삼광의료재단
서울특별시 서초구 바우뫼로41길 58 (양재동, 선화빌딩)
검사기관 11365200
Tel. 1661-5117
www.smlab.co.kr

Patient Name: 임양희
Gender: F
Sample ID: N25-112

Primary Tumor Site: ovary
Collection Date: 2025.07.11

Sample Cancer Type: Ovarian Cancer

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Report Highlights

12 Relevant Biomarkers
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Relevant Ovarian Cancer Findings

Gene	Finding	Gene	Finding
BRAF	None detected	NTRK1	None detected
BRCA1	None detected	NTRK2	None detected
BRCA2	None detected	NTRK3	None detected
ERBB2	None detected	RET	None detected

Genomic Alteration	Finding
Tumor Mutational Burden	***5.71 Mut/Mb measured***
Genomic Instability	***GIM 6 (Low)***

HRD Status: ***HR Proficient (HRD-)***

Relevant Biomarkers

Tier	Genomic Alteration	Relevant Therapies (In this cancer type)	Relevant Therapies (In other cancer type)	Clinical Trials
IIC	*PIK3CA p.(E545A) c.1634A>C* phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha Allele Frequency: 19.30% Locus: chr3:178936092 Transcript: NM_006218.4	None*	**inavolisib + palbociclib + hormone therapy** [1 / I] **alpelisib + hormone therapy** [1, 2 / II+] **capivasertib + hormone therapy** [1, 2 / II+]	6
IIC	*KRAS p.(G12D) c.35G>A* KRAS proto-oncogene, GTPase Allele Frequency: 66.80% Locus: chr12:25398284 Transcript: NM_033360.4	None*	bevacizumab + chemotherapy [I]	24

*** 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	*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*	9
IIC	*ATM deletion* ATM serine/threonine kinase Locus: chr11:108098341	None*	None*	3
IIC	*CDKN2A deletion* cyclin dependent kinase inhibitor 2A Locus: chr9:21968178	None*	None*	3
IIC	*ATM p.(S1891*) c.5672C>A* ATM serine/threonine kinase Allele Frequency: 73.28% Locus: chr11:108175577 Transcript: NM_000051.4	None*	None*	2
IIC	*NF2 deletion* neurofibromin 2 Locus: chr22:29999923	None*	None*	2
IIC	*ARID1A deletion* AT-rich interaction domain 1A Locus: chr1:27022875	None*	None*	1
IIC	*CDKN2B deletion* cyclin dependent kinase inhibitor 2B Locus: chr9:22005728	None*	None*	1
IIC	*FBXW7 deletion* F-box and WD repeat domain containing 7 Locus: chr4:153243999	None*	None*	1
IIC	*SMAD4 deletion* SMAD family member 4 Locus: chr18:48573387	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

ABRAXAS1 deletion, AXIN1 deletion, CHEK1 deletion, CHEK2 deletion, DPYD p.(M166V) c.496A>G, ERCC4 deletion, FANCA deletion, FANCG deletion, KMT2A deletion, MRE11 deletion, Microsatellite stable, PALB2 deletion, PPP2R2A deletion, RAD51 deletion, SDHB deletion, SLX4 deletion, TSC2 deletion, TNFRSF14 deletion, ERRFI1 deletion, ENO1 deletion, PGD deletion, SPEN deletion, EPHA2 deletion, TET2 deletion, INPP4B deletion, FAT1 deletion, HLA-A deletion, HLA-B deletion, JAK2 deletion, SDHD deletion, MGA deletion, MGA p.(L1764) c.5291T>A, PDIA3 deletion, B2M deletion, CREBBP deletion, CYLD deletion, CBFB deletion, CTCF deletion, CDH1 deletion, NQO1 p.(P187S) c.559C>T, ZFHX3 deletion, DSC3 deletion, DSC1 deletion, SMAD2 deletion, RUNX1 deletion, EP300 deletion, ZRSR2 deletion, BCOR deletion, DDX3X deletion, RBM10 deletion, Tumor Mutational Burden, Genomic Instability (Low)*

Variant Details

DNA Sequence Variants

Gene	Amino Acid Change	Coding	Variant ID	Locus	Allele Frequency	Transcript	Variant Effect
PIK3CA	p.(E545A)	c.1634A>C	COSM12458	chr3:178936092	19.30%	NM_006218.4	missense
KRAS	p.(G12D)	c.35G>A	COSM521	chr12:25398284	66.80%	NM_033360.4	missense
ATM	p.(S1891*)	c.5672C>A	.	chr11:108175577	73.28%	NM_000051.4	nonsense
DPYD	p.(M166V)	c.496A>G	.	chr1:98165091	99.70%	NM_000110.4	missense
MGA	p.(L1764*)	c.5291T>A	.	chr15:42040913	70.76%	NM_001164273.1	nonsense
NQO1	p.(P187S)	c.559C>T	.	chr16:69745145	98.80%	NM_000903.3	missense
CEP44	p.(T351A)	c.1051A>G	.	chr4:175237406	10.64%	NM_001145314.1	missense
PRDM1	p.(A30G)	c.89C>G	.	chr6:106536122	48.77%	NM_001198.4	missense
KMT2C	p.(P860S)	c.2578C>T	.	chr7:151935866	26.05%	NM_170606.3	missense

Copy Number Variations

Gene	Locus	Copy Number	CNV Ratio
SMARCB1	chr22:24129273	0.92	0.54
MTAP	chr9:21802646	1	0.58
ATM	chr11:108098341	1	0.6
CDKN2A	chr9:21968178	0.56	0.39
NF2	chr22:29999923	0.96	0.56
ARID1A	chr1:27022875	0.9	0.54
CDKN2B	chr9:22005728	0.88	0.53
FBXW7	chr4:153243999	0.99	0.57
SMAD4	chr18:48573387	0.93	0.55
ABRAXAS1	chr4:84383635	0.92	0.55
AXIN1	chr16:338145	0.89	0.54
CHEK1	chr11:125496639	1	0.64
CHEK2	chr22:29083868	1	0.63
ERCC4	chr16:14013959	1.01	0.59
FANCA	chr16:89804984	1.05	0.6
FANCG	chr9:35074046	0.99	0.58
KMT2A	chr11:118307146	1	0.58
MRE11	chr11:94153270	1.01	0.59
PALB2	chr16:23614759	1	0.67
PPP2R2A	chr8:26149298	1	0.58
RAD51	chr15:40990871	1.29	0.7

Variant Details (continued)

Copy Number Variations (continued)

Gene	Locus	Copy Number	CNV Ratio
SDHB	chr1:17345303	1.01	0.58
SLX4	chr16:3632292	1.06	0.6
TSC2	chr16:2098579	0.94	0.55
TNFRSF14	chr1:2488070	0.98	0.57
ERRFI1	chr1:8073246	1.07	0.61
ENO1	chr1:8921399	1.02	0.59
PGD	chr1:10459132	0.92	0.54
SPEN	chr1:16174516	1.01	0.58
EPHA2	chr1:16451707	1.05	0.6
TET2	chr4:106155068	1	0.58
INPP4B	chr4:142949914	1.05	0.6
FAT1	chr4:187509708	1.11	0.62
HLA-A	chr6:29910229	1.13	0.63
HLA-B	chr6:31322252	1.24	0.68
JAK2	chr9:5021954	1.13	0.64
SDHD	chr11:111957573	0.83	0.51
MGA	chr15:41961065	1.13	0.63
PDIA3	chr15:44038719	0.94	0.55
B2M	chr15:45003690	0.9	0.54
CREBBP	chr16:3777679	0.94	0.56
CYLD	chr16:50783549	1.11	0.62
CBFB	chr16:67063242	0.86	0.52
CTCF	chr16:67644720	1.02	0.59
CDH1	chr16:68771249	1.05	0.6
ZFHX3	chr16:72820995	0.89	0.54
DSC3	chr18:28574139	0.9	0.54
DSC1	chr18:28710424	0.9	0.54
SMAD2	chr18:45368152	1.05	0.6
RUNX1	chr21:36164357	0.92	0.54
EP300	chr22:41489001	1	0.58
ZRSR2	chrX:15808582	1.25	0.68
BCOR	chrX:39911340	1.19	0.66
DDX3X	chrX:41193501	1.11	0.62
RBM10	chrX:47006798	1.18	0.65

Variant Details (continued)

Copy Number Variations (continued)

Gene	Locus	Copy Number	CNV Ratio
PDGFRA	chr4:55131078	1.17	0.65
KIT	chr4:55589693	1.08	0.62
KDR	chr4:55955541	1.02	0.59
PRDM9	chr5:23509577	1.24	0.68
FGFR1	chr8:38271452	1.02	0.59
CD274	chr9:5456050	1.08	0.62
PDCD1LG2	chr9:5522530	1.23	0.67
EMSY	chr11:76157926	0.83	0.51
YAP1	chr11:101981594	0.89	0.53
CBL	chr11:119103202	0.98	0.57
SOCS1	chr16:11348676	0.64	0.43
YES1	chr18:724481	1.01	0.58
SETBP1	chr18:42281265	0.79	0.49
BCL2	chr18:60795830	0.73	0.46
U2AF1L5	chr21:44513260	1.02	0.59
ARAF	chrX:47422311	1.06	0.6

Biomarker Descriptions

PIK3CA p.(E545A) c.1634A>C

phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha

Background: The PIK3CA gene encodes the phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha of the class I phosphatidylinositol 3-kinase (PI3K) enzyme[203]. PI3K is a heterodimer that contains a p85 regulatory subunit, which couples one of four p110 catalytic subunits to activated tyrosine protein kinases[204,205]. The p110 catalytic subunits include p110α, β, δ, γ and are encoded by genes PIK3CA, PIK3CB, PIK3CD, and PIK3CG, respectively[204]. PI3K catalyzes the conversion of phosphatidylinositol (4,5)-bisphosphate (PI(4,5)P2) into phosphatidylinositol (3,4,5)-trisphosphate (PI(3,4,5)P3) while the phosphatase and tensin homolog (PTEN) catalyzes the reverse reaction[206,207]. The reversible phosphorylation of inositol lipids regulates diverse aspects of cell growth and metabolism[206,207,208,209]. Recurrent somatic alterations in PIK3CA are frequent in cancer and result in the activation of PI3K/AKT/MTOR pathway, which can influence several hallmarks of cancer including cell proliferation, apoptosis, cancer cell metabolism and invasion, and genetic instability[210,211,212].

Alterations and prevalence: Recurrent somatic activating mutations in PIK3CA are common in diverse cancers and are observed in 20-30% of breast, cervical, and uterine cancers and 10-20% of bladder, gastric, head and neck, and colorectal cancers[4,5]. Activating mutations in PIK3CA commonly occur in exons 10 and 21 (previously referred to as exons 9 and 20 due to exon 1 being untranslated)[213,214]. These mutations typically cluster in the exon 10 helical (codons E542/E545) and exon 21 kinase (codon H1047) domains, each having distinct mechanisms of activation[215,216,217]. PIK3CA resides in the 3q26 cytoband, a region frequently amplified (10-30%) in diverse cancers including squamous carcinomas of the lung, cervix, head and neck, and esophagus, and in serous ovarian and uterine cancers[4,5].

Potential relevance: The PI3K inhibitor, alpelisib[218], is FDA-approved (2019) in combination with fulvestrant for the treatment of patients with PIK3CA-mutated, hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative, advanced or metastatic breast cancer. Additionally, a phase Ib study of alpelisib with letrozole in patients with metastatic estrogen receptor (ER)-positive breast cancer showed the clinical benefit rate, defined as lack of disease progression ≥ 6 months, was 44% (7/16) in PIK3CA-mutated tumors and 20% (2/20) in PIK3CA wild-type tumors[219]. Specifically, exon 20 H1047R mutations were associated

Biomarker Descriptions (continued)

with more durable clinical responses in comparison to exon 9 E545K mutations[219]. However, alpelisib did not improve response when administered with letrozole in patients with ER+ early breast cancer with PIK3CA mutations[220]. The FDA also approved the kinase inhibitor, capivasertib (2023)[221] in combination with fulvestrant for locally advanced or metastatic HR-positive, HER2-negative breast cancer with one or more PIK3CA/AKT1/PTEN-alterations following progression after endocrine treatment. The kinase inhibitor, inavolisib[222], is also FDA-approved (2024) in combination with palbociclib and fulvestrant for the treatment of adults with endocrine-resistant, PIK3CA-mutated, HR-positive, and HER2-negative breast cancer. Case studies with mTOR inhibitors sirolimus and temsirolimus report isolated cases of clinical response in PIK3CA mutated refractory cancers[223,224].

KRAS p.(G12D) c.35G>A

KRAS proto-oncogene, GTPase

Background: The KRAS proto-oncogene encodes a GTPase that functions in signal transduction and is a member of the RAS superfamily which also includes NRAS and HRAS. RAS proteins mediate the transmission of growth signals from the cell surface to the nucleus via the PI3K/AKT/MTOR and RAS/RAF/MEK/ERK pathways, which regulate cell division, differentiation, and survival[225,226,227].

Alterations and prevalence: Recurrent mutations in RAS oncogenes cause constitutive activation and are found in 20-30% of cancers. KRAS mutations are observed in up to 10-20% of uterine cancer, 30-35% of lung adenocarcinoma and colorectal cancer, and about 60% of pancreatic cancer[4]. The majority of KRAS mutations consist of point mutations occurring at G12, G13, and Q61[4,228,229]. Mutations at A59, K117, and A146 have also been observed but are less frequent[5,230].

Potential relevance: The FDA has approved the small molecule inhibitors, sotorasib[231] (2021) and adagrasib[232] (2022), for the treatment of adult patients with KRAS G12C-mutated locally advanced or metastatic non-small cell lung cancer (NSCLC). Sotorasib and adagrasib are also useful in certain circumstances for KRAS G12C-mutated pancreatic adenocarcinoma[148]. The FDA has also granted breakthrough therapy designation (2022) to the KRAS G12C inhibitor, GDC-6036[233], for KRAS G12C-mutated non-small cell lung cancer. The SHP2 inhibitor, BBP-398[234] was granted fast track designation (2022) in combination with sotorasib for previously treated patients with KRAS G12C-mutated metastatic NSCLC. The RAF/MEK clamp, avutometinib[235] was also granted fast track designation (2024) in combination with sotorasib for KRAS G12C-mutated metastatic NSCLC who have received at least one prior systemic therapy and have not been previously treated with a KRAS G12C inhibitor. The KRAS G12C inhibitor, BBO-8520[236], was granted fast track designation in 2025 for previously treated KRAS G12C-mutated patients with metastatic NSCLC. The KRAS G12C inhibitor, D3S-001[237], was granted fast track designation in 2024 for KRAS G12C-mutated patients with advanced unresectable or metastatic colorectal cancers. The PLK1 inhibitor, onvansertib[238], was granted fast track designation (2020) in combination with bevacizumab and FOLFIRI for second-line treatment of patients with KRAS-mutated metastatic colorectal cancer (mCRC). The EGFR antagonists, cetuximab[239] and panitumumab[240], are contraindicated for treatment of colorectal cancer patients with KRAS mutations in exon 2 (codons 12 and 13), exon 3 (codons 59 and 61), and exon 4 (codons 117 and 146)[230]. Additionally, KRAS mutations are associated with poor prognosis in NSCLC[241].

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[95]. The SWI/SNF complex remodels chromatin at promoter and enhancer elements to alter and regulate gene expression[95,96]. 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[118]. Germline mutations in SMARCB1 are associated with rhabdoid tumor predisposition syndrome and familial schwannomatosis[119,120].

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[96]. SMARCB1 is often the only detected mutation in malignant rhabdoid tumors[118]. Somatic mutations in SMARCB1 are observed in 3% of uterine corpus endometrial carcinoma, stomach adenocarcinoma, and kidney chromophobe[4,5]. Alterations in SMARCB1 are also observed in pediatric cancers[4,5]. 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)[4,5]. Biallelic deletion of SMARCB1 is observed in 22% of embryonal tumors and less than 1% of B-lymphoblastic leukemia/lymphoma (4 in 731 cases)[4,5].

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[121,122].

Biomarker Descriptions (continued)

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[328,329]. 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[329].

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[329,330]. 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[4,5]. Somatic mutations in MTAP have been found in 3% of uterine corpus endometrial carcinoma[4,5].

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

ATM deletion, ATM p.(S1891*) c.5672C>A

ATM serine/threonine kinase

Background: The ATM gene encodes a serine/threonine kinase that belongs to the phosphatidylinositol-3-kinase related kinases (PIKKs) family of genes that also includes ATR and PRKDC (also known as DNA-PKc)[126]. ATM and ATR act as master regulators of DNA damage response. Specifically, ATM is involved in double-stranded break (DSB) repair while ATR is involved in single-stranded DNA (ssDNA) repair[127]. ATM is recruited to the DNA damage site by the MRE11/RAD50/NBN (MRN) complex that senses DSB[127,128]. Upon activation, ATM phosphorylates several downstream proteins such as the NBN, MDC1, BRCA1, CHK2 and TP53BP1 proteins[129]. ATM is a tumor suppressor gene and loss of function mutations in ATM are implicated in the BRCAness phenotype, which is characterized by a defect in homologous recombination repair (HRR), mimicking BRCA1 or BRCA2 loss[43,44]. Germline mutations in ATM often result in Ataxia-telangiectasia, a hereditary disease also referred to as DNA damage response syndrome that is characterized by chromosomal instability[130].

Alterations and prevalence: Recurrent somatic mutations in ATM are observed in 17% of endometrial carcinoma, 15% of undifferentiated stomach adenocarcinoma, 13% of bladder urothelial carcinoma, 12% of colorectal adenocarcinoma, 9% of melanoma as well as esophagogastric adenocarcinoma and 8% of non-small cell lung cancer[4,5].

Potential relevance: The PARP inhibitor, olaparib[131] is approved (2020) for metastatic castration-resistant prostate cancer (mCRPC) with deleterious or suspected deleterious, germline or somatic mutations in HRR genes that includes ATM. Additionally, talazoparib[53] in combination with enzalutamide is approved (2023) for metastatic castration-resistant prostate cancer (mCRPC) with mutations in HRR genes that includes ATM. Consistent with other genes associated with the BRCAness phenotype, ATM mutations may aid in selecting patients likely to respond to PARP inhibitors[43,132,133]. Specifically, in a phase II trial of metastatic, castration-resistant prostate cancer, four of six patients with germline or somatic ATM mutations demonstrated clinical responses to olaparib[134]. In 2022, the FDA granted fast track designation to the small molecule inhibitor, pidnarulex[37], for BRCA1/2, PALB2, or other homologous recombination deficiency (HRD) mutations in breast and ovarian cancers.

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)[270]. The INK4 family regulates cell cycle progression by inhibiting CDK4 or CDK6, thereby preventing the phosphorylation of Rb[271,272,273]. CDKN2A encodes two alternative transcript variants, namely p16 and p14ARF, both of which exhibit differential tumor suppressor functions[274]. 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[1,274,275]. CDKN2A aberrations commonly co-occur with CDKN2B[270]. Loss of CDKN2A/p16 results in downstream inactivation of the Rb and p53 pathways, leading to uncontrolled cell proliferation[276]. Germline mutations of CDKN2A are known to confer a predisposition to melanoma and pancreatic cancer[277,278].

Biomarker Descriptions (continued)

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[279]. 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[4,5]. 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[4,5]. Alterations in CDKN2A are also observed in pediatric cancers[5]. 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[5]. 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)[5].

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[122,280,281]. Additionally, deletion of CDKN2B is a molecular marker used in staging Grade 4 pediatric IDH-mutant astrocytoma[282]. Currently, no therapies are approved for CDKN2A aberrations. However, CDKN2A LOF leading to CDK4/6 activation may confer sensitivity to CDK inhibitors such as palbociclib and abemaciclib[283,284,285]. Alternatively, CDKN2A expression and Rb inactivation demonstrate resistance to palbociclib in cases of glioblastoma multiforme[286]. 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[287,288,289,290].

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[155,156,157]. 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[155,156,157,158]. NF2 functions as a tumor suppressor wherein loss of function mutations are shown to confer a predisposition to tumor development[156,157,159]. 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[156,157,159].

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[4]. Biallelic loss of NF2 is also observed in approximately 8% of mesothelioma cases[4].

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)[160].

ARID1A deletion

AT-rich interaction domain 1A

Background: The ARID1A gene encodes the AT-rich interaction domain 1A tumor suppressor protein[1]. ARID1A, also known as BAF250A, belongs to the ARID1 subfamily that also includes AR1D1B[1,94]. ARID1A and ARID1B are mutually exclusive subunits of the BAF variant of the SWI/SNF chromatin-remodeling complex[94,95]. The BAF complex is a multisubunit protein that consists of SMARCB1/IN1, SMARCC1/BAF155, SMARCC2/BAF170, SMARCA4/BRG1 or SMARCA2/BRM, and ARID1A or ARID1B[95]. The BAF complex remodels chromatin at promoter and enhancer elements to alter and regulate gene expression[95,96]. ARID1A binds to transcription factors and coactivator/corepressor complexes to alter transcription[94]. Recurrent inactivating mutations in BAF complex subunits, including ARID1A, lead to transcriptional dysfunction thereby, altering its tumor suppressor function[94].

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[96]. The majority of ARID1A inactivating mutations are nonsense or frameshift mutations[94]. Somatic mutations in ARID1A have been identified in 50% of ovarian clear cell carcinoma, 30% of endometrioid carcinoma, and 24-43% of uterine corpus endometrial carcinoma, bladder urothelial carcinoma, and stomach adenocarcinoma[4,5,95]. In microsatellite stable (MSS) colorectal cancer, mutations in ARID1A have been observed to correlate with increased tumor mutational burden (TMB) and expression of genes involved in the immune response[97].

Biomarker Descriptions (continued)

Potential relevance: Currently, no therapies are approved for ARID1A aberrations. However, the FDA has granted fast track designation (2022) to HSF1 pathway inhibitor, NXP-800[98], for the treatment of platinum resistant ARID1A-mutated ovarian carcinoma. Tulmimetostat[99], dual inhibitor of EZH2 and EZH1, was also granted a fast track designation (2023) for the treatment of patients with advanced, recurrent or metastatic endometrial cancer harboring ARID1A mutations and who have progressed on at least one prior line of treatment.

CDKN2B deletion

cyclin dependent kinase inhibitor 2B

Background: CDKN2B encodes cyclin dependent kinase inhibitor 2B, a cell cycle regulator that controls G1/S progression[1,270]. 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)[270]. The INK4 family regulates cell cycle progression by inhibiting CDK4 or CDK6, thereby preventing the phosphorylation of Rb[271,272,273]. CDKN2B is a tumor suppressor and aberrations in this gene commonly co-occur with CDKN2A[270]. Germline mutations in CDKN2B are linked to pancreatic cancer predisposition and familial renal cell carcinoma[1,295,296].

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[4,5]. Somatic mutations in CDKN2B are observed in 2% of uterine carcinosarcoma[4,5]. 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% of pediatric bone cancers, 6% of embryonal tumors, and 2% of peripheral nervous system cancers[4,5]. Somatic mutations in CDKN2B are observed in less than 1% of bone cancer (1 in 327 cases)[4,5].

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[282].

FBXW7 deletion

F-box and WD repeat domain containing 7

Background: The FBXW7 gene encodes a member of the F-box protein family that functions as the substrate recognition component of the SCF complex, which is responsible for protein ubiquitination and subsequent degradation by the proteasome[170]. FBXW7 is a tumor suppressor gene that plays a crucial role in the degradation and turnover of various proto-oncogenes. Aberrations such as mutations or deletions that alter the tumor suppression function can lead to the deregulation of downstream genes, including MYC, MTOR, and NOTCH1, thereby promoting cell proliferation and survival[170,171,172,173,174,175,176].

Alterations and prevalence: Mutations in FBXW7 occur at high frequencies in various malignancies, including 40% of uterine carcinoma and 10-15% of stomach, bladder, cervical, and colorectal cancers[4,5,177,178,179].

Potential relevance: The FDA has granted fast track designation (2024) to the small molecule PKMYT1 inhibitor, lunresertib[180], in combination with camonsertib for the treatment of adult patients with FBXW7 mutated endometrial cancer and platinum resistant ovarian cancer. Missense mutations in FBXW7 are associated with poor prognosis and worse overall survival (OS) in comparison to FBXW7 wild-type metastatic colorectal cancer[177]. In a clinical case report, a patient with FBXW7 R465H-mutated, EGFR/ALK-wildtype lung adenocarcinoma demonstrated tumor shrinkage after treatment with the mTOR inhibitor temsirolimus. In a phase I clinical trial of sirolimus, one hepatocellular fibrolamellar carcinoma patient with the FBXW7 E192A mutation demonstrated stable disease for over 6 months[176].

SMAD4 deletion

SMAD family member 4

Background: The SMAD4 gene encodes the SMAD family member 4, a transcription factor that belongs to a family of 8 SMAD genes that can be divided into three main classes. SMAD4 (also known as DPC4) belongs to the common mediator SMAD (co-SMAD) class while SMAD1, SMAD2, SMAD3, SMAD5, and SMAD8 are part of the regulator SMAD (R-SMAD) class. The inhibitory SMAD (I-SMAD) class includes both SMAD6 and SMAD7[149,150]. SMAD4 is a tumor suppressor gene and functions as a mediator of the TGF-β and BMP signaling pathways that are implicated in cancer initiation and progression[150,309,310]. Loss of SMAD4 does not drive oncogenesis, but is associated with progression of cancers initiated by driver genes such as KRAS and APC[149,150]

Biomarker Descriptions (continued)

Alterations and prevalence: Inactivation of SMAD4 can occur due to mutations, allelic loss, homozygous deletions, and 18q loss of heterozygosity (LOH)[149]. Somatic mutations in SMAD4 occur in up to 20% of pancreatic, 12% of colorectal, and 8% of stomach cancers. Recurrent hotspot mutations including R361 and P356 occur in the mad homology 2 (MH2) domain leading to the disruption of the TGF-β signaling[5,310,311]. Copy number deletions occur in up to 12% of pancreatic, 10% of esophageal, and 13% of stomach cancers[4,5,312].

Potential relevance: Currently, no therapies are approved for SMAD4 aberrations. Clinical studies and meta-analyses have demonstrated that loss of SMAD4 expression confers poor prognosis and poor overall survival (OS) in colorectal and pancreatic cancers[150,310,313,314,315]. Importantly, SMAD4 is a predictive biomarker to fluorouracil based chemotherapy[316,317]. In a retrospective analysis of 241 colorectal cancer patients treated with fluorouracil, 21 patients with SMAD4 loss demonstrated significantly poor median OS when compared to SMAD4 positive patients (31 months vs 89 months)[317]. In another clinical study of 173 newly diagnosed and recurrent head and neck squamous cell carcinoma (HNSCC) patients, SMAD4 loss is correlated with cetuximab resistance in HPV-negative HNSCC tumors[318].

ABRAXAS1 deletion

family with sequence similarity 175 member A

Background: The ABRAXAS1 gene encodes the abraxas 1, BRCA1-A complex subunit[1]. ABRAXAS1, also known as FAM175A, is capable of binding both BRCA1 and RAP80 which promotes the BRCA1-A complex formation along with BABAM2 and BRCC36[139,140]. Following formation, the BRCA1-A complex is capable of recognizing polyubiquitylated histones, including H2AX, through recognition by RAP80, resulting in complex localization to sites of DNA damage such as double-strand breaks[139]. BRCA1 localization to DNA double-strand breaks through BRCA1-A is essential for DNA-damage signaling and repair[139]. Together with the rest of the BRCA1-A complex, ABRAXAS1 is suggested to function as a tumor suppressor where germline mutations in such genes have been associated with an increased risk of breast cancer[139,141].

Alterations and prevalence: Somatic mutations in ABRAXAS1 are observed in 3% of uterine corpus endometrial carcinoma, 2% of colorectal adenocarcinoma, and 1% of stomach adenocarcinoma and lung squamous cell carcinoma[4,5].

Potential relevance: Currently, no therapies are approved for ABRAXAS1 aberrations.

AXIN1 deletion

axin 1

Background: The AXIN1 gene encodes the axis inhibition protein 1, a cytoplasmic protein that contains a regulation of G-protein signaling (RGS) domain and a disheveled and axin (DIX) domain, which are responsible for a variety of protein-protein interactions and signaling regulation[1,161,162,163]. AXIN1 functions as a negative regulator of the WNT signaling pathway through facilitating β-catenin degradation[1,164,165,166]. The WNT signaling pathway is responsible for regulating several key components during embryogenesis and has been observed to be involved in tumorigenesis[167,168]. Consequently, the WNT signaling pathway is a target for therapeutic response in various cancer types[168]. AXIN1 has also been observed to function in complex with DAXX, HIPK2, and TP53 to regulate cell growth, apoptosis, and cellular development[169].

Alterations and prevalence: Somatic mutations of AXIN1 are observed in 7% of liver hepatocellular carcinoma, 6% of uterine corpus endometrial carcinoma, 4% of skin cutaneous melanoma, 3% of stomach adenocarcinoma and colorectal adenocarcinoma, and 2% of head and neck squamous cell carcinoma, kidney renal papillary cell carcinoma, pancreatic adenocarcinoma, and glioblastoma multiforme[4,5]. Biallelic deletion of AXIN1 is observed in 4% of diffuse large B-cell lymphoma and uterine carcinosarcoma, 3% of esophageal adenocarcinoma, and 2% of bladder urothelial carcinoma[4,5].

Potential relevance: Currently, no therapies are approved for AXIN1 aberrations.

CHEK1 deletion

checkpoint kinase 1

Background: The CHEK1 gene encodes the checkpoint kinase 1 protein and belongs to a family of serine/threonine checkpoint kinases, that also includes CHEK2[1]. Checkpoint kinases play an important role in S phase and G2/M transition and DNA damage induced cell cycle arrest[297]. CHEK1 is a tumor suppressor and it interacts with proteins involved in transcription regulation, cell-cycle arrest, and DNA repair including homologous recombination repair (HRR)[298,299]. Upon DNA damage, CHEK1 is phosphorylated and activated by DNA damage repair proteins ATM and ATR[298]. Activated CHEK1 subsequently phosphorylates and negatively regulates downstream proteins such as CDC25A thereby slowing or stalling DNA replication[298,300].

Alterations and prevalence: Recurrent somatic alterations of CHEK1 include mutations and copy number loss. Somatic mutations of CHEK1 are observed in 3% of endometrial carcinoma, 2% of non-small cell lung cancer and 1% of cervical squamous carcinoma

Biomarker Descriptions (continued)

cases[4,301]. CHEK1 copy number loss occurs in 10% of seminoma, 8% of non-seminomatous germ cell tumor, 5% of ocular melanoma, and 3% of melanoma cases[4,301].

Potential relevance: The PARP inhibitor, olaparib[131] is approved (2020) for metastatic castration-resistant prostate cancer (mCRPC) with deleterious or suspected deleterious, germline or somatic mutations in HRR genes that includes CHEK1. In 2022, the FDA granted fast track designation to the small molecule inhibitor, pidnarulex[37], for BRCA1/2, PALB2, or other homologous recombination deficiency (HRD) mutations in breast and ovarian cancers.

CHEK2 deletion

checkpoint kinase 2

Background: The CHEK2 gene encodes the checkpoint kinase-2 serine/threonine kinase, which is a cell-cycle checkpoint regulator. In response to DNA damage, CHEK2 is phosphorylated by ATM and subsequently phosphorylates and negatively regulates CDC25C to prevent entry into mitosis[359]. CHEK2 also stabilizes p53, leading to cell-cycle arrest in G1 phase, and is capable of phosphorylating BRCA1 and promoting DNA repair including homologous recombination repair (HRR)[299,360,361]. Germline mutations in the CHEK2 gene are associated with Li-Fraumeni syndrome and inherited risk of breast cancer[362,363,364].

Alterations and prevalence: Consistent with its role as a tumor suppressor, CHEK2 is enriched for deleterious truncating mutations. Somatic mutations in CHEK2 are common (2-6%) in uterine carcinoma, bladder carcinoma, and lung adenocarcinoma[4,5]. CHEK2 gene deletions are observed in adrenocortical carcinoma, thymoma, and prostate cancer[4,5].

Potential relevance: The PARP inhibitor, olaparib[131] is approved (2020) for metastatic castration-resistant prostate cancer (mCRPC) with deleterious or suspected deleterious, germline or somatic mutations in HRR genes that includes CHEK2. Additionally, talazoparib[53] in combination with enzalutamide is approved (2023) for mCRPC with mutations in HRR genes that includes CHEK2. In 2022, the FDA granted fast track designation to the small molecule inhibitor, pidnarulex[37], for BRCA1/2, PALB2, or other homologous recombination deficiency (HRD) mutations in breast and ovarian cancers.

DPYD p.(M166V) c.496A>G

dihydropyrimidine dehydrogenase

Background: The DPYD gene (also known as DPD) encodes dihydropyrimidine dehydrogenase, the initial and rate-limiting enzyme that catalyzes the reduction of uracil and thymidine in the pyrimidine catabolism pathway[1,2]. DPYD is responsible for the inactivation and liver clearance of fluoropyrimidines (fluorouracil, capecitabine, and other analogs), which are the core chemotherapies used in the treatment of solid tumors, such as colorectal, pancreatic, gastric, breast, and head and neck cancers[3]. Inherited DPYD polymorphisms, including DPYD*2A, DPYD*13, DPYD c.2846A>T, and DPYD c.1129-5923T>G, can result in DPD deficiency, which is characterized by impaired enzymatic activity and confers an increased risk of severe toxicity to fluoropyrimidine drugs due to an increase in systemic drug exposure[3].

Alterations and prevalence: Somatic mutations in DPYD have been observed in 20% of skin cutaneous melanoma, 9% of uterine corpus endometrial carcinoma, 6% of stomach adenocarcinoma, 5% of diffuse large B-cell lymphoma and colorectal adenocarcinoma, 4% of lung adenocarcinoma, 3% of bladder urothelial carcinoma, head and neck squamous cell carcinoma, and lung squamous cell carcinoma, and 2% of adrenocortical carcinoma, cervical squamous cell carcinoma, uterine carcinosarcoma, pancreatic adenocarcinoma, esophageal adenocarcinoma, liver hepatocellular carcinoma, and sarcoma[4,5]. Biallelic loss of DPYD has been observed in 4% of pheochromocytoma and paraganglioma and 2% of esophageal adenocarcinoma and lung squamous cell carcinoma[4,5].

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

ERCC4 deletion

ERCC excision repair 4, endonuclease catalytic subunit

Background: The ERCC4 gene encodes ERCC excision repair 4, endonuclease catalytic subunit, also known as XPF[1]. The ERCC4-ERCC1 heterodimer is a structure-specific endonuclease which creates the 5' incision at sites of DNA damage during nucleotide excision repair (NER), while ERCC5 creates the 3' incision[420]. Together with ERCC5, the ERCC4-ERCC1 heterodimer is involved in the removal of damaged DNA, leading to ATR activation and DNA damage repair[420]. Germline mutations in ERCC4 are associated with Xeroderma Pigmentosum (XP) complementation group F, a multisystem degenerative disorder that results in photo-sensitivity and a predisposition to skin cancer[421].

Biomarker Descriptions (continued)

Alterations and prevalence: Somatic mutations in ERCC4 are observed in 8% of uterine corpus endometrial carcinoma, 4% of skin cutaneous melanoma, 3% of stomach adenocarcinoma, 2% of colorectal adenocarcinoma, lung adenocarcinoma, uterine carcinosarcoma, and cervical squamous cell carcinoma[4,5].

Potential relevance: Currently, no therapies are approved for ERCC4 aberrations.

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[80,81]. 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[80]. Monoubiquitination of the ID2 complex promotes co-localization with BRCA1/2, which is critical in BRCA mediated DNA repair[82,83]. 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[44,84]. 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[85,86]. Of those diagnosed with FA, mutations in FANCA are the most common and confer predisposition to myelodysplastic syndrome, acute myeloid leukemia, and solid tumors[81,86,87,88,89].

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

Potential relevance: The PARP inhibitor, talazoparib[53] 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[90,91]. FANCA copy number loss along with reduced expression has also been associated with genetic instability in sporadic acute myeloid leukemia (AML)[89].

FANCG deletion

Fanconi anemia complementation group G

Background: The FANCG gene encodes the FA complementation group G protein, a member of Fanconi Anemia (FA) family, which also includes FANCA, FANCB, FANCC, FANCD1 (BRCA2), FANCD2, FANCE, FANCF, 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[80,81]. 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[80]. Monoubiquitination of the ID2 complex promotes co-localization with BRCA1/2, which is critical in BRCA mediated DNA repair[82,83]. 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[44,84]. 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[85,86].

Alterations and prevalence: Somatic mutations in FANCG are observed in 3% of uterine corpus endometrial carcinoma and skin cutaneous melanoma, and 2% of diffuse large B-cell lymphoma (DLBCL), uterine carcinosarcoma, and colorectal adenocarcinoma[4,5].

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

KMT2A deletion

lysine methyltransferase 2A

Background: The KMT2A gene encodes lysine methyltransferase 2A, a transcriptional coactivator and histone H3 lysine 4 (H3K4) methyltransferase[1,100]. KMT2A, also known as mixed lineage leukemia (MLL), is part of the SET domain protein methyltransferase superfamily[100]. KMT2A influences the epigenetic regulation of several cellular functions, including neurogenesis, hematopoiesis, and osteogenesis[101]. Located at the chromosomal position 11q23, KMT2A is the target of recurrent chromosomal rearrangements observed in several leukemia subtypes, including MLL, acute myeloid leukemia (AML), and acute lymphoblastic leukemia (ALL)[102]. These translocations encode KMT2A fusion proteins that are oncogenic with simultaneous loss of KMT2A H3K4 methyltransferase

Biomarker Descriptions (continued)

activity[102]. Loss of methyltransferase activity, along with gain-of-function partner gene activation, contributes to increased HOX gene expression and promotes the transformation of hematopoietic cells into leukemic stem cells[102,103,104,105].

Alterations and prevalence: KMT2A fusions are observed in 3-10% of adult AML cases with the highest frequencies in therapy-related AML (9%) and patients younger than 60 years (5%)[4,5,102,106]. KMT2A rearrangements including t(4;11)(q21;q23)/AFF1::KMT2A, t(9;11)(p22;q23)/MLLT3::KMT2A, t(11;19)(q23;p13.3)/KMT2A::MLLT1, t(10;11)(p12;q23)/MLLT10::KMT2A, and t(6;11)(q27;q23)/AFDN::KMT2A translocations account for about 80% of all KMT2A rearranged leukemias[102]. KMT2A alterations observed in solid tumors include nonsense or frameshift mutations, which result in KMT2A truncation and loss of methyltransferase activity[4,107]. KMT2A alterations are also observed in pediatric cancers[4,5]. In infant acute leukemic cases, KMT2A rearrangement is reported in more than 70% of pediatric patients diagnosed with either AML or ALL and is observed in 5% of T-lymphoblastic leukemia/lymphoma[4,5,102,108,109].

Potential relevance: KMT2A fusions are associated with variable prognosis based on the partner genes involved in the fusion[70,71]. For example, t(6;11)(q27;q23)/AFDN::KMT2A fusions are associated with poor prognosis, whereas t(9;11)(p22;q23)/MLLT3::KMT2A fusions confer a more favorable or intermediate prognosis in AML[110,111,112]. Additionally, 11q23 rearrangements define an unfavorable karyotype in patients diagnosed with primary myelofibrosis (PMF) and may confer intermediate to high risk depending on concurrent cytogenetic abnormalities[27]. KMT2A fusion is also associated with poor risk in adult and pediatric ALL[30,113,114]. Translocations in KMT2A are recognized by the World Health Organization (WHO) as a molecular subtype of B-lymphoblastic leukemia/lymphoma with KMT2A-rearrangement[115]. In 2024, the FDA approved the oral menin inhibitor, revumenib[116], for the treatment of adult and pediatric patients 1 year and older with relapsed or refractory acute leukemia harboring a KMT2A rearrangement. In 2024, the FDA also granted fast track designation to the small molecule inhibitor, DSP-5336, for the treatment of patients with relapsed or refractory AML with KMT2A rearrangements[117].

MRE11 deletion

MRE11 homolog, double strand break repair nuclease

Background: The MRE11 gene encodes the meiotic recombination 11 protein, a nuclear protein that is part of the multisubunit MRE11/RAD50/NBN (MRN) complex, which is necessary for the maintenance of genomic stability[39]. The MRN complex is involved in the repair of double-stranded breaks (DSB) through two mechanisms namely homologous recombination repair (HRR) and non-homologous end joining (NHEJ)[40,41,42]. Dimerization of MRE11 is required for DNA binding of the MRN complex, and it acts as a 3'–5' exonuclease and ssDNA endonuclease upon binding DNA[39]. MRE11 is a tumor suppressor gene and loss of function mutations are implicated in the BRCAness phenotype, characterized by a defect in the HRR pathway mimicking BRCA1 or BRCA2 loss[43,44]. Germline mutations in MRE11 have been identified as candidate susceptibility aberrations in colorectal cancer and a hallmark of ataxia-telangiectasia-like disorder (ALTD), a heritable disease resulting in progressive cerebellar degeneration and cancer predisposition[45,46,47,48].

Alterations and prevalence: Somatic mutations in MRE11 are observed in 6-7% of uterine cancer as well as 2-3% of lung adenocarcinoma and melanoma[4]. Mutations in the T11 polypyrimidine tract of MRE11 intron 5 are associated with aberrant splicing and reduced MRE11 protein expression. The presence of MRE11 splice variants is frequently observed in mismatch repair deficient (dMMR)/microsatellite instability (MSI-H) colorectal and endometrial cancers[49,50,51,52]

Potential relevance: The PARP inhibitor, talazoparib[53] in combination with enzalutamide is approved (2023) for metastatic castration-resistant prostate cancer (mCRPC) with mutations in HRR genes that includes MRE11. Loss of function in HRR genes, including MRE11, may confer sensitivity to DNA damaging agents and PARP inhibitors[43,44]. Specifically, loss of MRE11 protein expression has been observed to predict sensitivity to PARP inhibitors in colorectal, breast, and endometrial cancers in vitro[54,55,56].

Microsatellite stable

Background: Microsatellites are short tandem repeats (STR) of 1 to 6 bases of DNA between 5 to 50 repeat units in length. There are approximately 0.5 million STRs that occupy 3% of the human genome[181]. Microsatellite instability (MSI) is defined as a change in the length of a microsatellite in a tumor as compared to normal tissue[182,183]. MSI is closely tied to the status of the mismatch repair (MMR) genes. In humans, the core MMR genes include MLH1, MSH2, MSH6, and PMS2[184]. Mutations and loss of expression in MMR genes, known as defective MMR (dMMR), lead to MSI. In contrast, when MMR genes lack alterations, they are referred to as MMR proficient (pMMR). Consensus criteria were first described in 1998 and defined MSI-high (MSI-H) as instability in two or more of the following five markers: BAT25, BAT26, D5S346, D2S123, and D17S250[185]. Tumors with instability in one of the five markers were defined as MSI-low (MSI-L) whereas, those with instability in zero markers were defined as MS-stable (MSS)[185]. Tumors classified as MSI-L are often phenotypically indistinguishable from MSS tumors and tend to be grouped with MSS[186,187,188,189,190]. MSI-H is a hallmark of Lynch syndrome (LS), also known as hereditary non-polyposis colorectal cancer, which is caused by germline mutations in the MMR genes[183]. LS is associated with an increased risk of developing colorectal cancer, as well as other cancers, including endometrial and stomach cancer[182,183,187,191].

Biomarker Descriptions (continued)

Alterations and prevalence: The MSI-H phenotype is observed in 30% of uterine corpus endothelial carcinoma, 20% of stomach adenocarcinoma, 15-20% of colon adenocarcinoma, and 5-10% of rectal adenocarcinoma[182,183,192,193]. MSI-H is also observed in 5% of adrenal cortical carcinoma and at lower frequencies in other cancers such as esophageal, liver, and ovarian cancers[192,193].

Potential relevance: Anti-PD-1 immune checkpoint inhibitors including pembrolizumab[194] (2014) and nivolumab[195] (2015) are approved for patients with MSI-H or dMMR colorectal cancer who have progressed following chemotherapy. Pembrolizumab[194] is also approved as a single agent, for the treatment of patients with advanced endometrial carcinoma that is MSI-H or dMMR with disease progression on prior therapy who are not candidates for surgery or radiation. Importantly, pembrolizumab is approved for the treatment of MSI-H or dMMR solid tumors that have progressed following treatment, with no alternative option and is the first anti-PD-1 inhibitor to be approved with a tumor agnostic indication[194]. Dostarlimab[196] (2021) is also approved for dMMR recurrent or advanced endometrial carcinoma or solid tumors that have progressed on prior treatment and is recommended as a subsequent therapy option in dMMR/MSI-H advanced or metastatic colon or rectal cancer[188,197]. The cytotoxic T-lymphocyte antigen 4 (CTLA-4) blocking antibody, ipilimumab[198] (2011), is approved alone or in combination with nivolumab in MSI-H or dMMR colorectal cancer that has progressed following treatment with chemotherapy. MSI-H may confer a favorable prognosis in colorectal cancer although outcomes vary depending on stage and tumor location[188,199,200]. Specifically, MSI-H is a strong prognostic indicator of better overall survival (OS) and relapse free survival (RFS) in stage II as compared to stage III colorectal cancer patients[200]. The majority of patients with tumors classified as either MSS or pMMR do not benefit from treatment with single-agent immune checkpoint inhibitors as compared to those with MSI-H tumors[201,202]. However, checkpoint blockade with the addition of chemotherapy or targeted therapies have demonstrated response in MSS or pMMR cancers[201,202].

PALB2 deletion

partner and localizer of BRCA2

Background: The PALB2 gene encodes the partner and localizer of BRCA2 protein that binds to and promotes intranuclear localization of the breast cancer 2 early onset (BRCA2) protein[142]. Also known as FANCN, PALB2 belongs to the Fanconi Anemia (FA) complementation group of proteins that also include FANCA, FANCB, FANCC, FANCD1 (BRCA2), FANCD2, FANCE, FANCF, FANCG, FANCI, FANCJ (BRIP1), FANCL, and FANCM. FA genes are tumor suppressors that play a role in interstrand cross-link (ICL) DNA repair through homologous recombination repair (HRR) of double-strand breaks (DSB) and nucleotide excision repair (NER)[80]. Loss of function mutations of genes in the FA family and HRR pathway, including PALB2, can result in the BRCAness phenotype, characterized by a defect in the HRR pathway, mimicking BRCA1 or BRCA2 loss[44,84]. 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[85,86]. Specifically, biallelic germline mutations resulting in PALB2 loss of function confer a predisposition to pediatric malignancies[143,144]. Additionally, monoallelic germline mutations in PALB2 have been associated with an increased risk of developing breast cancer[143,145].

Alterations and prevalence: Somatic alterations in PALB2 include missense or truncating mutations and are observed in 2-6% of melanoma, uterine, bladder, breast, lung, stomach and colorectal cancers[4].

Potential relevance: The PARP inhibitor, olaparib[131] is approved (2020) for metastatic castration-resistant prostate cancer (mCRPC) with deleterious or suspected deleterious, germline or somatic mutations in HRR genes that includes PALB2. Additionally, talazoparib[53] in combination with enzalutamide is approved (2023) for mCRPC with mutations in HRR genes that includes PALB2. In a phase II trial of patients with metastatic, castration-resistant prostate cancer, one patient exhibiting a somatic PALB2 frameshift mutation exhibited durable response to olaparib for 39 weeks[134,146]. However, olaparib resistance was observed following 9-months of treatment due to the emergence of a secondary deletion which restored the PALB2 reading frame, a resistance mechanism similar to that observed in PARPi treated BRCA mutated patients[146,147]. In 2022, the FDA granted fast track designation to the small molecule inhibitor, pidnarulex[37], for BRCA1/2, PALB2, or other homologous recombination deficiency (HRD) mutations in breast and ovarian cancers. Rucaparib is recommended as a maintenance therapy for germline or somatic PALB2 mutations in metastatic pancreatic cancer[148].

PPP2R2A deletion

protein phosphatase 2 regulatory subunit Balpha

Background: The PPP2R2A gene encodes the protein phosphatase 2 regulatory subunit B alpha, a member of a large heterotrimeric serine/threonine phosphatase 2A (PP2A) family. Proteins of the PP2A family includes 3 subunits— the structural A subunit (includes PPP2R1A and PPP2R1B), the regulatory B subunit (includes PPP2R2A, PPP2R5, PPP2R3, and STRN), and the catalytic C subunit (PPPP2CA and PPP2CB)[32,33]. PPA2 proteins are essential tumor suppressor genes that regulate cell division and possess pro-apoptotic activity through negative regulation of the PI3K/AKT pathway[34]. Specifically, PPP2R2A modulates ATM phosphorylation which is critical in the regulation of the homologous recombination repair (HRR) pathway[32].

Alterations and prevalence: Copy number loss and downregulation of PPP2R2A is commonly observed in solid tumors including breast and non-small cell lung cancer and define an aggressive subgroup of luminal-like breast cancer[32,33,35,36]. Biallelic loss of PPP2R2A is

Biomarker Descriptions (continued)

observed in 4-8% of breast invasive carcinoma, lung, colorectal, bladder, liver, and prostate cancers, as well as 4% of diffuse large B-cell lymphoma[4].

Potential relevance: Currently no therapies are approved for PPP2R2A aberrations. However, in 2022, the FDA granted fast track designation to the small molecule inhibitor, pidnarulex[37], for BRCA1/2, PALB2, or other homologous recombination deficiency (HRD) mutations in breast and ovarian cancers. Loss of PPP2R2A in pre-clinical and xenograft models have been shown to inhibit homologous recombination DNA directed repair and may predict sensitivity to PARP inhibitors such as veliparib[32]. Olaparib treatment in prostate cancer with PPP2R2A mutations is not recommended due to unfavorable risk benefit[38].

RAD51 deletion

RAD51 recombinase

Background: The RAD51 gene encodes the RAD51 recombinase protein and is a member of the RAD51 protein family that also includes RAD51B (RAD51L1), RAD51C (RAD51L2), RAD51D (RAD51L3), XRCC2, and XRCC3 paralogs. The RAD51 family proteins are involved in homologous recombination repair (HRR) and DNA repair of double-strand breaks (DSB)[135]. RAD51 interacts with many DNA repair and cell cycle genes, including BRCA1, BRCA2, p53, and ATM[136]. RAD51 is expressed in proliferating cells in the S or S/G2 phases of the cell cycle and mediates DNA strand invasion and homologous pairing between DNA duplexes[137,138]. RAD51 is a tumor suppressor gene. Loss of function mutations in RAD51 can lead to deficiencies in DSB repair and are implicated in the BRCAness phenotype, which is characterized by a defect in HRR, mimicking BRCA1 or BRCA2 loss[43,44,137].

Alterations and prevalence: Somatic mutations in RAD51 have been described in breast and prostate cancers[136].

Potential relevance: Currently, no therapies are approved for RAD51 aberrations.

SDHB deletion

succinate dehydrogenase complex iron sulfur subunit B

Background: The SDHB gene encodes succinate dehydrogenase complex iron sulfur subunit B, a subunit of the succinate dehydrogenase (SDH) enzyme complex[1]. The SDH enzyme complex, also known as complex II of the mitochondrial respiratory chain, is composed of four subunits encoded by SDHA, SDHB, SDHC, and SDHD[75,76]. SDH is a key mitochondrial enzyme complex that catalyzes the oxidation of succinate to fumarate in the tricarboxylic acid cycle and transfers the electrons to ubiquinone in the electron transport chain[75,76]. SDHB iron clusters facilitate the transfer of electrons from FADH2 to ubiquinone[78]. Mutations in SDH genes lead to abnormal stabilization of hypoxia-inducible factors and pseudo-hypoxia, thereby promoting cell proliferation, angiogenesis, and tumorigenesis[75,76]. Sporadic and inherited pathogenic mutations in SDHB are known to confer an increased risk for paragangliomas, pheochromocytomas, and gastrointestinal stromal tumors[1,79].

Alterations and prevalence: Somatic mutations in SDHB are observed in 1% cervical squamous cell carcinoma, uterine corpus endometrial carcinoma, skin cutaneous melanoma, colorectal adenocarcinoma, stomach adenocarcinoma, thymoma, lung squamous cell carcinoma, and kidney renal clear cell carcinoma[4,5]. Biallelic loss of SDHB is observed in 6% of cholangiocarcinoma and 2% of pheochromocytoma and paraganglioma[4,5].

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

SLX4 deletion

SLX4 structure-specific endonuclease subunit

Background: The SLX4 gene encodes the SLX4 structure-specific endonuclease subunit[1]. SLX4, also known as FANCP, is a tumor suppressor protein that functions as a scaffold for DNA repair endonucleases[393]. SLX4 functions in DNA repair mechanisms including double-strand break (DSB) repair and interstrand crosslink repair[393,394,395]. Specifically, SLX4 localizes at DSB sites and recruits and interacts with other repair proteins such as ERCC1-XPF, MUS81-EME1, and SLX1[393,394,395]. Germline SLX4 mutations are associated with Fanconi Anemia, a genetic condition characterized by genomic instability and congenital abnormalities, including bone marrow failure and cancer predisposition[394].

Alterations and prevalence: Recurrent somatic mutations in SLX4 are observed in 11% of uterine corpus endometrial carcinoma, 9% of skin cutaneous melanoma, 6% of stomach adenocarcinoma, and 4% of bladder urothelial carcinoma[4,5].

Potential relevance: Currently, no therapies are approved for SLX4 aberrations.

Biomarker Descriptions (continued)

TSC2 deletion

tuberous sclerosis 2

Background: The TSC2 gene encodes the tuberin protein. TSC2 and TSC1 (also known as hamartin) form a complex through their respective coiled-coil domains[267]. The TSC1-TSC2 complex is a negative regulator of the mTOR signaling pathway that regulates cell growth, cell proliferation, and protein and lipid synthesis[268]. Specifically, the TSC1-TSC2 complex acts as a GTPase activating (GAP) protein that inhibits the G-protein RHEB and keeps it in an inactivated state (RHEB-GDP). GTP bound RHEB (RHEB-GTP) is required to activate the mTOR complex 1 (mTORC1). TSC1 and TSC2 are tumor suppressor genes. Loss of function mutations in TSC1 and TSC2 lead to dysregulation of the mTOR pathway[267,269]. Inactivating germline mutations in TSC1 and TSC2 are associated with tuberous sclerosis complex (TSC), an autosomal dominant neurocutaneous and progressive disorder that presents with multiple benign tumors in different organs[267].

Alterations and prevalence: Somatic mutations are observed in up to 8% of skin cutaneous melanoma, 7% of uterine corpus endometrial carcinoma, and 4% of cervical squamous cell carcinoma[4,5].

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

TNFRSF14 deletion

TNF receptor superfamily member 14

Background: The TNFRSF14 gene encodes TNF receptor superfamily member 14[1]. TNFRSF14, also known as HVEM, belongs to the tumor necrosis factor superfamily of cell surface receptors (TNFRSF), which interact with the tumor necrosis factor superfamily (TNFSF) of cytokines[302]. TNFSF-TNFRSF interactions regulate several signaling pathways, including those involved in immune cell differentiation, survival, and death[302]. TNFRSF14 can be stimulated by several ligands, including the TNFSF14 ligand (also known as LIGHT), BTLA, and CD160[302,303]. Following ligand binding to TNFRSF in T-cells, TNFRSF proteins aggregate at the cell membrane and initiate co-signaling cascades which promotes activation, differentiation, and survival[302]. In lymphoma, binding of TNFRSF14 by TNFSF14 has been observed to enhance Fas-induced apoptosis, suggesting a tumor suppressor role[303].

Alterations and prevalence: Somatic mutations in TNFRSF14 are observed in 5% of diffuse large B-cell lymphoma (DLBCL), and 2% of skin cutaneous melanoma[4,5]. Biallelic loss of TNFRSF14 occurs in 8% of DLBCL and uveal melanoma, 3% of cholangiocarcinoma, and 2% of adrenocortical carcinoma and liver hepatocellular carcinoma[4,5].

Potential relevance: Currently, no therapies are approved for TNFRSF14 aberrations. Somatic mutations in TNFRSF14 are diagnostic for follicular lymphoma[72]. In addition, TNFRSF14 mutations are associated with poor prognosis in follicular lymphoma[304,305].

ERRFI1 deletion

ERBB receptor feedback inhibitor 1

Background: ERRFI1 encodes ERBB receptor feedback inhibitor 1, a scaffold adaptor protein[1,407]. As an early response gene, expression of ERRFI1 is induced by several stimuli such as stress, hormones, and growth factors such as EGF[407,408]. ERRFI1 directly binds to EGFR resulting in inhibition of EGFR catalytic activity as well as EGFR lysosomal degradation[407,409]. As a tumor suppressor, ERRFI1 induces apoptosis and inhibits proliferation and invasion[407,410,411,412,413]. ERRFI1 downregulation has been identified in several cancer types and loss of ERRFI1 promotes proliferation and migration[407,410,411,414,415].

Alterations and prevalence: Somatic mutations in ERRFI1 are observed in 4% of uterine corpus endometrial carcinoma and 2% of skin cutaneous melanoma, uterine carcinosarcoma, and colorectal adenocarcinoma[4,5]. Biallelic loss of ERRFI1 is observed in 6% of cholangiocarcinoma, 4% of adrenocortical carcinoma and diffuse large B-cell lymphoma, and 2% of liver hepatocellular carcinoma, pheochromocytoma and paraganglioma, and glioblastoma multiforme[4,5].

Potential relevance: Currently, no therapies are approved for ERRFI1 aberrations.

ENO1 deletion

enolase 1

Background: The ENO1 gene encodes enolase 1 and its alternatively spliced protein isoform, c-MYC promoter binding protein 1 (MBP1)[1,365]. ENO1 is a glycolytic enzyme that catalyzes the dehydration of 2-phosphoglyceric acid to phosphoenolpyruvic acid during glycolysis[365]. In addition to its role in glycolysis, ENO1 acts as a cell surface plasminogen receptor and is involved in cytoskeleton reorganization, stabilization of the mitochondrial membrane, and modulation of several oncogenic pathways, including PI3K/AKT, AMPK/mTOR and Wnt/β-catenin[365,366,367]. ENO1 has been found to be overexpressed in various cancers contributing to upregulation

Biomarker Descriptions (continued)

of glycolysis, cancer cell survival and proliferation, chemoresistance, extracellular matrix degradation, migration, invasion, and metastases[365,366,368]. In contrast, MBP1 is known to repress c-MYC transcription under cellular stress and low glucose conditions, leading to suppression of cellular proliferation, migration, and invasion[365,366].

Alterations and prevalence: Somatic mutations in ENO1 are observed in 3% uterine corpus endometrial carcinoma and kidney chromophobe, and 2% of diffuse large B-cell lymphoma, skin cutaneous melanoma, and cervical squamous cell carcinoma[4,5]. Amplification of ENO1 is observed in 2% of adrenocortical carcinoma, pancreatic adenocarcinoma, esophageal adenocarcinoma, ovarian serous cystadenocarcinoma, and sarcoma[4,5]. Biallelic loss of ENO1 is observed in 6% of cholangiocarcinoma, 4% of adrenocortical carcinoma, and 2% of pheochromocytoma and paraganglioma, liver hepatocellular carcinoma, and diffuse large B-cell lymphoma[4,5].

Potential relevance: Currently, no therapies are approved for ENO1 aberrations.

PGD deletion

phosphogluconate dehydrogenase

Background: The PGD gene encodes phosphogluconate dehydrogenase, an essential enzyme of the pentose phosphate pathway (PPP) that catalyzes oxidative decarboxylation of 6-phosphogluconate to ribulose-5-phosphate and reduction of NADP+ to NADPH[1,291]. PPP mediated generation of pentose phosphates and NADPH is essential for nucleic acid synthesis and fatty acid synthesis, respectively, making it a crucial metabolic pathway for cancer cell survival and proliferation[292,293]. Although biallelic deletion appears to be more common than amplification across cancer types, post-translational modifications and overexpression of PGD in cancer have also been observed to result in elevated PPP activity, which is associated with cancer cell proliferation[291,294].

Alterations and prevalence: Somatic mutations in PGD have been observed in 4% of skin cutaneous melanoma, 3% of uterine corpus endometrial carcinoma, 2% of diffuse large B-cell lymphoma, stomach adenocarcinoma, and bladder urothelial carcinoma[4,5]. Biallelic loss of PGD has been observed in 4% of adrenocortical carcinoma, 3% of cholangiocarcinoma, and 2% of pheochromocytoma and paraganglioma and diffuse large B-cell lymphoma[4,5]. Amplification of PGD has been observed in 2% of esophageal adenocarcinoma, ovarian serous cystadenocarcinoma, stomach adenocarcinoma, and sarcoma[4,5].

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

SPEN deletion

spen family transcriptional repressor

Background: SPEN encodes spen family transcriptional repressor[1]. SPEN plays a role in chromosome X inactivation and regulation of transcription[388,389,390]. As a transcriptional repressor, SPEN sequesters transcriptional activators and interacts with other repressors and chromatin remodeling complexes, such as histone deacetylases (HDACs) and the NuRD complex[388,390]. In ERα-positive breast cancers, SPEN binds ERα in a ligand-independent manner and negatively regulates the transcription of ERα targets, acting as a tumor suppressor gene to regulate cell proliferation, tumor growth, and survival[391,392].

Alterations and prevalence: Somatic mutations in SPEN are observed in 13% of skin cutaneous melanoma, 12% of uterine corpus endometrial carcinoma, 10% of stomach adenocarcinoma, 7% of diffuse large B-cell lymphoma, bladder urothelial carcinoma, and colorectal adenocarcinoma, 6% of cervical squamous cell carcinoma, 5% of head and neck squamous cell carcinoma and lung adenocarcinoma, 4% of lung squamous cell carcinoma and ovarian serous cystadenocarcinoma, 3% of kidney renal clear cell carcinoma, kidney renal papillary cell carcinoma, breast invasive carcinoma, glioblastoma multiforme, and acute myeloid leukemia, and 2% of pancreatic adenocarcinoma, adrenocortical carcinoma, liver hepatocellular carcinoma, uterine carcinosarcoma, and esophageal adenocarcinoma[4,5]. Biallelic loss of SPEN is observed in 6% of cholangiocarcinoma and 2% of pheochromocytoma and paraganglioma[4,5].

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

EPHA2 deletion

EPH receptor A2

Background: The EPHA2 gene encodes the EPH receptor A2[1]. EPHA2 is a member of the erythropoietin-producing hepatocellular carcinoma (Eph) receptors, a group of receptor tyrosine kinases divided into EPHA (EphA1-10) and EPHB (EphB1-6) classes of proteins[92,93]. Like classical tyrosine kinase receptors, Eph activation is initiated by ligand binding resulting downstream signaling involved in various cellular processes including cell growth, differentiation, and apoptosis[93]. Specifically, Eph-EphrinA ligand interaction

Biomarker Descriptions (continued)

regulates pathways critical for malignant transformation and key downstream target proteins including PI3K, SRC, Rho and Rac1 GTPases, MAPK, and integrins[92,93].

Alterations and prevalence: Somatic mutations in EPHA2 are observed in 11% of cholangiocarcinoma, 7% of uterine corpus endometrial carcinoma, stomach adenocarcinoma, and skin cutaneous melanoma, 6% of bladder urothelial carcinoma, and 5% of diffuse large B-cell lymphoma (DLBCL) and cervical squamous cell carcinoma[4,5].

Potential relevance: Currently, no therapies are approved for EPHA2 aberrations.

TET2 deletion

tet methylcytosine dioxygenase 2

Background: TET2 encodes the tet methylcytosine dioxygenase 2 protein and belongs to the ten-eleven translocation (TET) family, which also includes TET1 and TET3[1,320]. The TET enzymes are involved in DNA methylation, specifically in the conversion of 5-methylcytosine to 5-hydroxymethylcytosine[321,322]. The TET proteins contain a C-terminal core catalytic domain that consists of a cysteine-rich domain and a double-stranded ß-helix domain (DSBH)[321,322]. TET1 and TET3 possess a DNA-binding N-terminal CXXC zinc finger domain, whereas TET2, lacking this domain, is regulated by the neighboring CXXC4 protein, which harbors a CXXC domain and recruits TET2 to unmethylated CpG sites[321,322]. As a tumor suppressor gene, loss of function mutations in TET2 are associated with loss of catalytic activity and transformation to hematological malignancies[320,323,324].

Alterations and prevalence: Somatic TET2 mutations, including nonsense, frameshift, splice site, and missense mutations, are observed in 20-25% of myelodysplastic syndrome (MDS) associated diseases, including 40-60% chronic myelomonocytic leukemia (CMML)[253]. TET2 mutations at H1881 and R1896 are frequently observed in myeloid malignancies[323,325]. TET2 mutations are also observed in 9% of uterine corpus endometrial carcinoma and acute myeloid leukemia (AML), 8% of skin cutaneous melanoma, 7% of diffuse large B-cell lymphoma (DLBCL), 4% of colorectal adenocarcinoma, lung squamous cell carcinoma, and stomach adenocarcinoma, and 2% of sarcoma, esophageal adenocarcinoma, bladder urothelial carcinoma, cervical squamous cell carcinoma, lung adenocarcinoma, uterine carcinosarcoma, and kidney chromophobe[4,5]. Alterations in TET2 are also observed in the pediatric population[5]. Somatic mutations are observed in 3% of Hodgkin lymphoma (2 in 61 cases) and leukemia (9 in 311 cases), and less than 1 % of bone cancer (3 in 327 cases), B-lymphoblastic leukemia/lymphoma (2 in 252 cases), peripheral nervous system cancers (5 in 1158 cases), glioma (1 in 297 cases), and embryonal tumor (1 in 332 cases)[5]. Biallelic deletion of TET2 is observed in 2% of leukemia (6 in 250 cases), and less than 1% of Wilms tumor (1 in 136 cases) and B-lymphoblastic leukemia/lymphoma (4 in 731 cases)[5].

Potential relevance: The presence of TET2 mutations may be used as one of the major diagnostic criteria in pre-primary myelofibrosis (pre-PMF) and overt PMF in the absence of JAK2/CALR/MPL mutations[27]. TET2 mutations are associated with poor prognosis in PMF and an increased rate of transformation to leukemia[326]. TET2 mutations may be utilized for the diagnosis of angioimmunoblastic T-cell lymphoma (AITL) versus other peripheral T-cell lymphomas (PTCLs)[327].

INPP4B deletion

inositol polyphosphate-4-phosphatase type II B

Background: INPP4B encodes inositol polyphosphate 4-phosphatase type II, a member of the inositol polyphosphate 4-phosphatase family which also includes INPP4A[1,422]. INPP4B, along with PTEN and PIPP, is a phosphoinositide phosphatase that modulates the PI3K/AKT signaling pathway by hydrolyzing phosphatidylinositol 3,4-bisphosphate to generate phosphatidylinositol 3-phosphate, thereby suppressing the PI3K/AKT signaling cascade[423]. Although overexpression of INPP4B has been observed in several tumor types and is suggested to be associated with poor outcomes and response to therapy, alterations including mutations leading to loss of INPP4B function have been observed to result in enhanced AKT signaling, cell proliferation, and decreased survival in other tumor types, supporting a tumor suppressor role for INPP4B[424,425].

Alterations and prevalence: Somatic mutations in INPP4B are observed in 9% of uterine corpus endometrial carcinoma, 5% of diffuse large B-cell lymphoma, 4% of lung adenocarcinoma, 3% of skin cutaneous melanoma, head and neck squamous cell carcinoma, and stomach adenocarcinoma, and 2% of cervical squamous cell carcinoma, lung squamous cell carcinoma, bladder urothelial carcinoma, colorectal adenocarcinoma, and uterine carcinosarcoma[4,5]. Biallelic loss of INPP4B is observed in 2% of bladder urothelial carcinoma, uterine carcinosarcoma, and brain lower grade glioma[4,5]. Amplification of INPP4B is observed in 3% of cholangiocarcinoma and esophageal adenocarcinoma, and 2% of sarcoma, stomach adenocarcinoma, and ovarian serous cystadenocarcinoma[4,5].

Potential relevance: Currently, no therapies are approved for INPP4B aberrations.

Biomarker Descriptions (continued)

FAT1 deletion

FAT atypical cadherin 1

Background: FAT1 encodes the FAT atypical cadherin 1 protein, a member of the cadherin superfamily characterized by the presence of cadherin-type repeats[1,319]. FAT cadherins, which also include FAT2, FAT3, and FAT4, are transmembrane proteins containing a cytoplasmic domain and a number of extracellular laminin G-like motifs and EGF-like motifs, which contributes to their individual functions[319]. The cytoplasmic tail of FAT1 is known to interact with a number of protein targets involved in cell adhesion, proliferation, migration, and invasion[319]. FAT1 has been observed to influence the regulation of several oncogenic pathways, including the WNT/β-catenin, Hippo, and MAPK/ERK signaling pathways, as well as epithelial to mesenchymal transition[319]. Alterations of FAT1 lead to down-regulation or loss of function, supporting a tumor suppressor role for FAT1[319].

Alterations and prevalence: Somatic mutations in FAT1 are predominantly truncating although, the R1627Q mutation has been identified as a recurrent hotspot[4,5]. Mutations in FAT1 are observed in 22% of head and neck squamous cell carcinoma, 20% of uterine corpus endometrial carcinoma, 14% of lung squamous cell carcinoma and skin cutaneous melanoma, and 12% diffuse large b-cell lymphoma and bladder urothelial carcinoma[4,5]. Biallelic loss of FAT1 is observed in 7% of head and neck squamous cell carcinoma, 6% of lung squamous cell carcinoma, 5% of esophageal adenocarcinoma, and 4% of diffuse large b-cell lymphoma, stomach adenocarcinoma and uterine carcinosarcoma[4,5].

Potential relevance: Currently, no therapies are approved for FAT1 aberrations.

HLA-A deletion

major histocompatibility complex, class I, A

Background: The HLA-A gene encodes the major histocompatibility complex, class I, A[1]. MHC (major histocompatibility complex) class I molecules are located on the cell surface of nucleated cells and present antigens from within the cell for recognition by cytotoxic T cells[331]. MHC class I molecules are heterodimers composed of two polypeptide chains, α and B2M[332]. 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[333,334,335]. Downregulation of MHC class I promotes tumor evasion of the immune system, suggesting a tumor suppressor role for HLA-A[336].

Alterations and prevalence: Somatic mutations in HLA-A are observed in 7% of diffuse large B-cell lymphoma (DLBCL), 4% of cervical squamous cell carcinoma and head and neck squamous cell carcinoma, 3% of colorectal adenocarcinoma, and 2% of uterine corpus endometrial carcinoma and stomach adenocarcinoma[4,5]. Biallelic loss of HLA-A is observed in 4% of DLBCL[4,5].

Potential relevance: Currently, no therapies are approved for HLA-A 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[331]. MHC class I molecules are heterodimers composed of two polypeptide chains, α and B2M[332]. 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[333,334,335]. Downregulation of MHC class I promotes tumor evasion of the immune system, suggesting a tumor suppressor role for HLA-B[336].

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

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)[1,11]. JAK2 is a member of the Janus kinase (JAK) family, which includes JAK1, JAK2, JAK3, and TYK2[11]. Janus kinases are characterized by the presence of a second phosphotransferase-related or pseudokinase domain immediately N-terminal to the PTK domain[12]. JAK kinases function with signal

Biomarker Descriptions (continued)

transducer and activator of transcription (STAT) proteins to facilitate intracellular signal transduction required for cytokine receptor and interferon-alpha/beta/gamma signaling[12,13,14]. Since JAK2 functions in interferon receptor signaling, inactivation of JAK2 is proposed to inhibit the presentation of tumor antigens and contribute to immune evasion[15,16].

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[17,18]. The JAK2 V617F mutation is rarely observed in acute myeloid leukemia (AML)[19,20]. Mutations in the pseudokinase domain of JAK2, including R683G, have been detected in 8% of ALL[21,22]. JAK2 fusions are observed in myeloid and lymphoid leukemias with partner genes including TEL, PCM1, and BCR[23,24,25,26]. JAK2 fusions are infrequently observed in solid tumors[4]. As with JAK1, truncating mutations in JAK2 are common in solid tumors and particularly enriched in uterine cancers[4]. 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[4,5]. Alterations in JAK2 are also observed in pediatric cancers[4,5]. 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)[4,5]. JAK2 fusions are observed in 10% of B-lymphoblastic leukemia/lymphoma and 1% of leukemia (1 in 107 cases)[4,5]. 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)[4,5].

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)[27,28]. Ruxolitinib[29] (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[30]. 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[31]. Some case studies report efficacy with ruxolitinib in myeloid and lymphoid leukemias, although duration of complete response was limited[23,24,25,26].

SDHD deletion

succinate dehydrogenase complex subunit D

Background: The SDHD gene encodes succinate dehydrogenase complex subunit D of the succinate dehydrogenase (SDH) enzyme complex[1,74]. The SDH enzyme complex, also known as complex II of the mitochondrial respiratory chain, is composed of four subunits encoded by SDHA, SDHB, SDHC, and SDHD[75,76]. SDH is a key mitochondrial enzyme complex that catalyzes the oxidation of succinate to fumarate in the tricarboxylic acid cycle and transfers the electrons to ubiquinone in the electron transport chain[75,76]. SDHD, along with SDHC, anchors SDHA and SDHB to the inner mitochondrial membrane and provides a binding site for ubiquinone[74]. Mutations in SDH genes lead to abnormal stabilization of hypoxia-inducible factors and pseudo-hypoxia, thereby promoting cell proliferation, angiogenesis, and tumorigenesis[74,75,76]. Inherited pathogenic mutations in SDHD have been associated with paragangliomas and gastrointestinal stromal tumors[1,74,77].

Alterations and prevalence: Somatic mutations in SDHD are observed in 1% of mesothelioma, uterine corpus endometrial carcinoma, adrenocortical carcinoma, esophageal adenocarcinoma, colorectal adenocarcinoma, and lung adenocarcinoma[4,5]. Biallelic loss of SDHD is observed in 3% of testicular germ cell tumors, skin cutaneous melanoma, cervical squamous cell carcinoma, and uveal melanoma, and 2% of sarcoma and uterine carcinosarcoma[4,5].

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

MGA deletion, MGA p.(L1764*) c.5291T>A

MGA, MAX dimerization protein

Background: The MGA gene encodes MAX dimerization protein MGA, a member of the basic helix-loop-helix leucine zipper (bHLHZ) transcription factor superfamily[1,416]. Specifically, MGA belongs to group B of the bHLHZ superfamily, which also includes MYC, MAD, and MNT[417]. MGA is capable of heterodimerization with the MAX bHLHZ transcription factor, which results in DNA recognition and transcriptional regulation of target genes involved in cell growth and proliferation[416]. MGA suppresses MYC activity, potentially resulting in MYC target gene downregulation[418]. Mutations in MGA have been observed to correlate with high TMB and deficiency in DNA repair[419].

Alterations and prevalence: Somatic mutations in MGA are predominantly missense or truncating and are observed in 16% of uterine corpus endometrial carcinoma, 13% of skin cutaneous melanoma, 8% of stomach adenocarcinoma and lung adenocarcinoma, and 6% of colorectal adenocarcinoma and bladder urothelial carcinoma[4,5]. MGA biallelic deletion is observed in 6% of diffuse large B-

Biomarker Descriptions (continued)

cell lymphoma (DLBCL), 3% of mesothelioma, and 2% of ovarian serous cystadenocarcinoma, lung adenocarcinoma, and colorectal adenocarcinoma[4,5].

Potential relevance: Currently, no therapies are approved for MGA aberrations. However, MGA mutation has been observed to be enriched in non-small cell lung cancer (NSCLC) patients with higher objective response rates to immune checkpoint inhibitor (ICI) therapy[419].

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[57]. PDIA3 has also been identified as being involved EGFR regulation, mTOR signaling, and associated with the major histocompatibility complex (MHC) protein loading complex (PLC)[58]. 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[58,59,60].

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[4,5]. 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[4,5].

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[57]. Conversely, PDIA3 loss is correlated with aggressive disease and poor survival in gastric cancer and head and neck cancer[59,60].

B2M deletion

beta-2-microglobulin

Background: The B2M gene encodes the beta-2-microglobulin protein[1]. B2M is an extracellular component of the major histocompatibility class (MHC) class I and is important for proper folding and transport of MHC class I to the cell surface of nucleated cells[403]. MHC class I molecules are located on the cell surface and present antigens from within the cell for recognition by cytotoxic T cells[331]. Peptide antigen presentation by MHC class I requires B2M, and mutation or loss of B2M prevents presentation and results in escape from immune recognition[404]. In cancer, mutations or loss of B2M allows for immune evasion by tumor cells, thereby preventing their destruction and supporting a tumor suppressor role for B2M[404].

Alterations and prevalence: Somatic mutations in B2M are observed in 22% of diffuse large B-cell lymphoma (DLBCL), 5% of stomach adenocarcinoma, 4% of colorectal adenocarcinoma, 3% of uterine corpus endometrial carcinoma and cholangiocarcinoma, and 2% of cervical squamous cell carcinoma and skin cutaneous melanoma[4,5]. Biallelic loss of B2M is observed in 8% of DLBCL 5% of mesothelioma, and 2% of lung adenocarcinoma and skin cutaneous melanoma[4,5].

Potential relevance: Currently, no therapies are approved for B2M aberrations. Loss of B2M has been implicated in resistance to immunotherapy in melanoma[404,405]. However, B2M mutations in microsatellite instability-high colorectal carcinomas show response to immune checkpoint inhibitors[406].

CREBBP deletion

CREB binding protein

Background: The CREBBP gene encodes the CREB binding protein (also known as CBP), a highly conserved and ubiquitously expressed tumor suppressor. CREBBP is a member of the KAT3 family of lysine acetyl transferases, which, along with EP300, interact with over 400 diverse proteins, including Cyclin D1, p53, and BCL6[61,62]. CREBBP functions as a global transcriptional coactivator through the modification of lysines on nuclear proteins[61]. CREBBP binds to cAMP-response element binding protein (CREB) and is known to play a role in embryonic development, growth, and chromatin remodeling[61]. Upon disruption of normal CREBBP functions through genomic alterations, cells become susceptible to defects in differentiation and malignant transformation[63]. Inherited CREBBP mutations and deletions result in Rubinstein-Taybi syndrome (RTS), a developmental disorder with an increased susceptibility to solid tumors[64].

Alterations and prevalence: Mutations in CREBBP are observed in up to 12% of bladder urothelial carcinoma, uterine corpus endometrial carcinoma, and skin cutaneous melanoma, and in 5-10% of stomach adenocarcinoma, lung squamous cell carcinoma, and cervical squamous cell carcinoma[4,5]. CREBBP is frequently mutated in 15-17% of small cell lung cancer (SCLC)[65]. Inactivating mutations and deletions of CREBBP account for over 70% of all B-cell non-Hodgkin lymphoma diagnoses including 60% of follicular lymphoma and 30% of diffuse large-B-cell lymphoma (DLBCL)[61]. The rare t(11;16)(q23;p13) translocation fuses CREBBP with the

Biomarker Descriptions (continued)

partner gene KMT2A/MLL, in 0.2% secondary AML and 0.1% myelodysplastic syndrome (MDS)[66,67,68]. Elevated expression of CBP was detected in lung cancer cells and tumor tissue as compared to normal lung cells in one study[69].

Potential relevance: The t(8;16)(p11.2;p13.3) translocation resulting in KAT6A::CREBBP fusion is associated with poor/adverse risk in AML[70,71]. A mutation in CREBBP is a diagnostic marker of diffuse large B-cell lymphoma[72]. SCLC patients with CREBBP-positive tumors demonstrate lower overall survival (OS) and disease-free survival (DFS) compared to those with CREBBP-negative tumors[73].

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[1,6]. DUBs are responsible for protein deubiquitination, thereby counter-regulating the post-transcriptional ubiquitin modification of proteins within the cell[7]. 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[8,9]. 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[10]. Mutations in CYLD were originally identified in patients with familial cylindromatosis, a genetic condition that predisposes patients to the development of skin appendage tumors[9,10]. 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[9].

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[4,5]. Biallelic loss of CYLD has been observed in 2% of prostate adenocarcinoma, diffuse large B-cell lymphoma, sarcoma, and uterine carcinosarcoma[4,5].

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

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[369,370,371]. 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[370,371]. In cancer, mutations in CBFB have been implicated in decreased protein stability and loss of function, supporting a tumor suppressor role for CBFB[371]

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[4]. Biallelic deletions in CBFB are found in 2% of ovarian serous cystadenocarcinoma, prostate adenocarcinoma, and breast invasive carcinoma[4]. 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[372]. Translocations often result in CBFB::MYH11 fusion, which can exist as one of multiple transcripts, depending on the exons fused[372].

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)[28,70,71].

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[123]. 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[123,124,125]. CTCF mutations lead to disruption of TAD boundaries which alters gene expression and may promote oncogenesis[123].

Biomarker Descriptions (continued)

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[4,5].

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)[1,396]. 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[397]. 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[398,399]. 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[400].

Alterations and prevalence: Mutations in CDH1 are predominantly missense or truncating and have been observed to result in loss of function[4,5,401,402]. 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[4,5]. 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[4,5].

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

ZFHX3 deletion

zinc finger homeobox 3

Background: ZFHX3 encodes zinc finger homeobox 3, a large transcription factor composed of several DNA binding domains, including seventeen zinc finger domains and four homeodomains[1,337,338]. Functionally, ZFHX3 is found to be necessary for neuronal and myogenic differentiation[338,339]. ZFHX3 is capable of binding and repressing transcription of α-fetoprotein (AFP), thereby negatively regulating the expression of MYB and cancer cell growth[340,341,342,343,344]. In addition, ZFHX3 has been observed to be altered in several cancer types, supporting a tumor suppressor role for ZFHX3[340,343,345,346].

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[4,5]. 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[4,5].

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

DSC3 deletion

desmocollin 3

Background: The DSC3 gene encodes desmocollin 3, a member of the desmocollin (DSC) subfamily of the cadherin superfamily, which also includes DSC1 and DSC2[1]. DSCs along with desmogleins (DSGs) function as membrane-spanning constituents of the desmosomes[255]. Desmosomes are protein complexes in the intracellular junctions that confer stability and strengthen cell-cell adhesion[256]. Deregulation of DSC expression is suggested to impact β-catenin signaling and has been observed in a number of cancer types, supporting a potential role for DSC3 in tumorigenesis[255,257,258,259].

Biomarker Descriptions (continued)

Alterations and prevalence: Somatic mutations in DSC3 are observed in 19% of skin cutaneous melanoma, 8% of uterine corpus endometrial carcinoma, 5% of diffuse large B-cell lymphoma, 4% of lung adenocarcinoma, and 3% of bladder urothelial carcinoma[4,5]. Biallelic deletion of DSC3 is observed in 2% of pancreatic adenocarcinoma and esophageal adenocarcinoma[4,5].

Potential relevance: Currently, no therapies are approved for DSC3 aberrations.

DSC1 deletion

desmocollin 1

Background: The DSC1 gene encodes desmocollin 1, a member of the desmocollin (DSC) subfamily of the cadherin superfamily, which also includes DSC2 and DSC3[1]. DSCs along with desmogleins (DSGs) function as membrane-spanning constituents of the desmosomes[255]. Desmosomes are protein complexes in the intracellular junctions that confer stability and strengthen cell-cell adhesion[256]. Deregulation of DSC expression is suggested to impact β-catenin signaling and has been observed in a number of cancer types, supporting a potential role for DSC1 in tumorigenesis[255,257,258,259].

Alterations and prevalence: Somatic mutations in DSC1 are observed in 17% of skin cutaneous melanoma, 8% of uterine corpus endometrial carcinoma, 4% of uterine carcinosarcoma, and 3% of lung adenocarcinoma, lung squamous cell carcinoma, and colorectal adenocarcinoma[4,5]. Biallelic deletion of DSC1 is observed in 2% of pancreatic adenocarcinoma and esophageal adenocarcinoma[4,5].

Potential relevance: Currently, no therapies are approved for DSC1 aberrations.

SMAD2 deletion

SMAD family member 2

Background: The SMAD2 gene encodes the SMAD family member 2, a transcription factor that belongs to a family of 8 SMAD genes that can be divided into three main classes[1,149,150]. SMAD1, SMAD2, SMAD3, SMAD5, and SMAD8 are part of the regulator SMAD (R-SMAD) class while SMAD4 belongs to the common mediator SMAD (co-SMAD) class. The inhibitory SMAD (I-SMAD) class includes both SMAD6 and SMAD7[149,150]. As part of the R-SMAD class, SMAD2 functions by mediating signal transmission in the transforming growth factor beta (TGF-β) signaling pathway, a pathway critical in cell growth, differentiation, and tumor development[150]. Following activation of type I TGF-β receptors, SMAD2 and SMAD3 are activated via phosphorylation and form a complex with SMAD4, leading to nuclear translocation and activation or repression of target genes[151,152]. Deregulation of SMAD2, including mutation and loss of expression, has been observed in cancer leading to disruption of SMAD2/3/4 complex formation and tumorigenesis, supporting a tumor suppressor role for SMAD2[152,153].

Alterations and prevalence: Somatic mutations in SMAD2 are observed in 5% of uterine corpus endometrial carcinoma and colorectal adenocarcinoma, 3% of skin cutaneous melanoma, and 2% of stomach adenocarcinoma and lung adenocarcinoma[4,5]. The nonsense, truncating mutation, p.S464*, is the most commonly observed alteration and is recurrent[4,5,152]. Two recurrent hotspot mutations R321 and P305 occur in the mad homology 2 (MH2) domain leading to the disruption of the heterotrimeric SMAD2/SMAD3-SMAD4 complex[4,5,154]. SMAD2 deletion is observed in 4% of esophageal adenocarcinoma and 3% of pancreatic adenocarcinoma[4,5].

Potential relevance: Currently, no therapies are approved for SMAD2 aberrations.

RUNX1 deletion

RUNX family transcription factor 1

Background: The RUNX1 gene encodes the runt-related transcription factor (RUNX) 1, part of the RUNX family of transcription factors, which also includes RUNX2 and RUNX3[242]. All RUNX proteins share several conserved regions with similar functionality, including a highly conserved N-terminal ‘runt’ domain responsible for binding DNA, a C-terminal region composed of an activation domain, inhibitory domain, protein-interacting motifs, and a nuclear matrix targeting signal[243]. Each of these proteins interacts with core binding factor beta (CBFβ) to form the core binding factor (CFB) complex[243]. Consequently, RUNX1, RUNX2, and RUNX3 are collectively known as core binding factor alpha (CBFα) since they can each function as the alpha subunit of CBF[244]. Specifically, CBFβ binds to the 'runt' domain of RUNX1, leading to RUNX1 stabilization and increased affinity of the CFB complex for promoters involved in hematopoietic differentiation and cell cycle regulation[245,246]. RUNX1 is frequently mutated in various hematological malignancies[246]. Germline mutations in RUNX1 result in a rare autosomal dominant condition known as familial platelet disorder with predisposition to acute myeloid leukemia (FPD/AML)[247,248]. Somatic mutations and chromosomal translocations in RUNX1 are often observed in myelodysplastic syndrome (MDS), acute myeloid leukemia (AML), acute lymphoblastic leukemia (ALL), and chronic myelomonocytic leukemia (CMML)[246].

Alterations and prevalence: RUNX1 is frequently rearranged in hematological malignancies with over 50 different observed translocations[249]. RUNX1 translocations occur in 4% of all AML[4,5]. A recurrent translocation, t(8;21)(q22;q22), results in

Biomarker Descriptions (continued)

RUNX1::RUNX1T1 fusion and is observed in 5-10% of AML[214]. The RUNX1::RUNX1T1 fusion, consists of the runt-homology domain (RHD) of RUNX1 and the majority of RUNX1T1, which promotes oncogenesis by altering transcriptional regulation of RUNX1 target genes[214,246]. Another translocation, t(12;21)(q34;q11), results in ETV6::RUNX1 fusion and is observed in 2% of adult ALL[250]. Somatic mutations in RUNX1 include missense, nonsense, and frameshift mutations resulting in loss of function or dominant negative effects[246]. RUNX1 somatic mutations are observed in approximately 10% of AML, 10-15% of MDS, 5% of uterine corpus endometrial carcinoma, 4% of breast invasive carcinoma, 3% of bladder urothelial carcinoma, and 2% of colorectal adenocarcinoma[4,5,246]. Biallelic deletion of RUNX1 is observed in 7% of esophageal adenocarcinoma and 2% of stomach adenocarcinoma[4,5]. Alterations in RUNX1 are common in pediatric cancers, particularly the ETV6::RUNX1 fusion, which is observed in 20-25% of childhood ALL[250,251]. Overall, RUNX1 fusions are observed in 12% of B-lymphoblastic leukemia/lymphoma[4,5]. Somatic mutations in RUNX1 are observed in 5% of T-lymphoblastic leukemia/lymphoma, and less than 1% of bone cancer (3 in 327 cases), B-lymphoblastic leukemia/lymphoma (1 in 252 cases), glioma (1 in 297 cases), and embryonal tumor (1 in 332 cases)[4,5]. Biallelic deletion of RUNX1 is observed in 5% of leukemia and less than 1% of B-lymphoblastic leukemia/lymphoma (5 in 731 cases)[4,5].

Potential relevance: AML with RUNX1::RUNX1T1 fusions is considered a distinct molecular subtype by the World Health Organization (WHO)[28]. Translocations involving RUNX1, specifically t(8;21)(q22;q22)/RUNX1::RUNX1T1, is associated with favorable risk in AML[71]. The translocation t(12;21)(q34;q11) that results in ETV6::RUNX1 fusion is associated with standard risk in adult ALL and favorable risk in pediatric ALL[30,113,252]. On the other hand, mutations in RUNX1 confer poor prognosis in AML, MDS, and systemic mastocytosis (SM)[71,253,254].

EP300 deletion

E1A binding protein p300

Background: The EP300 gene encodes the E1A binding protein p300[1]. EP300 is a member of the KAT3 family of lysine acetyl transferases, which, along with CREBBP (also known as CBP), interact with over 400 diverse proteins, including Cyclin D1, p53, and BCL6[61,62]. EP300 functions as a transcriptional coactivator and has been observed to activate members of the E2F transcription factor family, thereby regulating expression of genes required for cell cycle G1/S phase transition[306,307]. Along with transcriptional coactivation, EP300 also functions in the formation of the transcription pre-initiation complex[306]. Inherited EP300 mutations result in Rubinstein-Taybi syndrome (RTS), a developmental disorder with an increased susceptibility to solid tumors[64].

Alterations and prevalence: Somatic mutations in EP300 are observed in 15% of bladder urothelial carcinoma, 14% of uterine corpus endometrial carcinoma, 12% of cervical squamous cell carcinoma, 8% of skin cutaneous melanoma, 7% of head and neck squamous cell carcinoma, and 5% of stomach adenocarcinoma, lung squamous cell carcinoma, esophageal adenocarcinoma, and colorectal adenocarcinoma[4,5]. Inactivating EP300 mutations are associated with lack of acetylation activity of EP300, resulting in altered expression of protein targets[308].

Potential relevance: Currently, no therapies are approved for EP300 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[264]. ZRSR2 interacts with components of the pre-spliceosome assembly including SRSF2 and U2AF2/U2AF1 heterodimer[264,265]. 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[264,266].

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[5,253].

Potential relevance: Mutation of ZRSR2 is associated with poor prognosis in myelodysplastic syndromes as well as poor/adverse risk in acute myeloid leukemia (AML)[70,71,253].

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[373,374]. BCOR also associates with class I and II histone deacetylases (HDACs), suggesting an alternate mechanism

Biomarker Descriptions (continued)

for BCOR-mediated transcriptional repression independent of BCL6[374]. Genetic alterations in BCOR result in protein dysfunction, which suggests BCOR functions as a tumor suppressor gene[375,376,377].

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)[4,253,378,379]. 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[4,5]. Although less common, BCOR fusions and internal tandem duplications (ITDs) have been reported in certain rare cancer types[380,381,382]. Specifically, BCOR::CCNB3 rearrangements define a particular subset of sarcomas with Ewing sarcoma-like morphology known as BCOR::CCNB3 sarcomas (BCS)[383,384]. Alterations in BCOR are also observed in pediatric cancers[4,5]. 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)[4,5]. 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[380].

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[122,385]. Additionally, translocation t(x;22)(p11;q13) resulting in ZC3H7B::BCOR fusion is a useful ancillary diagnostic marker of high-grade endometrial stromal sarcoma[122]. 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[28,70,71,253,378]. 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%)[379]. Additionally, BCOR ITDs and BCOR::EP300 fusion are molecular alterations of significance in pediatric gliomas[386,387].

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[1,347]. 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)[347,348,349,350]. In DEAD-box proteins, the DEAD domain interacts with β- and γ-phosphates of ATP through Mg2+ and is required for ATP hydrolysis[347]. DDX3X is involved in several processes including the unwinding of double-stranded RNA, splicing of pre-mRNA, RNA export, transcription, and translation[351,352,353,354,355,356,357,358]. Deregulation of DDX3X has been shown to impact cancer progression by modulating proliferation, metastasis, and drug resistance[351].

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[4,5]. 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[4,5].

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

RBM10 deletion

RNA binding motif protein 10

Background: RBM10 encodes RNA binding motif protein 10, a member of the RNA binding proteins (RBP) family[1,260]. RBM10 regulates RNA splicing and post-transcriptional modification of mRNA[260,261]. 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[260]. RBM10 has been observed to promote transformation and proliferation in lung cancer, supporting an oncogenic role for RBM10[262,263].

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[4,5]. Biallelic loss of RBM10 is observed in 3% of esophageal adenocarcinoma and 2% of head and neck squamous cell carcinoma[4,5]. 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[4,5].

Biomarker Descriptions (continued)

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

Alerts Informed By Public Data Sources

Current FDA Information

Contraindicated Not recommended Resistance Breakthrough Fast Track

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

KRAS p.(G12D) c.35G>A

cetuximab

Cancer type: Colorectal Cancer **Label as of:** 2021-09-24 **Variant class:** KRAS G12 mutation

Indications and usage:

Erbitux® is an epidermal growth factor receptor (EGFR) antagonist indicated for treatment of:

Head and Neck Cancer

- Locally or regionally advanced squamous cell carcinoma of the head and neck in combination with radiation therapy.
- Recurrent locoregional disease or metastatic squamous cell carcinoma of the head and neck in combination with platinum-based therapy with fluorouracil.
- Recurrent or metastatic squamous cell carcinoma of the head and neck progressing after platinum-based therapy.

Colorectal Cancer

K-Ras wild-type, EGFR-expressing, metastatic colorectal cancer as determined by FDA-approved test

- in combination with FOLFIRI for first-line treatment,
- in combination with irinotecan in patients who are refractory to irinotecan-based chemotherapy,
- as a single agent in patients who have failed oxaliplatin- and irinotecan-based chemotherapy or who are intolerant to irinotecan.

Limitations of Use: Erbitux® is not indicated for treatment of Ras-mutant colorectal cancer or when the results of the Ras mutation tests are unknown.

BRAF V600E Mutation-Positive Metastatic Colorectal Cancer (CRC)

- in combination with encorafenib, for the treatment of adult patients with metastatic colorectal cancer (CRC) with a BRAF V600E mutation, as detected by an FDA-approved test, after prior therapy.

Reference:

https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/125084s279lbl.pdf

KRAS p.(G12D) c.35G>A (continued)

panitumumab

Cancer type: Colorectal Cancer **Label as of:** 2025-01-16 **Variant class:** KRAS G12 mutation

Indications and usage:

VECTIBIX® is an epidermal growth factor receptor (EGFR) antagonist indicated for the treatment of:

Adult patients with wild-type RAS (defined as wild-type in both KRAS and NRAS as determined by an FDA-approved test) Metastatic Colorectal Cancer (mCRC)*:

- In combination with FOLFOX for first-line treatment.
- As monotherapy following disease progression after prior treatment with fluoropyrimidine, oxaliplatin, and irinotecan-containing chemotherapy.

KRAS G12C-mutated Metastatic Colorectal Cancer (mCRC)*

- In combination with sotorasib, for the treatment of adult patients with KRAS G12C-mutated mCRC, as determined by an FDA-approved test, who have received prior treatment with fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapy.

*Limitations of Use: VECTIBIX® is not indicated for the treatment of patients with RAS-mutant mCRC unless used in combination with sotorasib in KRAS G12C-mutated mCRC. VECTIBIX® is not indicated for the treatment of patients with mCRC for whom RAS mutation status is unknown.

Reference:

https://www.accessdata.fda.gov/drugsatfda_docs/label/2025/125147s213lbl.pdf

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

Current NCCN Information

Contraindicated Not recommended Resistance Breakthrough Fast Track

NCCN information is current as of 2025-05-01. To view the most recent and complete version of the guideline, go online to NCCN.org.
For NCCN International Adaptations & Translations, search www.nccn.org/global/what-we-do/international-adaptations.

Some variant specific evidence in this report may be associated with a broader set of alterations from the NCCN Guidelines. Specific variants listed in this report were sourced from approved therapies or scientific literature. These therapeutic options are appropriate for certain population segments with cancer. Refer to the NCCN Guidelines® for full recommendation.

KRAS p.(G12D) c.35G>A

cetuximab

Cancer type: Colon Cancer **Variant class:** KRAS G12 mutation

Summary:
NCCN Guidelines® include the following supporting statement(s):
- "Patients with any known KRAS mutation (exon 2, 3, 4) or NRAS mutation (exon 2, 3, 4) should not be treated with either cetuximab or panitumumab, unless given as part of a regimen targeting a KRAS G12C mutation."

Reference: NCCN Guidelines® - NCCN-Colon Cancer [Version 3.2025]

cetuximab

Cancer type: Rectal Cancer **Variant class:** KRAS G12 mutation

Summary:
NCCN Guidelines® include the following supporting statement(s):
- "Patients with any known KRAS mutation (exons 2, 3, and 4) or NRAS mutation (exons 2, 3, and 4) should not be treated with either cetuximab or panitumumab, unless given as part of a regimen targeting a KRAS G12C mutation."

Reference: NCCN Guidelines® - NCCN-Rectal Cancer [Version 2.2025]

panitumumab

Cancer type: Colon Cancer **Variant class:** KRAS G12 mutation

Summary:
NCCN Guidelines® include the following supporting statement(s):
- "Patients with any known KRAS mutation (exon 2, 3, 4) or NRAS mutation (exon 2, 3, 4) should not be treated with either cetuximab or panitumumab, unless given as part of a regimen targeting a KRAS G12C mutation."

Reference: NCCN Guidelines® - NCCN-Colon Cancer [Version 3.2025]

KRAS p.(G12D) c.35G>A (continued)

panitumumab

Cancer type: Rectal Cancer **Variant class:** KRAS G12 mutation

Summary:
NCCN Guidelines® include the following supporting statement(s):

- "Patients with any known KRAS mutation (exons 2, 3, and 4) or NRAS mutation (exons 2, 3, and 4) should not be treated with either cetuximab or panitumumab, unless given as part of a regimen targeting a KRAS G12C mutation."

Reference: NCCN Guidelines® - NCCN-Rectal Cancer [Version 2.2025]

Current EMA Information

Contraindicated Not recommended Resistance Breakthrough Fast Track

EMA information is current as of 2025-05-14. For the most up-to-date information, search www.ema.europa.eu.

KRAS p.(G12D) c.35G>A

cetuximab, cetuximab + oxaliplatin

Cancer type: Colorectal Cancer **Label as of:** 2025-01-16 **Variant class:** KRAS G12 mutation

Reference:

https://www.ema.europa.eu/en/documents/product-information/erbitux-epar-product-information_en.pdf

panitumumab + oxaliplatin

Cancer type: Colorectal Cancer **Label as of:** 2025-05-07 **Variant class:** KRAS G12 mutation

Reference:

https://www.ema.europa.eu/en/documents/product-information/vectibix-epar-product-information_en.pdf

Current ESMO Information

Contraindicated Not recommended Resistance Breakthrough Fast Track

ESMO information is current as of 2025-05-01. For the most up-to-date information, search www.esmo.org.

KRAS p.(G12D) c.35G>A

cetuximab

Cancer type: Colorectal Cancer **Variant class:** KRAS G12 mutation

Summary:
ESMO Clinical Practice Guidelines include the following supporting statement:

- "The presence of RAS mutations is associated with resistance to anti-EGFR mAbs and knowing the expanded RAS mutational status is mandatory for use of both cetuximab and panitumumab, avoiding anti-EGFR mAb treatment when a RAS mutation is confirmed".
- "RAS testing is mandatory before treatment with anti-EGFR mAbs and can be carried out on either the primary tumor or other metastatic sites [III, A]".

Reference: ESMO Clinical Practice Guidelines - ESMO-Metastatic Colorectal Cancer [Ann Oncol (2023); https://doi.org/10.1016/j.annonc.2022.10.003 (published)]

panitumumab

Cancer type: Colorectal Cancer **Variant class:** KRAS G12 mutation

Summary:
ESMO Clinical Practice Guidelines include the following supporting statement:

- "The presence of RAS mutations is associated with resistance to anti-EGFR mAbs and knowing the expanded RAS mutational status is mandatory for use of both cetuximab and panitumumab, avoiding anti-EGFR mAb treatment when a RAS mutation is confirmed".
- "RAS testing is mandatory before treatment with anti-EGFR mAbs and can be carried out on either the primary tumor or other metastatic sites [III, A]".

Reference: ESMO Clinical Practice Guidelines - ESMO-Metastatic Colorectal Cancer [Ann Oncol (2023); https://doi.org/10.1016/j.annonc.2022.10.003 (published)]

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 (continued)

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 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

PIK3CA p.(E545A) c.1634A>C

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
alpelisib + fulvestrant	○	○	○	○	✖
capivasertib + fulvestrant	○	○	○	✖	✖
inavolisib + palbociclib + fulvestrant	○	○	✖	✖	✖
HTL-0039732, atezolizumab	✖	✖	✖	✖	● (I/II)
JS-105, chemotherapy	✖	✖	✖	✖	● (I/II)
STX-478, hormone therapy	✖	✖	✖	✖	● (I/II)
JS-105	✖	✖	✖	✖	● (I)
RLY-2608	✖	✖	✖	✖	● (I)
SNV-4818, hormone therapy	✖	✖	✖	✖	● (I)

KRAS p.(G12D) c.35G>A

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
bevacizumab + CAPOX	✖	✖	✖	○	✖
bevacizumab + FOLFIRI	✖	✖	✖	○	✖
bevacizumab + FOLFOX	✖	✖	✖	○	✖
bevacizumab + FOLFOXIRI	✖	✖	✖	○	✖
avutometinib, defactinib	✖	✖	✖	✖	● (II)
olaparib + selumetinib, selumetinib	✖	✖	✖	✖	● (II)
regorafenib	✖	✖	✖	✖	● (II)
anti-KRAS G12D mTCR	✖	✖	✖	✖	● (I/II)
DN-022150	✖	✖	✖	✖	● (I/II)
ERAS-0015	✖	✖	✖	✖	● (I/II)
GDC-7035	✖	✖	✖	✖	● (I/II)
GFH-375	✖	✖	✖	✖	● (I/II)
HRS-4642, adebrelimab, SHR-9839, chemotherapy	✖	✖	✖	✖	● (I/II)
IMM-1-104	✖	✖	✖	✖	● (I/II)
RNK-08954	✖	✖	✖	✖	● (I/II)
TSN-1611	✖	✖	✖	✖	● (I/II)
YL-15293	✖	✖	✖	✖	● (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

KRAS p.(G12D) c.35G>A (continued)

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
ASP-4396	✖	✖	✖	✖	● (I)
AST-NS2101	✖	✖	✖	✖	● (I)
HMPL-415	✖	✖	✖	✖	● (I)
JAB-3312	✖	✖	✖	✖	● (I)
KRAS TCR, aldesleukin, SLATE 001, chemotherapy	✖	✖	✖	✖	● (I)
KRAS-EphA-2-CAR-DC, anti-PD-1, ipilimumab	✖	✖	✖	✖	● (I)
Nest-1	✖	✖	✖	✖	● (I)
PT-0253	✖	✖	✖	✖	● (I)
QLC-1101	✖	✖	✖	✖	● (I)
RMC-6236	✖	✖	✖	✖	● (I)
RMC-9805, RMC-6236	✖	✖	✖	✖	● (I)

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)
GTA-182	✖	✖	✖	✖	● (I)
ISM-3412	✖	✖	✖	✖	● (I)

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

Relevant Therapy Summary (continued)

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

MTAP deletion (continued)

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
MRTX-1719	✖	✖	✖	✖	● (I)
PH020-803	✖	✖	✖	✖	● (I)
S-095035	✖	✖	✖	✖	● (I)
SYH-2039	✖	✖	✖	✖	● (I)

ATM deletion

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

CDKN2A deletion

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

ATM p.(S1891*) c.5672C>A

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
talazoparib	✖	✖	✖	✖	● (II)
tuvusertib, PL-0264	✖	✖	✖	✖	● (I)

NF2 deletion

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

ARID1A deletion

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
tucidinostat, catequentinib, PD-1 Inhibitor, anti-PD-L1 antibody	✖	✖	✖	✖	● (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

CDKN2B deletion

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

FBXW7 deletion

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
ARTS-021	✖	✖	✖	✖	● (I/II)

SMAD4 deletion

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

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

HRR Details

Gene/Genomic Alteration	Finding
LOH percentage	***27.63%***
ATM	***CNV, CN:1.0***
ATM	***LOH, 11q22.3(108098341-108236285)x1***
CHEK1	***CNV, CN:1.0***
CHEK1	***LOH, 11q24.2(125496639-125525271)x1***
CHEK2	***CNV, CN:1.0***
CHEK2	***LOH, 22q12.1(29083868-29130729)x1***
PALB2	***CNV, CN:1.0***
PALB2	***LOH, 16p12.2(23614759-23652528)x1***

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

Thermo Fisher Scientific's Ion Torrent Oncomine Reporter software was used in generation of this report. Software was developed and designed internally by Thermo Fisher Scientific. The analysis was based on Oncomine Reporter (6.1.1 data version 2025.06(006)). The data presented here are from a curated knowledge base of publicly available information, but may not be exhaustive. FDA information was sourced from www.fda.gov and is current as of 2025-05-14. NCCN information was sourced from www.nccn.org and is current as of 2025-05-01. EMA information was sourced from www.ema.europa.eu and is current as of 2025-05-14. ESMO information was sourced from www.esmo.org and is current as of 2025-05-01. Clinical Trials information is current as of 2025-05-01. For the most up-to-date information regarding a particular trial, search www.clinicaltrials.gov by NCT ID or search local clinical trials authority website by local identifier listed in 'Other identifiers.' Variants are reported according to HGVS nomenclature and classified following AMP/ASCO/CAP guidelines (Li et al. 2017). Based on the data sources selected, variants, therapies, and trials listed in this report are listed in order of potential clinical significance but not for predicted efficacy of the therapies.

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