cytokinesis 3

Background: The DOCK3 gene encodes dedicator of cytokinesis 3, a member of the DOCK (dedicator of cytokinesis) family of guanine nucleotide exchange factors (GEFs)[1]. As a GEF, DOCK3 functions by catalyzing the exchange of GDP for GTP, and activates the G protein, Rac1, thereby facilitating RAC1 mediated signaling[391]. Consequently, DOCK3 has been observed to facilitate the regulation of several cellular processes including axonal outgrowth, cytoskeletal organization, and cell adhesion[1,392,393]. Unlike other GEFs found to be altered in cancer, DOCK3 has been shown to exhibit tumor suppressor like properties through inhibition of β-catenin/WNT signaling[394,395]. Additionally knockdown of DOCK3 has been observed to inhibit tumor cell adhesion, migration, and invasion in non-small cell lung cancer cell lines, further supporting a tumor suppressive role for DOCK3[393].

Alterations and prevalence: Somatic mutations in DOCK3 are observed in 21% of skin cutaneous melanoma, 16% of uterine corpus endometrial carcinoma, 12% of stomach adenocarcinoma, 9% of colorectal adenocarcinoma, 6% of esophageal adenocarcinoma, 4% of sarcoma, and lung adenocarcinoma, 3% of bladder urothelial carcinoma, lung squamous cell carcinoma, cervical squamous cell carcinoma, and 2% of diffuse large B-cell lymphoma, pancreatic adenocarcinoma, head and neck squamous cell carcinoma, kidney renal papillary cell carcinoma, ovarian serous cystadenocarcinoma, liver hepatocellular carcinoma, and kidney chromophobe[5,6]. Biallelic loss of DOCK3 is observed in 4% of diffuse large B-cell lymphoma, 3% of esophageal adenocarcinoma and kidney renal clear cell carcinoma, and 2% of sarcoma[5,6].

Potential relevance: Currently, no therapies are approved for DOCK3 aberrations.

MAP3K1 deletion

mitogen-activated protein kinase kinase kinase 1

Background: The MAP3K1 gene encodes the mitogen-activated protein kinase kinase kinase 1, also known as MEKK1[1]. Activation of MAPK proteins occurs through a kinase signaling cascade[259,260,262]. Specifically, MAP3Ks are responsible for phosphorylation of MAP2K family members[259,260,262]. Once activated, MAP2Ks are responsible for the phosphorylation of various MAPK proteins whose signaling is involved in several cellular processes including cell proliferation, differentiation, and inflammation[259,260,262]. MAP3K1 is known to exist in two protein configurations, including a full length and an N-terminal truncated form possessing an intact kinase domain[349]. The full length MAP3K1 is observed to regulate cell survival and migration, whereas the truncated form is observed to promote apoptosis[349]. MAP3K1 also regulates JNK activation and contains an E3 ligase domain responsible for ubiquitylating c-JUN and MAPK1/MAPK3[349].

Alterations and prevalence: Somatic mutations in MAP3K1 are observed in 13% of uterine corpus endometrial carcinoma, 8% of breast invasive carcinoma, 5% of colorectal adenocarcinoma, and 4% of esophageal carcinoma and skin cutaneous melanoma[5,6]. MAP3K1

Biomarker Descriptions (continued)

mutations are most frequently observed in hormone receptor positive breast cancer as opposed to other subtypes[349]. MAP3K1 biallelic deletions have been observed in 4% of ovarian serous cystadenocarcinoma, and prostate adenocarcinoma[5,6].

Potential relevance: Currently, no therapies are approved for MAP3K1 aberrations.

RASA1 deletion

RAS p21 protein activator 1

Background: The RASA1 gene encodes the Ras p21 protein activator 1[1]. RASA1 is a member of the RasGAP family, which includes RASA2[83,84]. RASA1 functions as a dual-specificity GTPase activating protein (GAP) by accelerating RAS and RAP GTPase activity and promoting the inactive GDP-bound form[83]. RASA1 activity is influential in several cellular processes including in growth, proliferation, differentiation, and apoptosis[83]. In tumorigenesis, loss of RASA1 function inhibits RAS regulation, leading to activation of the MAPK/MEK/ERK or PI3K/AKT pathways[83]. Mutations or epigenetic inactivation of RASA1 have been observed in diverse cancer types[83].

Alterations and prevalence: Somatic mutations in RASA1 are observed in 11% of uterine corpus endometrial carcinoma, 6% of lung squamous cell carcinoma, 5% of stomach adenocarcinoma and of skin cutaneous melanoma, 4% of colorectal adenocarcinoma, head and neck squamous cell carcinoma, colorectal carcinoma, and uterine carcinosarcoma, and 3% of esophageal adenocarcinoma[5,6]. Biallelic deletions are observed in 4% of ovarian serous cystadenocarcinoma, and 2% of skin cutaneous melanoma[5,6].

Potential relevance: Currently, no therapies are approved for RASA1 aberrations.

ERAP1 deletion

endoplasmic reticulum aminopeptidase 1

Background: The ERAP1 gene encodes the endoplasmic reticulum aminopeptidase 1 protein[1]. ERAP1, and structurally related ERAP2, are zinc metallopeptidases which play a role in antigen processing within the immune response pathway[350,351]. 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[350,352]. ERAP1 has also been shown to be involved in the shedding of cytokine receptors (including TNFR1, IL6-Ra, and type II IL-II receptor) and is observed to be secreted by macrophages, which is believed to enhance phagocytosis[350,353,354]. Mutations in ERAP1 leads to a predisposition for HPV-induced cervical carcinoma[350,355].

Alterations and prevalence: Somatic mutations in ERAP1 are observed in 7% of uterine corpus endometrial carcinoma, 3% of skin cutaneous melanoma and stomach adenocarcinoma, and 2% of diffuse large B-cell lymphoma (DLBCL) and colorectal adenocarcinoma[5,6]. Biallelic deletions are observed in 2% of ovarian serous cystadenocarcinoma and prostate adenocarcinoma, and 1% of colorectal adenocarcinoma, mesothelioma, stomach adenocarcinoma, and esophageal adenocarcinoma[5,6].

Potential relevance: Currently, no therapies are approved for ERAP1 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[350,351]. 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[350,352]. 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[350].

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[5,6]. Deletions are observed in 2% of ovarian serous cystadenocarcinoma, prostate adenocarcinoma, and 1% of colorectal adenocarcinoma, mesothelioma, esophageal adenocarcinoma, and lung squamous cell carcinoma[5,6].

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

Biomarker Descriptions (continued)

TPMT amplification

thiopurine S-methyltransferase

Background: The TPMT gene encodes thiopurine S-methyltransferase, a cytosolic enzyme that methylates aromatic and heterocyclic sulfhydryl compounds such as thiopurines[1,310,311]. TPMT is the major enzyme responsible for the metabolic inactivation of thiopurine chemotherapeutic drugs used in the treatment of acute lymphoblastic leukemia (ALL), including, 6-mercaptopurine, 6-thioguanine, and azathioprine[310,311,312]. Inherited TPMT polymorphisms, including TPMT*2, TPMT*3A, TPMT*3B, TPMT*3C, and TPMT*8, can result in TPMT deficiency, which is characterized by impaired enzymatic activity and confers an increased risk of severe toxicity to thiopurine drugs due to an increase in systemic drug exposure[310,312].

Alterations and prevalence: Somatic mutations in TPMT are observed in 2% of uterine corpus endometrial carcinoma and colorectal adenocarcinoma[5,6]. Biallelic loss of TPMT is observed in 1% of stomach adenocarcinoma, esophageal adenocarcinoma, and adrenocortical carcinoma[5,6]. Amplification of TPMT is observed in 7% of ovarian serous cystadenocarcinoma, 6% of bladder urothelial carcinoma, 4% of diffuse large B-cell lymphoma, uveal melanoma, uterine carcinosarcoma, and skin cutaneous melanoma, 3% of cholangiocarcinoma, and 2% of breast invasive carcinoma, uterine corpus endometrial carcinoma, and liver hepatocellular carcinoma[5,6].

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

HLA-B deletion

major histocompatibility complex, class I, B

Background: The HLA-B gene encodes the major histocompatibility complex, class I, B[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[282]. MHC class I molecules are heterodimers composed of two polypeptide chains, α and B2M[283]. 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[284,285,286]. Downregulation of MHC class I promotes tumor evasion of the immune system, suggesting a tumor suppressor role for HLA-B[287].

Alterations and prevalence: Somatic mutations in HLA-B are observed in 10% of diffuse large B-cell lymphoma (DLBCL), 5% of cervical squamous cell carcinoma and stomach adenocarcinoma, 4% of head and neck squamous cell carcinoma and colorectal adenocarcinoma, 3% of uterine cancer, and 2% of esophageal adenocarcinoma and skin cutaneous melanoma[5,6]. Biallelic loss of HLA-B is observed in 5% of DLBCL[5,6].

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

JAK2 deletion

Janus kinase 2

Background: The JAK2 gene encodes Janus kinase 2, a non-receptor protein tyrosine kinase (PTK)[1,12]. JAK2 is a member of the Janus kinase (JAK) family, which includes JAK1, JAK2, JAK3, and TYK2[12]. Janus kinases are characterized by the presence of a second phosphotransferase-related or pseudokinase domain immediately N-terminal to the PTK domain[13]. JAK kinases function with signal transducer and activator of transcription (STAT) proteins to facilitate intracellular signal transduction required for cytokine receptor and interferon-alpha/beta/gamma signaling[13,14,15]. Since JAK2 functions in interferon receptor signaling, inactivation of JAK2 is proposed to inhibit the presentation of tumor antigens and contribute to immune evasion[16,17].

Alterations and prevalence: Clonal expansion of hematopoietic cells in myeloproliferative neoplasms (MPNs) is associated with loss of heterozygosity on chromosome 9p and subsequently the acquisition of a dominant somatic gain-of-function V617F mutation in the pseudokinase domain of JAK2[18,19]. The JAK2 V617F mutation is rarely observed in acute myeloid leukemia (AML)[20,21]. Mutations in the pseudokinase domain of JAK2, including R683G, have been detected in 8% of ALL[22,23]. JAK2 fusions are observed in myeloid and lymphoid leukemias with partner genes including TEL, PCM1, and BCR[24,25,26,27]. JAK2 fusions are infrequently observed in solid tumors[5]. As with JAK1, truncating mutations in JAK2 are common in solid tumors and particularly enriched in uterine cancers[5]. JAK2 is amplified in 4% of sarcoma, diffuse large B-cell lymphoma, and head and neck squamous cell carcinoma, 3% of ovarian serous cystadenocarcinoma, and 2% of esophageal adenocarcinoma, uterine corpus endometrial carcinoma, stomach adenocarcinoma, bladder urothelial carcinoma, and uterine carcinosarcoma[5,6]. Alterations in JAK2 are also observed in pediatric cancers[5,6]. Somatic mutations are observed in 6% of B-lymphoblastic leukemia/lymphoma, 3% of soft tissue sarcoma, 2% of T-lymphoblastic leukemia/lymphoma, and less than 1% of leukemia (3 in 354 cases), bone cancer (2 in 327 cases), glioma (1 in 297 cases), Wilms tumor (1 in 710 cases), and peripheral nervous system tumors (1 in 1158 cases)[5,6]. JAK2 fusions are observed in 10% of B-lymphoblastic leukemia/

Biomarker Descriptions (continued)

lymphoma and 1% of leukemia (1 in 107 cases)[5,6]. JAK2 is amplified in 1% of Wilms tumor (2 in 136 cases) and less than 1% of B-lymphoblastic leukemia/lymphoma (4 in 731 cases)[5,6].

Potential relevance: Currently, no therapies are approved for JAK2 aberrations. JAK2 V617F and JAK2 exon 12 mutations are considered major diagnostic criteria of polycythemia vera (PV)[28,29]. Ruxolitinib[30] (2011) is a JAK1/2 inhibitor FDA approved for PMF and PV, although specific JAK2 alterations are not indicated. Other JAK inhibitors including tofacitinib (2012) and baricitinib (2018) are approved for the treatment of rheumatoid arthritis. JAK2 mutations and fusions are associated with poor risk in acute lymphoblastic leukemia[31]. Clinical cases associated with high tumor mutational burden (TMB) but failure to respond to anti-PD1 therapy were associated with loss of function mutations in JAK1/2[32]. Some case studies report efficacy with ruxolitinib in myeloid and lymphoid leukemias, although duration of complete response was limited[24,25,26,27].

LARP4B deletion

La ribonucleoprotein domain family member 4B

Background: The LARP4B gene encodes the La ribonucleoprotein 4B protein[1]. La-related proteins (LARPs) are RNA binding proteins and can be split into 5 families, LARP1, La, LARP4, LARP6, and LARP7[35]. Along with LARP4, LARP4B is part of the LARP4 family and is observed to bind AU-rich regions in the 3' untranslated regions of mRNAs[35]. In glioma, LARP4B has been observed to induce mitotic arrest and apoptosis in vitro, supporting a tumor suppressor role for LARP4B[36].

Alterations and prevalence: Somatic mutations in LARP4B are observed in 8% of uterine corpus endometrial carcinoma, 7% of stomach adenocarcinoma, 5% of colorectal adenocarcinoma and skin cutaneous melanoma, 4% of uterine carcinosarcoma, and 2% of lung adenocarcinoma, lung squamous cell carcinoma, esophageal adenocarcinoma, and bladder urothelial carcinoma[5,6]. Biallelic deletions in LARP4B are observed in 4% of diffuse large B-cell lymphoma (DLBCL), 3% of sarcoma and testicular germ cell tumors, and 2% of mesothelioma, stomach adenocarcinoma, and lung squamous cell carcinoma[5,6].

Potential relevance: Currently, no therapies are approved for LARP4B aberrations.

GATA3 deletion

GATA binding protein 3

Background: The GATA3 gene encodes GATA binding protein 3, a member of the GATA family of zinc-finger transcription factors, which also includes GATA1, GATA2, and GATA4-6[1,214,215]. The GATA family regulates transcription of many genes by binding to the DNA consensus sequence T/A(GATA)A/G[215]. GATA3 functions in the differentiation of immune cells and tissue development[216,217]. As GATA3 also functions in luminal cell development and cell function, it is a common marker of the gene expression profile in luminal breast cancer[216].

Alterations and prevalence: Somatic mutations in GATA3 are observed in 12% of breast invasive carcinoma, 4% of uterine corpus endometrial carcinoma and stomach adenocarcinoma, and 3% of colorectal adenocarcinoma and skin cutaneous melanoma[5,6]. Biallelic loss of GATA3 is observed in 2% of diffuse large B-cell lymphoma (DLBCL)[5,6]. Alterations in GATA3 are also observed in the pediatric population[6]. Somatic mutations are observed in 6% of non-Hodgkin lymphoma (1 in 17 cases), 3% of soft tissue sarcoma (1 in 38 cases), 2% of T-lymphoblastic leukemia/lymphoma (1 in 41 cases) and Hodgkin lymphoma (1 in 61 cases), and less than 1% of bone cancer (3 in 327 cases), embryonal tumor (3 in 332 cases), and leukemia (1 in 311 cases)[6]. Biallelic deletion is observed in 1% of peripheral nervous system cancers (1 in 91 cases), less than 1% of leukemia (1 in 250 cases) and B-lymphoblastic leukemia/lymphoma (1 in 731 cases)[6].

Potential relevance: Currently, no therapies are approved for GATA3 aberrations. Low GATA3 expression is associated with invasion and poor prognosis in breast cancer[216,218].

MAPK8 deletion

mitogen-activated protein kinase 8

Background: The MAPK8 gene encodes the mitogen-activated protein kinase 8, also known as JNK1[1]. MAPK8 is involved in the JNK signaling pathway along with MAP3K4, MAP3K12, MAP2K4, MAP2K7, MAPK9, and MAPK10[259,260,261]. Activation of MAPK proteins occurs through a kinase signaling cascade[259,260,262]. Specifically, MAP3Ks are responsible for phosphorylation of MAP2K family members[259,260,262]. Once activated, MAP2Ks are responsible for the phosphorylation of various MAPK proteins whose signaling is involved in several cellular processes including cell proliferation, differentiation, and inflammation[259,260,262].

Biomarker Descriptions (continued)

Alterations and prevalence: Somatic mutations in MAPK8 are observed in 4% of uterine corpus endometrial carcinoma, 3% of skin cutaneous melanoma, and 2% of colorectal adenocarcinoma[5,6]. Biallelic deletions are observed in 1% of bladder urothelial carcinoma, esophageal adenocarcinoma, adrenocortical carcinoma, and skin cutaneous melanoma[5,6].

Potential relevance: Currently, no therapies are approved for MAPK8 aberrations.

ARID5B deletion

AT-rich interaction domain 5B

Background: The ARID5B gene encodes the AT-rich interaction domain 5B protein[1]. ARID5B, also known as MRF2, belongs to the ARID superfamily that also includes ARID1A, ARID1B, and ARID2[33,34]. ARID5B forms a complex with PHF2, which is capable of histone demethylation leading to transcriptional activation of target genes[34]. ARID5B is known to be essential for the development of hematopoietic cells[34]. Several single-nucleotide polymorphisms (SNPs) in ARID5B have been associated with susceptibility of acute lymphoblastic leukemia (ALL)[34].

Alterations and prevalence: Somatic mutations in ARID5B are observed in 15% of uterine corpus endometrial carcinoma, 6% of skin cutaneous melanoma, 5% of diffuse large B-cell lymphoma, 4% of stomach adenocarcinoma[5,6]. Biallelic loss of ARID5B is observed in 1% of kidney chromophobe, lung squamous cell carcinoma, and skin cutaneous melanoma[5,6].

Potential relevance: Currently, no therapies are approved for ARID5B aberrations.

CYP2C9 deletion

cytochrome P450 family 2 subfamily C member 9

Background: The CYP2C9 gene encodes cytochrome P450 family 2 subfamily C member 9, a member of the cytochrome P450 superfamily of proteins[1]. The cytochrome P450 proteins are monooxygenases that play important roles in the biotransformation of xenobiotics and carcinogens, and the synthesis of cholesterol, steroids and other lipids[1,263]. CYP2C9 catalyzes the oxidation of arachidonic acid to epoxyeicosatrienoic acids (EETs) and also inactivates several NSAIDs, including cyclooxygenase inhibitors and chemopreventive agents[264,265]. EETs are mitogenic and pro-angiogenic signaling molecules that have been shown to promote cancer cell growth and metastasis in vitro[264,265,266]. CYPC29 overexpression is found in several cancers supporting the role of EETs in vascularization and tumorigenesis[263,264,265,266]. Inherited CYP2C9 polymorphisms, including CYP2C9*2 and CYP2C9*3, can result in attenuated catalytic efficiency and reduced EETs leading to reduced proliferation and migration of cancer cells and less vascularized tumors[264]. Depending on the cancer type and treatment, individuals with these polymorphisms may have slower drug metabolism and therefore, altered drug responses which may make them more protected or more at risk of disease[264].

Alterations and prevalence: Somatic mutations in CYP2C9 are observed in 12% of skin cutaneous melanoma, 3% of uterine corpus endometrial carcinoma, and 2% of cervical squamous cell carcinoma, esophageal adenocarcinoma, lung adenocarcinoma, and kidney chromophobe[5,6]. Biallelic loss of CYP2C9 is observed in 2% diffuse large B-cell lymphoma and prostate adenocarcinoma[5,6]. Amplification of CYP2C9 is observed in 1% of pheochromocytoma, paraganglioma, and ovarian serous cystadenocarcinoma[5,6].

Potential relevance: Currently, no therapies are approved for CYP2C9.

SUFU deletion

SUFU negative regulator of hedgehog signaling

Background: SUFU encodes the SUFU negative regulator of hedgehog signaling protein, a protein integrally involved in inhibition of hedgehog pathway signaling[1]. During early human development, hedgehog pathway activation of the Gli/Ci family of zinc finger transcription factors is known to drive both cell proliferation and differentiation[197]. SUFU is capable of interacting and complexing with GLI1 and GLI2, thereby regulating transactivation of GLI1 and GLI2 target genes and inhibiting hedgehog pathway signaling[198,199]. Aberrant activation of the hedgehog signaling pathway has been implicated in several cancer types, supporting a tumor suppressor role for SUFU[200]. Germline mutations in SUFU confer a strong predisposition to medulloblastoma, particularly the desmoplastic/nodular subtype, and is observed almost exclusively in children less than 3 years of age[201].

Alterations and prevalence: Somatic mutations are observed in 4% endometrial carcinoma, 2% esophageal adenocarcinoma, and stomach adenocarcinoma[6]. Biallelic deletion of SUFU is observed in 2% of mesothelioma, diffuse large cell B-cell lymphoma, and prostate adenocarcinoma[6].

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

Biomarker Descriptions (continued)

DICER1 deletion

dicer 1, ribonuclease III

Background: The DICER1 gene encodes the dicer 1, ribonuclease III protein[1]. DICER1 is a member of the ribonuclease (RNase) III family that also includes DROSHA[276]. Both DICER and DROSHA are responsible for the processing of precursor non-coding RNA (primary miRNA) into micro-RNA (miRNA)[276,277]. Following primary miRNA processing to hairpin precursor miRNA (pre-miRNA) by DROSHA and DGCR8, pre-miRNA is then cleaved by DICER1 resulting in the production of mature miRNA[276]. Once processed, mature miRNA is capable of post-transcriptional gene repression by recognizing complimentary target sites on messenger RNA (mRNA)[276,277]. miRNAs are frequently dysregulated in cancer, potentially through DGCR8, DICER1, or DROSHA aberrations that impact miRNA processing[277,278,279,280]. Germline DICER1 mutations result in DICER1 syndrome, a rare genetic disorder that predisposes affected individuals to tumor development[281].

Alterations and prevalence: Somatic mutations in DICER1 are observed in 13% of uterine corpus endometrial carcinoma, 11% of skin cutaneous melanoma, and 4% of colorectal adenocarcinoma, bladder urothelial carcinoma, and uterine carcinosarcoma[5,6]. Biallelic loss of DICER1 is observed in 3% of cholangiocarcinoma and 2% kidney chromophobe[5,6].

Potential relevance: Currently, no therapies are approved for DICER1 aberrations.

PDIA3 deletion

protein disulfide isomerase family A member 3

Background: The PDIA3 gene encodes the protein disulfide isomerase family A member 3[1]. PDIA3 is a member of the protein disulfide isomerase (PDI) gene family, and acts as an enzymatic chaperone for reconstructing misfolded proteins[55]. PDIA3 has also been identified as being involved EGFR regulation, mTOR signaling, and associated with the major histocompatibility complex (MHC) protein loading complex (PLC)[56]. Deregulation of PDIA3, including both overexpression and loss, has been observed in several cancer types, suggesting that PDIA3 may exhibit differing roles depending on the tumor type[56,57,58].

Alterations and prevalence: Somatic mutations in PDIA3 are observed in 5% of uterine corpus endometrial carcinoma, 2% of colorectal adenocarcinoma, skin cutaneous melanoma, and 1% of stomach adenocarcinoma, bladder urothelial carcinoma, lung adenocarcinoma, pancreatic adenocarcinoma, and glioblastoma multiforme[5,6]. Deletions in PDIA3 are observed in 6% of diffuse large B-cell lymphoma 5% of mesothelioma, and 2% of lung adenocarcinoma, and ovarian serous cystadenocarcinoma[5,6].

Potential relevance: Currently, no therapies are approved for PDIA3 aberrations. Overexpression of PDIA3 in hepatocellular carcinoma and colon cancer is associated with advanced disease and poor prognosis[55]. Conversely, PDIA3 loss is correlated with aggressive disease and poor survival in gastric cancer and head and neck cancer[57,58].

CYLD deletion

CYLD lysine 63 deubiquitinase

Background: The CYLD gene encodes CYLD lysine 63 deubiquitinase, which is a deubiquitinating enzyme (DUB) and a member of the ubiquitin-specific protease (USP) family of deubiquitinases[1,7]. DUBs are responsible for protein deubiquitination, thereby counter-regulating the post-transcriptional ubiquitin modification of proteins within the cell[8]. CLYD contains a USP domain with a catalytic triad formed by Cys601, His871, and Asp889 that selectively hydrolyses K63-linked ubiquitin chains from signaling molecules and regulates cell survival, proliferation, and tumorigenesis[9,10]. CYLD plays a tumor suppressor role by negatively regulating NF-κB activation by deubiquitinating multiple NF-κB signaling components, including NEMO, Tak1, TRAF2, TRAF6, and RIP1[11]. Mutations in CYLD were originally identified in patients with familial cylindromatosis, a genetic condition that predisposes patients to the development of skin appendage tumors[10,11]. CYLD has also been found to be downregulated in melanoma, salivary gland tumors, head and neck cancer, colon and hepatocellular carcinoma, cervical cancer, lung cancer, and renal cell carcinoma[10].

Alterations and prevalence: Somatic mutations in CYLD have been observed in 6% of uterine corpus endometrial carcinoma, 3% of stomach adenocarcinoma, skin cutaneous melanoma, colorectal adenocarcinoma, head and neck squamous cell carcinoma, and lung squamous cell carcinoma, and 2% of thymoma, esophageal adenocarcinoma, lung adenocarcinoma, and kidney chromophobe[5,6]. Biallelic loss of CYLD has been observed in 2% of prostate adenocarcinoma, diffuse large B-cell lymphoma, sarcoma, and uterine carcinosarcoma[5,6].

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

Biomarker Descriptions (continued)

CBFB deletion

core-binding factor beta subunit

Background: The CBFB gene encodes the core-binding factor subunit beta, a member of the PEBP2/CBF transcription factor family[1]. CBFB is capable of heterodimerization with the RUNX protein family (RUNX1, RUNX2, and RUNX3) which results in the formation of the core binding factor (CFB) complex, a transcription factor complex responsible for the regulation of many critical functions in hematopoiesis and osteogenesis[329,330,331]. Although possessing no DNA-binding activity, CBFB has been observed to enhance stability and transcriptional activity of RUNX proteins, thereby exhibiting a critical role in RUNX mediated transcriptional regulation[330,331]. In cancer, mutations in CBFB have been implicated in decreased protein stability and loss of function, supporting a tumor suppressor role for CBFB[331]

Alterations and prevalence: Somatic mutations in CBFB are observed in 2% of diffuse large B-cell lymphoma, breast invasive carcinoma, and uterine corpus endometrial carcinoma[5]. Biallelic deletions in CBFB are found in 2% of ovarian serous cystadenocarcinoma, prostate adenocarcinoma, and breast invasive carcinoma[5]. Translocations including inv(16) and t(16;16) have been observed to be recurrent in de novo AML, occurring in 7-10% of patients, and have been associated with the AML M4 with bone barrow eosinophilia (M4Eo) subtype[332]. Translocations often result in CBFB::MYH11 fusion, which can exist as one of multiple transcripts, depending on the exons fused[332].

Potential relevance: Currently, no therapies are approved for CBFB aberrations. In AML, CBFB translocations, including inv(16) and t(16;16) which result in CBFB::MYH11 fusion, are associated with favorable prognosis and define a distinct molecular subtype of AML according to the World Health Organization (WHO)[29,208,209].

CTCF deletion

CCCTC-binding factor

Background: The CTCF gene encodes the CCCTC-binding factor, a member of the BORIS + CTCF gene family[1]. CTCF promotes the formation of cohesion-mediated loops, the formation of which organizes chromatin into self-interacting topologically associated domains (TADs) and influences gene expression[108]. Additionally, CTCF has been observed to function as a transcription factor through the binding of transcriptional start sites (TSS), but may also play a role in transcriptional repression[108,109,110]. CTCF mutations lead to disruption of TAD boundaries which alters gene expression and may promote oncogenesis[108].

Alterations and prevalence: Somatic mutations in CTCF are observed in 25% of uterine corpus endometrial carcinoma, 5% of stomach adenocarcinoma and uterine carcinosarcoma, 4% of colorectal adenocarcinoma, and 3% of bladder urothelial carcinoma, head and neck squamous cell carcinoma, and cholangiocarcinoma[5,6].

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

CDH1 deletion

cadherin 1

Background: The CDH1 gene encodes epithelial cadherin or E-cadherin, a member of the cadherin superfamily that includes the classical cadherins: neural cadherin (N-cadherin), retinal cadherin (R-cadherin), and placental cadherin (P-cadherin)[1,365]. E-cadherin proteins, composed of 5 extracellular cadherin repeats, a single transmembrane domain, and conserved cytoplasmic tail, are calcium-dependent transmembrane glycoproteins expressed in epithelial cells[1]. Extracellular E-cadherin monomers form homodimers with those on adjacent cells to form adherens junctions. Adherens junctions are reinforced by intracellular complexes formed between the cytoplasmic tail of E-cadherin and catenins, proteins which directly anchor cadherins to actin filaments[366]. E-cadherin is a critical tumor suppressor and when lost, results in epithelial-mesenchymal transition (EMT), anchorage-independent cell growth, loss of cell polarity, and tumor metastasis[367,368]. Germline mutations in CDH1 are enriched in a rare autosomal-dominant genetic malignancies such as hereditary diffuse gastric cancer, lobular breast cancer, and colorectal cancer[369].

Alterations and prevalence: Mutations in CDH1 are predominantly missense or truncating and have been observed to result in loss of function[5,6,370,371]. In cancer, somatic mutation of CDH1 is observed in 12% of invasive breast carcinoma, 10% of stomach adenocarcinoma, 7% of uterine corpus endometrial carcinoma, 4% of colorectal adenocarcinoma and skin cutaneous melanoma, 3% of bladder urothelial carcinomas, and 2% of lung squamous cell and liver hepatocelluar carcinomas[5,6]. Biallelic deletion of CDH1 is observed in 3% of prostate adenocarcinoma and ovarian serous cystadenocarcinoma, and 2% of esophageal adenocarcinoma, diffuse large B-cell lymphoma, and breast invasive carcinoma[5,6].

Potential relevance: Currently, no therapies are approved for CDH1 aberrations.

Biomarker Descriptions (continued)

ZFHX3 deletion

zinc finger homeobox 3

Background: ZFHX3 encodes zinc finger homeobox 3, a large transcription factor composed of several DNA binding domains, including seventeen zinc finger domains and four homeodomains[1,288,289]. Functionally, ZFHX3 is found to be necessary for neuronal and myogenic differentiation[289,290]. ZFHX3 is capable of binding and repressing transcription of α-fetoprotein (AFP), thereby negatively regulating the expression of MYB and cancer cell growth[291,292,293,294,295]. In addition, ZFHX3 has been observed to be altered in several cancer types, supporting a tumor suppressor role for ZFHX3[291,294,296,297].

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

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

PRKACA amplification

protein kinase cAMP-activated catalytic subunit alpha

Background: The PRKACA gene encodes the protein kinase cAMP-activated catalytic subunit alpha (C-alpha) of protein kinase A (PKA), an inactive tetrameric holoenzyme with two regulatory (R) subunits and two catalytic (C) subunits (namely PRKACA and PRKACB)[1]. PKA is a cAMP-dependent protein kinase involved in the phosphorylation of several downstream targets and an essential regulator of several cell signaling pathways including differentiation, proliferation, and apoptosis[1,103,104]. PKA is activated when the R subunits bind cAMP, which results in the dissociation of active monomeric C subunits and the subsequent phosphorylation of target proteins[1,103]. Aberrations in PRKACA are oncogenic, as they are predicted to abolish the interaction with R subunits leading to cAMP-independent activation of PKA[105]. Germline amplification and somatic mutation of PRKACA are associated with the development and pathogenesis of benign adrenal tumors leading to Cushing syndrome, which is characterized by overproduction of cortisol resulting in metabolic abnormalities[105,106].

Alterations and prevalence: Somatic mutations in PRKACA are predominantly missense and occur in about 2-3% of melanoma, diffuse large B-cell lymphoma, and uterine cancer[5,6]. PRKACA fusions have also been observed in 2% of liver cancer[5,6]. Specifically, PRKACA fusion with DNAJB1 has been observed to be recurrent in fibrolamellar hepatocellular carcinoma, which results in the retention of a functional PRKACA catalytic domain and increased protein levels[103,107]. PRKACA amplification is observed in about 11% of ovarian cancer and 2-3% of adrenocortical carcinoma, sarcoma, and uterine cancer[103,107].

Potential relevance: Currently, no therapies are approved for PRKACA 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[211]. ZRSR2 interacts with components of the pre-spliceosome assembly including SRSF2 and U2AF2/U2AF1 heterodimer[211,212]. 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[211,213].

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[6,207].

Potential relevance: Mutation of ZRSR2 is associated with poor prognosis in myelodysplastic syndromes as well as poor/adverse risk in acute myeloid leukemia (AML)[207,208,209].

Biomarker Descriptions (continued)

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[333,334]. BCOR also associates with class I and II histone deacetylases (HDACs), suggesting an alternate mechanism for BCOR-mediated transcriptional repression independent of BCL6[334]. Genetic alterations in BCOR result in protein dysfunction, which suggests BCOR functions as a tumor suppressor gene[335,336,337].

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)[5,207,338,339]. 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[340,341,342]. Specifically, BCOR::CCNB3 rearrangements define a particular subset of sarcomas with Ewing sarcoma-like morphology known as BCOR::CCNB3 sarcomas (BCS)[343,344]. 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[340].

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[97,345]. Additionally, translocation t(x;22)(p11;q13) resulting in ZC3H7B::BCOR fusion is a useful ancillary diagnostic marker of high-grade endometrial stromal sarcoma[97]. 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[29,207,208,209,338]. 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%)[339]. Additionally, BCOR ITDs and BCOR::EP300 fusion are molecular alterations of significance in pediatric gliomas[346,347].

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[8]. DUBs are responsible for protein deubiquitination, thereby counter-regulating post-transcriptional ubiquitin modification of proteins within the cell[8,46]. 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[1,298]. 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)[298,299,300,301]. In DEAD-box proteins, the DEAD domain interacts with β- and γ-phosphates of ATP through Mg2+ and is required for ATP hydrolysis[298]. DDX3X is involved in several processes including the unwinding of double-stranded RNA, splicing of pre-mRNA, RNA export, transcription, and translation[302,303,304,305,306,307,308,309]. Deregulation of DDX3X has been shown to impact cancer progression by modulating proliferation, metastasis, and drug resistance[302].

Biomarker Descriptions (continued)

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].

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[219]. 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[220]. KDM6A removes methylation of di- and trimethylated histone 3 lysine 27 (H3K27)[219,221]. 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[219]. Mutations in KDM6A lead to activation of the histone methyltransferase, EZH2, resulting in transcriptional repression[219]. KDM6A is believed to function as a tumor suppressor by antagonizing EZH2-mediated transcriptional repression and promoting transcriptional regulation[219,222].

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[222].

RBM10 deletion

RNA binding motif protein 10

Background: RBM10 encodes RNA binding motif protein 10, a member of the RNA binding proteins (RBP) family[1,179]. RBM10 regulates RNA splicing and post-transcriptional modification of mRNA[179,180]. 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[179]. RBM10 has been observed to promote transformation and proliferation in lung cancer, supporting an oncogenic role for RBM10[181,182].

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[1,221]. Methylation of histone lysine and arginine residues functions to regulate transcription and DNA damage response[220]. 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[220,221]. KDM5C alterations result in aberrant H3K4 trimethylation at active replication origins which can lead to stalled DNA replication[348].

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

Biomarker Descriptions (continued)

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.

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[1,79,80]. As a part of the cohesion-core complex, SMC1A plays a crucial role in chromosome segregation during mitosis and meiosis[79,81]. SMC1A also plays a role in cell cycle regulation, DNA damage repair, gene transcription regulation, and genomic organization[79]. SMC1A aberrations, including overexpression, have been observed in several cancer types and have been proposed to promote tumor formation and epithelial to mesenchymal transition[80,82].

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[1,85]. The WNT signaling pathway is responsible for regulating several key components during embryogenesis and has been observed to be involved in tumorigenesis[86,87]. Consequently, the WNT signaling pathway is a target for therapeutic response in various cancer types[87]. The AMER1 gene is located on the X chromosome and is commonly inactivated in Wilms tumor, a pediatric kidney cancer[88]. AMER1 has also been observed to influence cell proliferation, tumorigenesis, migration, invasion, and cell cycle arrest[85].

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)[89].

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[90]. Biallelic deletion of ZMYM3 is observed in 3% of cholangiocarcinoma and 2% of sarcoma and kidney chromophobe[5,6].

Biomarker Descriptions (continued)

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

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[202,203]. Components of the cohesion complex include SMC1A, SMC3, and RAD21, which bind to STAG1/STAG2 paralogs[204,205]. Inactivating mutations in STAG2 contribute to X-linked neurodevelopmental disorders, aneuploidy, and chromosomal instability in cancer[204,206].

Alterations and prevalence: Somatic mutations in STAG2 include nonsense, frameshift, splice site variants[207]. 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[6,207].

Potential relevance: Mutations in STAG2 are associated with poor prognosis and adverse risk in MDS and Acute Myeloid Leukemia[207,208,209]. 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[210].

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[267,268].

Alterations and prevalence: The majority of PHF6 aberrations are nonsense, frameshift (70%), or missense (30%) mutations, which result in complete loss of protein expression[267,269,270,271]. 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)[269,271]. Missense mutations recurrently involve codon C215 and the second zinc finger domain of PHF6[269]. PHF6 mutations are frequently observed in hematologic malignancies from male patients[267,269].

Potential relevance: Somatic mutations in PHF6 are associated with reduced overall survival in AML patients treated with high-dose induction chemotherapy[272].

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

SMARCB1 deletion

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
cabozantinib	✖	✖	✖	○	✖
pazopanib	✖	✖	✖	○	✖
sunitinib	✖	✖	✖	○	✖
nivolumab, ipilimumab	✖	✖	✖	✖	● (II)
tucidinostat, catequentinib, PD-1 Inhibitor, anti-PD-L1 antibody	✖	✖	✖	✖	● (II)
atezolizumab, tiragolumab	✖	✖	✖	✖	● (I/II)
tazemetostat, nivolumab, ipilimumab	✖	✖	✖	✖	● (I/II)

MTAP deletion

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
AMG 193	✖	✖	✖	✖	● (I/II)
TNG-456, abemaciclib	✖	✖	✖	✖	● (I/II)
TNG-462	✖	✖	✖	✖	● (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

MTAP deletion (continued)

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
AMG 193, pembrolizumab	✖	✖	✖	✖	● (I)
GTA-182	✖	✖	✖	✖	● (I)
ISM-3412	✖	✖	✖	✖	● (I)
MRTX-1719	✖	✖	✖	✖	● (I)
PH020-803	✖	✖	✖	✖	● (I)
S-095035	✖	✖	✖	✖	● (I)
SYH-2039	✖	✖	✖	✖	● (I)

CDKN2A deletion

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
palbociclib	✖	✖	✖	✖	● (II)
palbociclib, abemaciclib	✖	✖	✖	✖	● (II)
AMG 193	✖	✖	✖	✖	● (I/II)

NF2 deletion

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

NTRK1 amplification

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
larotrectinib	✖	✖	✖	✖	● (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.

Relevant Therapy Summary (continued)

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

BAP1 deletion

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

CDKN2B deletion

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
palbociclib, abemaciclib	✖	✖	✖	✖	● (II)

DDR2 amplification

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

FANCA deletion

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

FANCM deletion

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

PTEN deletion

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
palbociclib, gedatolisib	✖	✖	✖	✖	● (I)

RAD50 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.

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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