SML Samkwang Medical Lab

Patient Name:	이정복	**Primary Tumor Site:**	brain
Gender:	F	**Collection Date:**	2025.12.17
Sample ID:	N25-359		

Sample Cancer Type: Glioblastoma IDH-wildtype (Grade 4)

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Report Highlights

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Relevant Glioblastoma IDH-wildtype (Grade 4) Findings

Gene	Finding	Gene	Finding
BRAF	None detected	NTRK1	None detected
EGFR	*EGFR amplification, EGFRvIII*	NTRK2	None detected
FGFR1	None detected	NTRK3	None detected
FGFR2	None detected	RET	None detected
FGFR3	None detected	TERT	*TERT c.-124C>T*

Genomic Alteration	Finding
Tumor Mutational Burden	*7.58 Mut/Mb measured*

Relevant Biomarkers

Tier	Genomic Alteration	Relevant Therapies (In this cancer type)	Relevant Therapies (In other cancer type)	Clinical Trials
IA	*EGFR amplification* epidermal growth factor receptor Locus: chr7:55211010 **Diagnostic significance:** Glioblastoma IDH-wildtype (Grade 4)	None*	None*	10
IA	*TERT c.-124C>T* telomerase reverse transcriptase Allele Frequency: 46.47% Locus: chr5:1295228 Transcript: NM_198253.3 **Diagnostic significance:** Glioblastoma IDH-wildtype (Grade 4)	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.

Relevant Biomarkers (continued)

Tier	Genomic Alteration	Relevant Therapies (In this cancer type)	Relevant Therapies (In other cancer type)	Clinical Trials
IIC	*PDGFRA p.(D842V) c.2525A>T* platelet derived growth factor receptor alpha Allele Frequency: 41.54% Locus: chr4:55152093 Transcript: NM_006206.6	None*	**avapritinib** [1, 2 / I, II+] ripretinib	1
IIC	*SMARCB1 deletion* SWI/SNF related, matrix associated, actin dependent regulator of chromatin, subfamily b, member 1 Locus: chr22:24129273	None*	cabozantinib pazopanib sunitinib	2
IIC	*MTAP deletion* methylthioadenosine phosphorylase Locus: chr9:21802646	None*	None*	13
IIC	*CDKN2A deletion* cyclin dependent kinase inhibitor 2A Locus: chr9:21968178	None*	None*	5
IIC	*EGFRvIII* epidermal growth factor receptor Locus: chr7:55087058 - chr7:55223523	None*	None*	4
IIC	*PTEN deletion* phosphatase and tensin homolog Locus: chr10:89623659	None*	None*	4
IIC	*CHEK2 deletion* checkpoint kinase 2 Locus: chr22:29083868	None*	None*	1
IIC	*NF2 deletion* neurofibromin 2 Locus: chr22:29999923	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
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Prevalent cancer biomarkers without relevant evidence based on included data sources

*JAK2 deletion, MLH1 p.(V384D) c.1151T>A, Microsatellite stable, PTEN p.(K330Rfs*12) c.989_990delAA, RNASEH2B p.(H70Tfs*36) c.207_208insA, SDHB deletion, TCF7L2 deletion, TNFRSF14 deletion, ERRFI1 deletion, ENO1 deletion, PGD deletion, SPEN deletion, EPHA2 deletion, RPL5 p.(E82K) c.244G>A, HLA-B deletion, LARP4B deletion, GATA3 deletion, MAPK8 deletion, ARID5B deletion, CYP2C9 deletion, SUFU deletion, PDIA3 deletion, B2M deletion, NQO1 p.(P187S) c.559C>T, EP300 deletion, PHF6 p.(T170Nfs*2) c.508_509insA, Tumor Mutational Burden*

Variant Details

DNA Sequence Variants

Gene	Amino Acid Change	Coding	Variant ID	Locus	Allele Frequency	Transcript	Variant Effect
TERT	p.(?)	c.-124C>T	VCV001299388	chr5:1295228	46.47%	NM_198253.3	unknown

Variant Details (continued)

DNA Sequence Variants (continued)

Gene	Amino Acid Change	Coding	Variant ID	Locus	Allele Frequency	Transcript	Variant Effect
PDGFRA	p.(D842V)	c.2525A>T	COSM736	chr4:55152093	41.54%	NM_006206.6	missense
MLH1	p.(V384D)	c.1151T>A	.	chr3:37067240	51.85%	NM_000249.4	missense
PTEN	p.(K330Rfs*12)	c.989_990delAA	.	chr10:89720836	85.60%	NM_000314.8	frameshift Deletion
RNASEH2B	p.(H70Tfs*36)	c.207_208insA	.	chr13:51503676	2.97%	NM_024570.4	frameshift Insertion
RPL5	p.(E82K)	c.244G>A	COSM357798	chr1:93300390	41.54%	NM_000969.5	missense
NQO1	p.(P187S)	c.559C>T	.	chr16:69745145	46.90%	NM_000903.3	missense
PHF6	p.(T170Nfs*2)	c.508_509insA	.	chrX:133547605	2.32%	NM_032458.3	frameshift Insertion
DOCK3	p.(Y240H)	c.718T>C	.	chr3:51127787	50.64%	NM_004947.5	missense
NFKBIZ	p.(L671Rfs*2)	c.2012delT	.	chr3:101576211	44.46%	NM_031419.4	frameshift Deletion
GALNT17	p.(G243D)	c.728G>A	.	chr7:70881013	32.68%	NM_022479.3	missense
COG3	p.(T759Nfs*17)	c.2275_2276insA	.	chr13:46103965	2.61%	NM_031431.4	frameshift Insertion
OR4M2	p.(L309F)	c.927G>T	.	chr15:22369502	9.31%	NM_001004719.2	missense
BRIP1	p.(E675A)	c.2024A>C	.	chr17:59853835	53.97%	NM_032043.3	missense

Gene Fusions

Genes	Variant ID	Locus
EGFR::EGFR	EGFR-EGFR.E1E8.DelPositive.2	chr7:55087058 - chr7:55223523

Copy Number Variations

Gene	Locus	Copy Number	CNV Ratio
EGFR	chr7:55211010	9.22	4.28
SMARCB1	chr22:24129273	1.07	0.57
MTAP	chr9:21802646	1.18	0.62
CDKN2A	chr9:21968178	0.3	0.22
PTEN	chr10:89623659	1.08	0.58
CHEK2	chr22:29083868	1	0.59
NF2	chr22:29999923	1.12	0.6
JAK2	chr9:5021954	1.18	0.62
SDHB	chr1:17345303	1.2	0.64
TCF7L2	chr10:114710485	1.18	0.63
TNFRSF14	chr1:2488070	1.02	0.56
ERRFI1	chr1:8073246	1.22	0.65

Variant Details (continued)

Copy Number Variations (continued)

Gene	Locus	Copy Number	CNV Ratio
ENO1	chr1:8921399	1.12	0.6
PGD	chr1:10459132	1.1	0.59
SPEN	chr1:16174516	1.1	0.59
EPHA2	chr1:16451707	1.14	0.61
HLA-B	chr6:31322252	1.24	0.65
LARP4B	chr10:858847	1.09	0.59
GATA3	chr10:8097519	1.05	0.57
MAPK8	chr10:49609682	0.99	0.54
ARID5B	chr10:63661463	1.07	0.57
CYP2C9	chr10:96698378	0.84	0.47
SUFU	chr10:104263903	1.08	0.58
PDIA3	chr15:44038719	0.98	0.53
B2M	chr15:45003690	1.13	0.6
EP300	chr22:41489001	1.09	0.58
CD274	chr9:5456050	1.04	0.57
PDCD1LG2	chr9:5522530	1.16	0.62
RET	chr10:43609070	0.96	0.53
FGFR2	chr10:123239426	1.19	0.63

Biomarker Descriptions

EGFR amplification, EGFRvIII

epidermal growth factor receptor

Background: The EGFR gene encodes the epidermal growth factor receptor (EGFR), a member of the ERBB/human epidermal growth factor receptor (HER) tyrosine kinase family[1]. In addition to EGFR/ERBB1/HER1, other members of the ERBB/HER family include ERBB2/HER2, ERBB3/HER3, and ERBB4/HER4[116]. EGFR ligand-induced dimerization results in kinase activation and leads to stimulation of oncogenic signaling pathways, including the PI3K/AKT/MTOR and RAS/RAF/MEK/ERK pathways[117]. Activation of these pathways promotes cell proliferation, differentiation, and survival[118,119].

Alterations and prevalence: Recurrent somatic mutations in the tyrosine kinase domain (TKD) of EGFR are observed in approximately 10-20% of lung adenocarcinoma, and at higher frequencies in never-smoker, female, and Asian populations[18,19,120,121]. The most common mutations occur near the ATP-binding pocket of the TKD and include short in-frame deletions in exon 19 (EGFR exon 19 deletion) and the L858R amino acid substitution in exon 21[122]. These mutations constitutively activate EGFR resulting in downstream signaling, and represent 80% of the EGFR mutations observed in lung cancer[122]. A second group of less prevalent activating mutations includes E709K, G719X, S768I, L861Q, and short in-frame insertion mutations in exon 20[123,124,125,126]. EGFR activating mutations in lung cancer tend to be mutually exclusive to KRAS activating mutations[127]. In contrast, a different set of recurrent activating EGFR mutations in the extracellular domain includes R108K, A289V and G598V and are primarily observed in glioblastoma[122,128]. Amplification of EGFR is observed in several cancer types including 44% of glioblastoma multiforme, 12% of esophageal adenocarcinoma, 10% of head and neck squamous cell carcinoma, 8% of brain lower grade glioma, 6% of lung squamous cell carcinoma, 5% of bladder urothelial carcinoma cancer, lung adenocarcinoma, and stomach adenocarcinoma, 3% of cholangiocarcinoma, and 2% of cervical squamous cell carcinoma, sarcoma, and breast invasive carcinoma[18,19,121,128,129]. Deletion of exons 2-7, encoding the extracellular domain of EGFR (EGFRvIII), results in overexpression of a ligand-independent constitutively active

Biomarker Descriptions (continued)

protein and is observed in approximately 30% of glioblastoma[130,131,132]. Alterations in EGFR are rare in pediatric cancers[18,19]. Somatic mutations are observed in 2% of bone cancer and glioma, 1% of leukemia (4 in 354 cases), and less than 1% of B-lymphoblastic leukemia/lymphoma (2 in 252 cases), peripheral nervous system cancers (1 in 1158 cases), and embryonal tumors (3 in 332 cases)[18,19]. Amplification of EGFR is observed in 2% of bone cancer and less than 1% of Wilms tumor (1 in 136 cases), B-lymphoblastic leukemia/lymphoma (2 in 731 cases), and leukemia (1 in 250 cases)[18,19].

Potential relevance: Approved first-generation EGFR tyrosine kinase inhibitors (TKIs) include erlotinib[133] (2004) and gefitinib[134] (2015), which block the activation of downstream signaling by reversible interaction with the ATP-binding site. Although initially approved for advanced lung cancer, the discovery that drug sensitivity was associated with exon 19 and exon 21 activating mutations allowed first-generation TKIs to become subsequently approved for front-line therapy in lung cancer tumors containing exon 19 or exon 21 activating mutations[135]. Second-generation TKIs afatinib[136] (2013) and dacomitinib[137] (2018) bind EGFR and other ERBB/HER gene family members irreversibly and were subsequently approved. First- and second-generation TKIs afatinib, dacomitinib, erlotinib, and gefitinib are recommended for the treatment NSCLC harboring EGFR exon 19 insertions, exon 19 deletions, point mutations L861Q, L858R, S768I, and codon 719 mutations, whereas most EGFR exon 20 insertions, except p.A763_Y764insFQEA, confer resistance to the same therapies[138,139,140,141]. In 2025, the FDA approved the irreversible EGFR inhibitor, sunvozertinib[142], for the treatment of locally advanced or metastatic non-small cell lung cancer in adult patients with EGFR exon 20 insertion mutations whose disease has progressed on or after platinum-based chemotherapy. In 2022, the FDA granted breakthrough therapy designation to the irreversible EGFR inhibitor, CLN-081 (TPC-064)[143] for locally advanced or metastatic non-small cell lung cancer harboring EGFR exon 20 insertion mutations. In lung cancer containing EGFR exon 19 or 21 activating mutations, treatment with TKIs is eventually associated with the emergence of drug resistance[144]. The primary resistance mutation that emerges following treatment with first-generation TKI is T790M, accounting for 50-60% of resistant cases[122]. Third generation TKIs were developed to maintain sensitivity in the presence of T790M[144]. Osimertinib[145] (2015) is an irreversible inhibitor indicated for metastatic EGFR T790M positive lung cancer and for the first-line treatment of metastatic NSCLC containing EGFR exon 19 deletions or exon 21 L858R mutations. Like first-generation TKIs, treatment with osimertinib is associated with acquired resistance, specifically the C797S mutation, which occurs in 22-44% of cases[144]. The T790M and C797S mutations may be each selected following sequential treatment with a first-generation TKI followed by a third-generation TKI or vice versa[146]. T790M and C797S can occur in either cis or trans allelic orientation[146]. If C797S is observed following progression after treatment with a third-generation TKI in the first-line setting, sensitivity may be retained to first-generation TKIs[146]. If C797S co-occurs in trans with T790M following sequential treatment with first- and third-generation TKIs, patients may exhibit sensitivity to combination first- and third-generation TKIs, but resistance to third-generation TKIs alone[146,147]. However, C797S occurring in cis conformation with T790M, confers resistance to first- and third-generation TKIs[146]. Fourth-generation TKIs are in development to overcome acquired resistance mutations after osimertinib treatment, including BDTX-1535[148] (2024), a CNS-penetrating small molecule inhibitor, that received fast track designation from the FDA for the treatment of patients with EGFR C797S-positive NSCLC who have disease progression on or after a third-generation EGFR TKI. EGFR-targeting antibodies including cetuximab (2004), panitumumab (2006), and necitumumab (2016) are under investigation in combination with EGFR-targeting TKIs for efficacy against EGFR mutations[149]. The bispecific antibody, amivantamab[150] (2021), targeting EGFR and MET was approved for NSCLC tumors harboring EGFR exon 20 insertion mutations. A small molecule kinase inhibitor, lazertinib[151] (2024), was approved in combination with amivantamab as a first-line treatment for adult patients with locally advanced or metastatic NSCLC with EGFR exon 19 deletions or exon 21 L858R mutations. HLX-42[152], an anti-EFGR-antibody-drug conjugate (ADC) consisting of an anti-EGFR monoclonal antibody conjugated with a novel high potency DNA topoisomerase I (topo I) inhibitor, also received fast track designation (2024) for the treatment of patients with advanced or metastatic EGFR-mutated non-small cell lung cancer whose disease has progressed on a third-generation EGFR tyrosine kinase inhibitor. CPO301[153] (2023) received a fast track designation from the FDA for the treatment of EGFR mutations in patients with metastatic NSCLC who are relapsed/refractory or ineligible for EGFR targeting therapy such as 3rd-generation EGFR inhibitors, including osimertinib. The Oncoprex immunogene therapy quaratusugene ozeplasmid[154] (2020), in combination with osimertinib, received fast track designation from the FDA for NSCLC tumors harboring EGFR mutations that progressed on osimertinib alone. Amplification and mutations of EGFR commonly occur in H3-wild type IDH-wild type diffuse pediatric high-grade glioma[90,155,156].

TERT c.-124C>T

telomerase reverse transcriptase

Background: The TERT gene encodes telomerase reverse transcriptase, a component of the telomerase core enzyme along with the internal telomerase RNA template (TERC)[92]. TERT is repressed in most differentiated cells, resulting in telomerase silencing[92]. In cancer, telomerase reactivation is known to contribute to cellular immortalization[92,93]. Increased TERT expression results in telomerase activation, allowing for unlimited cancer cell proliferation through telomere stabilization[92]. In addition to its role in telomere maintenance, TERT has RNA-dependent RNA polymerase activity, which, when deregulated, can promote oncogenesis by facilitating mitotic progression and cancer cell stemness[92].

Alterations and prevalence: Somatic mutations are observed in 4% of skin cutaneous melanoma and uterine corpus endometrial carcinoma, 3% of kidney renal papillary cell carcinoma, and 2% of pancreatic adenocarcinoma, stomach adenocarcinoma, and sarcoma[18,19]. Additionally, TERT promoter mutations causing upregulation are observed in many cancer types, especially non-aural cutaneous melanoma (80% of cases), and glioblastoma (70% of cases)[93]. Specifically, TERT promoter mutations at C228T and C250T

Biomarker Descriptions (continued)

are recurrent and result in de novo binding sites for ETS transcription factors, leading to enhanced TERT transcription[92]. Amplification of TERT is observed in 15% of lung squamous cell carcinoma, 14% of esophageal adenocarcinoma, 13% of adrenocortical carcinoma and lung adenocarcinoma, and 10% of bladder urothelial carcinoma, 9% of ovarian serous cystadenocarcinoma, 6% of cervical squamous cell carcinoma, 5% of liver hepatocellular carcinoma, sarcoma, skin cutaneous melanoma, stomach adenocarcinoma, head and neck squamous cell carcinoma, 4% of uterine carcinosarcoma, 3% of uterine corpus endometrial carcinoma, breast invasive carcinoma, and 2% of diffuse large B-cell lymphoma[18,19]. TERT is overexpressed in over 85% of tumors and is considered a universal tumor associated antigen[94]. Alterations in TERT are rare in pediatric cancers[18,19]. Somatic mutations are observed in less than 1% of B-lymphoblastic leukemia/lymphoma (2 in 252 cases), glioma (2 in 297 cases), bone cancer (1 in 327 cases), and Wilms tumor (1 in 710 cases)[18,19]. TERT amplification is observed in 1-2% of peripheral nervous system cancers (2 in 91 cases), leukemia (2 in 250 cases), and B-lymphoblastic leukemia/lymphoma (5 in 731 cases)[18,19].

Potential relevance: Currently, no therapies are approved for TERT aberrations. TERT promoter mutations are diagnostic of oligodendroglioma IDH-mutant with 1p/19q co-deletion, while the absence of promoter mutations combined with an IDH mutation is characteristic of astrocytoma[95,96]. Due to its immunogenicity and near-universal expression on cancer cells, TERT has been a focus of immunotherapy research, including peptide, dendritic, and DNA vaccines as well as T-cell therapy[94].

PDGFRA p.(D842V) c.2525A>T

platelet derived growth factor receptor alpha

Background: The PDGFRA gene encodes the platelet derived growth factor receptor alpha, a member of the PDGF receptor type III receptor tyrosine kinase family, which includes PDGFRB, CSF1R, FLT1, FLT3, FLT4, KDR, and KIT[160,161]. PDGFRA is a receptor for platelet derived growth factors, which are mitogens for cells of mesenchymal origin[162]. PDGFRA may function as a homodimer or heterodimer with PDGFRB depending on the ligand[163]. The PDGFRA gene is physically adjacent to KIT and KDR on chromosome 4q12, and all 3 tyrosine kinases are often co-amplified in cancer[164]. Ligand binding to PDGFRA results in kinase activation and stimulation of downstream pathways, including the RAS/RAF/MEK/ERK and PI3K/AKT/MTOR pathways, which promotes cell proliferation and survival[165].

Alterations and prevalence: Recurrent somatic PDGFRA alterations are observed in both solid and hematological cancers and include activating mutations, gene amplification, and translocations generating PDGFRA gene fusions. Recurrent PDGFRA activating mutations, including D842V, V561D, N659K, and in-frame deletions in exon 18, are common in 30-40% of KIT negative gastrointestinal stromal tumors (GISTs) and approximately 7% overall[166,167,168,169]. PDGFRA recurrent mutations are also observed in 9% of skin cutaneous melanoma and uterine corpus endometrial carcinoma, 7% of lung adenocarcinoma, 5% of colorectal adenocarcinoma, 4% of lung squamous cell carcinoma, glioblastoma multiforme, and bladder urothelial carcinoma, 3% of stomach adenocarcinoma and head and neck squamous cell carcinoma, and 2% of cervical squamous cell carcinoma, liver hepatocellular carcinoma, brain lower grade glioma, and ovarian serous cystadenocarcinoma[18,19]. PDGFRA amplification is observed in 13% of glioblastoma multiforme, 5% of lung squamous cell carcinoma, 4% of brain lower grade glioma, 3% of sarcoma and skin cutaneous melanoma, and 2% of esophageal adenocarcinoma, testicular germ cell tumors, lung adenocarcinoma, uterine carcinosarcoma, and bladder urothelial carcinoma[18,19]. PDGFRA fusions are observed in gliomas and glioblastomas as well as eosinophilic leukemias, of which the FIP1L1::PDGFRA fusion defines approximately half of patients with hypereosinophilic syndrome[170,171,172]. Alterations of PDGFRA are rare in pediatric cancers[18,19]. Somatic mutations are observed in 2% of glioma, and less than 1% of embryonal tumors (3 in 332 cases), bone cancer (2 in 327 cases), and leukemia (1 in 354 cases)[18,19]. PDGFRA is amplified in 5% of bone cancer and less than 1% of Wilms tumor (1 in 136 cases)[18,19].

Potential relevance: Avapritinib[173] (2020) is a tyrosine kinase inhibitor (TKI) that is approved by the FDA for metastatic or unresectable gastrointestinal stromal tumors (GISTs) harboring PDGFRA exon 18 mutations, including PDGFRA D842V mutation. The FDA has granted fast track designation to crenolanib[174] (2017) for harboring PDGFRA D842V mutation. Imatinib[175] (2001) is a TKI approved for patients diagnosed with chronic eosinophilic leukemia harboring the FIP1L1::PDGFRA fusion. Additionally, imatinib is recommended for the treatment of GISTs harboring PDGFRA exon 18 mutations, with the exception of D842V[176]. Amplification of PDGFRA is a diagnostic marker of H3-wildtype and IDH-wildtype diffuse pediatric-type high-grade glioma[155,177]. PDGFRA rearrangements are associated with poor risk in pediatric acute lymphoblastic leukemia[178,179].

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[58]. The SWI/SNF complex remodels chromatin at promoter and enhancer elements to alter and regulate gene expression[58,59]. Independent of its functions in chromatin remodeling, SMARCB1 acts

Biomarker Descriptions (continued)

as a tumor suppressor and inhibits MYC activation, so loss of function in SMARCB1 enhances MYC activity[60]. Germline mutations in SMARCB1 are associated with rhabdoid tumor predisposition syndrome and familial schwannomatosis[61,62].

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[59]. SMARCB1 is often the only detected mutation in malignant rhabdoid tumors[60]. Somatic mutations in SMARCB1 are observed in 3% of uterine corpus endometrial carcinoma, stomach adenocarcinoma, and kidney chromophobe[18,19]. Alterations in SMARCB1 are also observed in pediatric cancers[18,19]. 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)[18,19]. Biallelic deletion of SMARCB1 is observed in 22% of embryonal tumors and less than 1% of B-lymphoblastic leukemia/lymphoma (4 in 731 cases)[18,19].

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[63,64].

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[49,50]. 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[50].

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[50,51]. 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[18,19]. Somatic mutations in MTAP have been found in 3% of uterine corpus endometrial carcinoma[18,19].

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

CDKN2A deletion

cyclin dependent kinase inhibitor 2A

Background: CDKN2A encodes cyclin dependent kinase inhibitor 2A, a cell cycle regulator that controls G1/S progression[1]. CDKN2A, also known as p16/INK4A, belongs to a family of INK4 cyclin-dependent kinase inhibitors, which also includes CDKN2B (p15/INK4B), CDKN2C (p18/INK4C), and CDKN2D (p19/INK4D)[219]. The INK4 family regulates cell cycle progression by inhibiting CDK4 or CDK6, thereby preventing the phosphorylation of Rb[220,221,222]. CDKN2A encodes two alternative transcript variants, namely p16 and p14ARF, both of which exhibit differential tumor suppressor functions[223]. 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[1,223,224]. CDKN2A aberrations commonly co-occur with CDKN2B[219]. Loss of CDKN2A/p16 results in downstream inactivation of the Rb and p53 pathways, leading to uncontrolled cell proliferation[225]. Germline mutations of CDKN2A are known to confer a predisposition to melanoma and pancreatic cancer[226,227].

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[228]. 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[18,19]. 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[18,19]. Alterations in CDKN2A are also observed in pediatric cancers[19]. 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%

Biomarker Descriptions (continued)

of embryonal tumors[19]. 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)[19].

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[64,229,230]. Additionally, deletion of CDKN2B is a molecular marker used in staging Grade 4 pediatric IDH-mutant astrocytoma[156]. 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[231,232,233]. Alternatively, CDKN2A expression and Rb inactivation demonstrate resistance to palbociclib in cases of glioblastoma multiforme[234]. 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[235,236,237,238].

PTEN deletion, PTEN p.(K330Rfs*12) c.989_990delAA

phosphatase and tensin homolog

Background: The PTEN gene encodes the phosphatase and tensin homolog, a tumor suppressor protein with lipid and protein phosphatase activities[194]. PTEN antagonizes PI3K/AKT signaling by catalyzing the dephosphorylation of phosphatidylinositol (3,4,5)-trisphosphate (PIP3) to PIP2 at the cell membrane, which inhibits the activation of AKT[195,196]. In addition, PTEN has been proposed to influence RAD51 loading at double strand breaks during homologous recombination repair (HRR) and regulate the G2/M checkpoint by influencing CHEK1 localization through AKT inhibition, thereby regulating HRR efficiency[197]. Germline mutations in PTEN are linked to hamartoma tumor syndromes, including Cowden disease, which are defined by uncontrolled cell growth and benign or malignant tumor formation[198]. PTEN germline mutations are also associated with inherited cancer risk in several cancer types[199].

Alterations and prevalence: PTEN is frequently altered in cancer by inactivating loss-of-function mutations and by gene deletion. PTEN mutations are observed in several cancers including 65% of uterine cancer, 34% of uterine corpus endometrial carcinoma, 20% of uterine carcinosarcoma, 11% of lung squamous cell carcinoma, and 5-10% of skin cutaneous melanoma, kidney chromophobe, stomach adenocarcinoma, stomach squamous cell carcinoma, and cervical squamous cell carcinoma[18,19]. Nearly half of somatic mutations in PTEN are stop-gain or frame-shift mutations that result in truncation of the protein reading frame. Recurrent missense or stop-gain mutations at codons R130, R173, and R233 result in loss of phosphatase activity and inhibition of wild-type PTEN[196,200,201,202,203]. PTEN gene deletion is observed in several cancers including 17% of prostate adenocarcinoma, 10% of lung squamous cell carcinoma and glioblastoma multiforme, 7% of skin cutaneous melanoma, 6% of diffuse large B-cell lymphoma, sarcoma, and 1-5% of breast invasive carcinoma, melanoma, sarcoma, ovarian serous cystadenocarcinoma, cervical squamous cell carcinoma, and uterine corpus endometrial carcinoma[18,19]. Alterations in PTEN are also observed in pediatric cancers[19]. Somatic mutations in PTEN are observed in 10% of T-lymphoblastic leukemia/lymphoma (4 in 41 cases), 6% of non-Hodgkin lymphoma (1 in 17 cases), 2% of glioma (7 in 297 cases), and 1% of bone cancer (4 in 327 cases) and embryonal tumors (4 in 332 cases)[19]. Biallelic deletion of PTEN is observed in 6% of glioma (1 in 16 cases), 5% of bone cancer (2 in 42 cases), 4% of B-lymphoblastic leukemia/lymphoma (10 in 250 cases), and less than 1% of embryonal tumors (5 in 731 cases)[19]. Structural alterations in PTEN are observed in less than 1% of bone cancer (1 in 150 cases)[19].

Potential relevance: Due to the role of PTEN in HRR, poly(ADP-ribose) polymerase inhibitors (PARPi) are being explored as a potential therapeutic strategy in PTEN deficient tumors[204,205]. In 2022, the FDA granted fast track designation to the small molecule inhibitor, pidnarulex[189], for BRCA1/2, PALB2, or other homologous recombination deficiency (HRD) mutations in breast and ovarian cancers. In 2023, the FDA approved the kinase inhibitor, capivasertib[206] in combination with fulvestrant for locally advanced or metastatic hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative breast cancer with one or more PIK3CA/AKT1/PTEN-alterations following progression after endocrine treatment.

CHEK2 deletion

checkpoint kinase 2

Background: The CHEK2 gene encodes the checkpoint kinase-2 serine/threonine kinase, a cell cycle checkpoint regulator[1]. In response to DNA damage, CHEK2 is phosphorylated by ATM and subsequently phosphorylates and negatively regulates CDC25C to prevent entry into mitosis[180]. 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)[181,182,183]. Germline mutations in the CHEK2 gene are associated with Li-Fraumeni syndrome and inherited risk of breast cancer[184,185,186]. Reduced expression of CHEK2 is associated with several cancers including breast cancer, colorectal cancer, and prostate cancer, supporting its role as a tumor suppressor[185].

Alterations and prevalence: Consistent with its role as a tumor suppressor, CHEK2 is enriched for deleterious truncating mutations[187]. Somatic mutations in CHEK2 are observed in 7% of uterine corpus endometrial carcinoma, 4% of uterine carcinosarcoma, 3% of cholangiocarcinoma, and 2% of diffuse large B-cell lymphoma, adrenocortical carcinoma, stomach adenocarcinoma, lung adenocarcinoma, colorectal adenocarcinoma, and kidney chromophobe[18,19]. Deletion of CHEK2 is observed in 3% of adrenocortical carcinoma and thymoma, and 2% of bladder urothelial carcinoma,[18,19]. Alterations in CHEK2 are also observed in pediatric cancers[19].

Biomarker Descriptions (continued)

Somatic mutations in CHEK2 are observed in less than 1% of bone cancer (2 in 327 cases), B-lymphoblastic leukemia/lymphoma (1 in 252 cases), glioma (1 in 297 cases), and peripheral nervous system cancers (1 in 1158 cancers)[19]. Deletion of CHEK2 is observed in less than 1% of B-lymphoblastic leukemia/lymphoma (3 in 731 cases)[19].

Potential relevance: The PARP inhibitor, olaparib[188] (2020) is approved for metastatic castration-resistant prostate cancer (mCRPC) with deleterious or suspected deleterious germline or somatic mutations in HRR genes, including CHEK2. Additionally, talazoparib[86](2023) in combination with enzalutamide is approved for mCRPC with mutations in HRR genes, including CHEK2. In 2022, the FDA granted fast track designation to the small molecule inhibitor, pidnarulex[189], for BRCA1/2, PALB2, or other homologous recombination deficiency (HRD) mutations in breast and ovarian cancers.

NF2 deletion

neurofibromin 2

Background: The NF2 gene encodes the cytoskeletal Merlin (Moesin-ezrin-radixin-like) protein[1]. NF2 is also known as Schwannomin due to its prevalence in neuronal Schwann cells[97]. 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[98,99,100]. 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[98,99,100,101]. NF2 functions as a tumor suppressor wherein loss of function mutations are shown to confer a predisposition to tumor development[97,99,100]. 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[97,99,100].

Alterations and prevalence: Somatic mutations in NF2 are predominantly misssense or truncating and are observed in about 23% of mesothelioma, 6% of cholangiocarcinoma, 4% of uterine corpus endometrial carcinoma, 3% of kidney renal papillary cell carcinoma (pRCC), bladder urothelial carcinoma, and cervical squamous cell carcinoma, and 2% of colorectal adenocarcinoma, skin cutaneous melanoma, lung squamous cell carcinoma, and liver hepatocellular carcinoma[18,19]. Biallelic loss of NF2 is observed in 8% of mesothelioma and 2% of thymoma[18,19]. Structural variants in NF2 are observed in 3% of cholangiocarcinoma and 2% of mesothelioma[18,19]. Alterations in NF2 are also observed in pediatric cancers[19]. Somatic mutations in NF2 are observed in less than 1% of bone cancer (2 in 327 cases) and glioma (1 in 297 cases)[19]. Biallelic deletion of NF2 is observed in less than 1% of B-lymphoblastic leukemia/lymphoma (1 in 731 cases)[19].

Potential relevance: Currently, no therapies are approved for NF2 aberrations.

JAK2 deletion

Janus kinase 2

Background: The JAK2 gene encodes Janus kinase 2, a non-receptor protein tyrosine kinase (PTK)[1,2]. JAK2 is a member of the Janus kinase (JAK) family, which includes JAK1, JAK2, JAK3, and TYK2[2]. Janus kinases are characterized by the presence of a second phosphotransferase-related or pseudokinase domain immediately N-terminal to the PTK domain[3]. JAK kinases function with signal transducer and activator of transcription (STAT) proteins to facilitate intracellular signal transduction required for cytokine receptor and interferon-alpha/beta/gamma signaling[3,4,5]. Since JAK2 functions in interferon receptor signaling, inactivation of JAK2 is proposed to inhibit the presentation of tumor antigens and contribute to immune evasion[6,7].

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[8,9]. The JAK2 V617F mutation is rarely observed in acute myeloid leukemia (AML)[10,11]. Mutations in the pseudokinase domain of JAK2, including R683G, have been detected in 8% of ALL[12,13]. JAK2 fusions are observed in myeloid and lymphoid leukemias with partner genes including TEL, PCM1, and BCR[14,15,16,17]. JAK2 fusions are infrequently observed in solid tumors[18]. As with JAK1, truncating mutations in JAK2 are common in solid tumors and particularly enriched in uterine cancers[18]. 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[18,19]. Alterations in JAK2 are also observed in pediatric cancers[18,19]. 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)[18,19]. JAK2 fusions are observed in 10% of B-lymphoblastic leukemia/lymphoma and 1% of leukemia (1 in 107 cases)[18,19]. 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)[18,19].

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)[20,21]. Ruxolitinib[22] (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

Biomarker Descriptions (continued)

approved for the treatment of rheumatoid arthritis. JAK2 mutations and fusions are associated with poor risk in acute lymphoblastic leukemia[23]. 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[24]. Some case studies report efficacy with ruxolitinib in myeloid and lymphoid leukemias, although duration of complete response was limited[14,15,16,17].

MLH1 p.(V384D) c.1151T>A

mutL homolog 1

Background: The MLH1 gene encodes the mutL homolog 1 protein[1]. MLH1 is a tumor suppressor gene that heterodimerizes with PMS2 to form the MutLα complex, PMS1 to form the MutLβ complex, and MLH3 to form the MutLγ complex[71]. The MutLα complex functions as an endonuclease that is specifically involved in the mismatch repair (MMR) process and mutations in MLH1 result in the inactivation of MutLα and degradation of PMS2[71,72]. Loss of MLH1 protein expression and MLH1 promoter hypermethylation correlates with mutations in these genes and are used to pre-screen colorectal cancer or endometrial hyperplasia[73,74]. MLH1, along with MSH6, MSH2, and PMS2 form the core components of the MMR pathway[71]. The MMR pathway is critical to the repair of mismatch errors which typically occur during DNA replication[71]. Deficiency in MMR (dMMR) is characterized by mutations and loss of expression in these genes[75]. dMMR is associated with microsatellite instability (MSI), which is defined as a change in the length of a microsatellite in a tumor as compared to normal tissue[76,77,78]. MSI-high (MSI-H) is a hallmark of Lynch Syndrome (LS), also known as hereditary non-polyposis colorectal cancer, which is caused by germline mutations in MMR genes[76,79]. LS is associated with an increased risk of developing colorectal cancer, as well as other cancers, including endometrial and stomach cancer[77,79,80,81]. Specifically, MLH1 mutations are associated with an increased risk of ovarian and pancreatic cancer[82,83,84,85].

Alterations and prevalence: Somatic mutations in MLH1 are observed in 6% of uterine corpus endometrial carcinoma, 4% of colorectal adenocarcinoma, and 2-3% of bladder urothelial carcinoma, stomach adenocarcinoma, and melanoma[18,19]. Alterations in MLH1 are observed in pediatric cancers[18,19]. Somatic mutations are observed in 1% of bone cancer and less than 1% of B-lymphoblastic leukemia/lymphoma (2 in 252 cases), embryonal tumor (2 in 332 cases), and leukemia (2 in 311 cases)[18,19].

Potential relevance: The PARP inhibitor, talazoparib[86] in combination with enzalutamide is approved (2023) for metastatic castration-resistant prostate cancer (mCRPC) with mutations in HRR genes that includes MLH1. Additionally, pembrolizumab (2014) is an anti-PD-1 immune checkpoint inhibitor that is approved for patients with MSI-H or dMMR solid tumors that have progressed on prior therapies[87]. Nivolumab (2015), an anti-PD-1 immune checkpoint inhibitor, is approved alone or in combination with the cytotoxic T-lymphocyte antigen 4 (CTLA-4) blocking antibody, ipilimumab (2011), for patients with dMMR colorectal cancer that have progressed on prior treatment[88,89]. MLH1 mutations are consistent with high grade in pediatric diffuse gliomas[90,91].

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[102]. Microsatellite instability (MSI) is defined as a change in the length of a microsatellite in a tumor as compared to normal tissue[77,79]. 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[78]. 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[103]. 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)[103]. Tumors classified as MSI-L are often phenotypically indistinguishable from MSS tumors and tend to be grouped with MSS[80,104,105,106,107]. 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[79]. LS is associated with an increased risk of developing colorectal cancer, as well as other cancers, including endometrial and stomach cancer[77,79,80,81].

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[77,79,108,109]. 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[108,109].

Potential relevance: Anti-PD-1 immune checkpoint inhibitors including pembrolizumab[87] (2014) and nivolumab[88] (2015) are approved for patients with MSI-H or dMMR colorectal cancer who have progressed following chemotherapy. Pembrolizumab[87] 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[87]. Dostarlimab[110] (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[105,111]. The cytotoxic T-lymphocyte antigen 4 (CTLA-4) blocking antibody, ipilimumab[89] (2011), is approved alone or in combination with nivolumab in MSI-H or dMMR colorectal cancer that has progressed

Biomarker Descriptions (continued)

following treatment with chemotherapy. MSI-H may confer a favorable prognosis in colorectal cancer although outcomes vary depending on stage and tumor location[105,112,113]. 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[113]. 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[114,115]. However, checkpoint blockade with the addition of chemotherapy or targeted therapies have demonstrated response in MSS or pMMR cancers[114,115].

RNASEH2B p.(H70Tfs*36) c.207_208insA

ribonuclease H2 subunit B

Background: The RNASEH2B gene encodes the ribonuclease H2 subunit B protein[1]. RNASEH2B functions as an auxiliary subunit of RNase H2 holoenzyme along with RNASEH2C and the catalytic subunit RNASEH2A[212,213]. RNase H2 is responsible for the removal of ribonucleotides that have been misincorporated in DNA, and also degrades DNA:RNA hybrids formed during transcription[212]. Specifically, RNase H2 is observed to interact with BRCA1 for DNA:RNA hybrid resolution at double-strand breaks (DSBs) through homologous recombination repair (HRR)[212].

Alterations and prevalence: Somatic mutations in RNASEH2B are observed in 3% of uterine corpus endometrial carcinoma, and 2% of skin cutaneous melanoma[18,19]. RNASEH2B biallelic deletions are observed in 10% of prostate adenocarcinoma, 7% sarcoma, 6% of bladder urothelial carcinoma, and 3% of ovarian serous cystadenocarcinoma[18,19].

Potential relevance: Currently, no therapies are approved for RNASEH2B 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[52,53]. 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[52,53]. SDHB iron clusters facilitate the transfer of electrons from FADH2 to ubiquinone[54]. Mutations in SDH genes lead to abnormal stabilization of hypoxia-inducible factors and pseudo-hypoxia, thereby promoting cell proliferation, angiogenesis, and tumorigenesis[52,53]. Sporadic and inherited pathogenic mutations in SDHB are known to confer an increased risk for paragangliomas, pheochromocytomas, and gastrointestinal stromal tumors[1,55].

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[18,19]. Biallelic loss of SDHB is observed in 6% of cholangiocarcinoma and 2% of pheochromocytoma and paraganglioma[18,19].

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

TCF7L2 deletion

transcription factor 7 like 2

Background: TCF7L2 encodes the transcription factor 7 like 2, a key component of the WNT signaling pathway[1,157]. Through its interaction with β-catenin, TCF7L2 functions as a central transcriptional regulator of the WNT pathway by modulating the expression of several genes involved in epithelial to mesenchymal transdifferentiation (EMT) and cancer progression, including MYC[157,158,159]. TCF7L2 is also responsible for the regulation of cell cycle inhibitors, including CDKN2C and CDKN2D, thereby influencing cell cycle progression[157]. Loss of TCF7L2 function is commonly observed in colorectal cancer due to mutations or copy number loss which has been correlated with increased tumor invasion and metastasis, supporting a tumor suppressor role for TCF7L2[157].

Alterations and prevalence: Somatic mutations of TCF7L2 are observed in 11% colorectal adenocarcinoma, 6% of uterine corpus endometrial carcinoma, 3% of stomach adenocarcinoma, and 2% of skin cutaneous melanoma and uterine carcinosarcoma[18,19]. Biallelic deletion of TCF7L2 is observed in 2% diffuse large B-cell lymphoma, brain lower grade glioma, and colorectal adenocarcinoma, and 1% of bladder urothelial carcinoma, mesothelioma, stomach adenocarcinoma, esophageal adenocarcinoma, liver hepatocellular carcinoma, and skin cutaneous melanoma[18,19].

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

Biomarker Descriptions (continued)

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[261]. TNFSF-TNFRSF interactions regulate several signaling pathways, including those involved in immune cell differentiation, survival, and death[261]. TNFRSF14 can be stimulated by several ligands, including the TNFSF14 ligand (also known as LIGHT), BTLA, and CD160[261,262]. 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[261]. In lymphoma, binding of TNFRSF14 by TNFSF14 has been observed to enhance Fas-induced apoptosis, suggesting a tumor suppressor role[262].

Alterations and prevalence: Somatic mutations in TNFRSF14 are observed in 5% of diffuse large B-cell lymphoma (DLBCL), and 2% of skin cutaneous melanoma[18,19]. Biallelic loss of TNFRSF14 occurs in 8% of DLBCL and uveal melanoma, 3% of cholangiocarcinoma, and 2% of adrenocortical carcinoma and liver hepatocellular carcinoma[18,19].

Potential relevance: Currently, no therapies are approved for TNFRSF14 aberrations. Somatic mutations in TNFRSF14 are diagnostic for follicular lymphoma[263]. In addition, TNFRSF14 mutations are associated with poor prognosis in follicular lymphoma[264,265].

ERRFI1 deletion

ERBB receptor feedback inhibitor 1

Background: ERRFI1 encodes ERBB receptor feedback inhibitor 1, a scaffold adaptor protein[1,252]. As an early response gene, expression of ERRFI1 is induced by several stimuli such as stress, hormones, and growth factors such as EGF[252,253]. ERRFI1 directly binds to EGFR resulting in inhibition of EGFR catalytic activity as well as EGFR lysosomal degradation[252,254]. As a tumor suppressor, ERRFI1 induces apoptosis and inhibits proliferation and invasion[252,255,256,257,258]. ERRFI1 downregulation has been identified in several cancer types and loss of ERRFI1 promotes proliferation and migration[252,255,256,259,260].

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[18,19]. 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[18,19].

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)[1,190]. ENO1 is a glycolytic enzyme that catalyzes the dehydration of 2-phosphoglyceric acid to phosphoenolpyruvic acid during glycolysis[190]. 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[190,191,192]. ENO1 has been found to be overexpressed in various cancers contributing to upregulation of glycolysis, cancer cell survival and proliferation, chemoresistance, extracellular matrix degradation, migration, invasion, and metastases[190,191,193]. 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[190,191].

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[18,19]. Amplification of ENO1 is observed in 2% of adrenocortical carcinoma, pancreatic adenocarcinoma, esophageal adenocarcinoma, ovarian serous cystadenocarcinoma, and sarcoma[18,19]. 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[18,19].

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

Biomarker Descriptions (continued)

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[1,239]. 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[240,241]. 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[239,242].

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[18,19]. 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[18,19]. Amplification of PGD has been observed in 2% of esophageal adenocarcinoma, ovarian serous cystadenocarcinoma, stomach adenocarcinoma, and sarcoma[18,19].

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[243,244,245]. 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[243,245]. 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[246,247].

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[18,19]. Biallelic loss of SPEN is observed in 6% of cholangiocarcinoma and 2% of pheochromocytoma and paraganglioma[18,19].

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[56,57]. 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[57]. Specifically, Eph-EphrinA ligand interaction regulates pathways critical for malignant transformation and key downstream target proteins including PI3K, SRC, Rho and Rac1 GTPases, MAPK, and integrins[56,57].

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[18,19].

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

RPL5 p.(E82K) c.244G>A

ribosomal protein L5

Background: The RPL5 gene encodes the ribosomal protein L5, a member of the L18P family of ribosomal proteins and a component of the 60S ribosomal subunit[1]. RPL5 binds 5S rRNA and forms a ribonucleoprotein complex consisting of RPL5, RPL11, and 5S

Biomarker Descriptions (continued)

rRNA that facilitates the nuclear transport of cytoplasmic 5s rRNA for assembly into ribosomes[1,25]. RPL5 is known to influence p53-dependent cell cycle arrest, senescence, or apoptosis in response to impaired ribosome biogenesis[25].

Alterations and prevalence: Somatic mutation of RPL5 is observed in 5% of uterine corpus endometrial carcinoma, 3% of skin cutaneous melanoma, and 2% of glioblastoma multiforme[18,19]. Biallelic deletion of RPL5 is observed in 2% of pheochromocytoma and paraganglioma and less than 1% in sarcoma, ovarian serous cystadenocarcinoma, lung adenocarcinoma, esophageal adenocarcinoma, breast invasive adenocarcinoma, cervical squamous cell carcinoma, and prostate adenocarcinoma[18,19]. High frequency of heterozygous deletion has also been observed in select cancer types including 34% of breast invasive carcinoma, 25% of skin cutaneous melanoma, and 8% of glioblastoma multiforme[26].

Potential relevance: Currently, no therapies are approved for RPL5 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[65]. MHC class I molecules are heterodimers composed of two polypeptide chains, α and B2M[66]. 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[67,68,69]. Downregulation of MHC class I promotes tumor evasion of the immune system, suggesting a tumor suppressor role for HLA-B[70].

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[18,19]. Biallelic loss of HLA-B is observed in 5% of DLBCL[18,19].

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

LARP4B deletion

La ribonucleoprotein domain family member 4B

Background: The LARP4B gene encodes the La ribonucleoprotein 4B protein[1]. La-related proteins (LARPs) are RNA binding proteins and can be split into 5 families, LARP1, La, LARP4, LARP6, and LARP7[33]. Along with LARP4, LARP4B is part of the LARP4 family and is observed to bind AU-rich regions in the 3' untranslated regions of mRNAs[33]. In glioma, LARP4B has been observed to induce mitotic arrest and apoptosis in vitro, supporting a tumor suppressor role for LARP4B[34].

Alterations and prevalence: Somatic mutations in LARP4B are observed in 8% of uterine corpus endometrial carcinoma, 7% of stomach adenocarcinoma, 5% of colorectal adenocarcinoma and skin cutaneous melanoma, 4% of uterine carcinosarcoma, and 2% of lung adenocarcinoma, lung squamous cell carcinoma, esophageal adenocarcinoma, and bladder urothelial carcinoma[18,19]. Biallelic deletions in LARP4B are observed in 4% of diffuse large B-cell lymphoma (DLBCL), 3% of sarcoma and testicular germ cell tumors, and 2% of mesothelioma, stomach adenocarcinoma, and lung squamous cell carcinoma[18,19].

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

GATA3 deletion

GATA binding protein 3

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

Alterations and prevalence: Somatic mutations in GATA3 are observed in 12% of breast invasive carcinoma, 4% of uterine corpus endometrial carcinoma and stomach adenocarcinoma, and 3% of colorectal adenocarcinoma and skin cutaneous melanoma[18,19]. Biallelic loss of GATA3 is observed in 2% of diffuse large B-cell lymphoma (DLBCL)[18,19]. Alterations in GATA3 are also observed in the pediatric population[19]. Somatic mutations are observed in 6% of non-Hodgkin lymphoma (1 in 17 cases), 3% of soft tissue sarcoma (1 in 38 cases), 2% of T-lymphoblastic leukemia/lymphoma (1 in 41 cases) and Hodgkin lymphoma (1 in 61 cases), and less than 1% of bone cancer (3 in 327 cases), embryonal tumor (3 in 332 cases), and leukemia (1 in 311 cases)[19]. Biallelic deletion is observed in 1% of

Biomarker Descriptions (continued)

peripheral nervous system cancers (1 in 91 cases), less than 1% of leukemia (1 in 250 cases) and B-lymphoblastic leukemia/lymphoma (1 in 731 cases)[19].

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

MAPK8 deletion

mitogen-activated protein kinase 8

Background: The MAPK8 gene encodes the mitogen-activated protein kinase 8, also known as JNK1[1]. MAPK8 is involved in the JNK signaling pathway along with MAP3K4, MAP3K12, MAP2K4, MAP2K7, MAPK9, and MAPK10[27,28,29]. Activation of MAPK proteins occurs through a kinase signaling cascade[27,28,30]. Specifically, MAP3Ks are responsible for phosphorylation of MAP2K family members[27,28,30]. Once activated, MAP2Ks are responsible for the phosphorylation of various MAPK proteins whose signaling is involved in several cellular processes including cell proliferation, differentiation, and inflammation[27,28,30].

Alterations and prevalence: Somatic mutations in MAPK8 are observed in 4% of uterine corpus endometrial carcinoma, 3% of skin cutaneous melanoma, and 2% of colorectal adenocarcinoma[18,19]. Biallelic deletions are observed in 1% of bladder urothelial carcinoma, esophageal adenocarcinoma, adrenocortical carcinoma, and skin cutaneous melanoma[18,19].

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

ARID5B deletion

AT-rich interaction domain 5B

Background: The ARID5B gene encodes the AT-rich interaction domain 5B protein[1]. ARID5B, also known as MRF2, belongs to the ARID superfamily that also includes ARID1A, ARID1B, and ARID2[31,32]. ARID5B forms a complex with PHF2, which is capable of histone demethylation leading to transcriptional activation of target genes[32]. ARID5B is known to be essential for the development of hematopoietic cells[32]. Several single-nucleotide polymorphisms (SNPs) in ARID5B have been associated with susceptibility of acute lymphoblastic leukemia (ALL)[32].

Alterations and prevalence: Somatic mutations in ARID5B are observed in 15% of uterine corpus endometrial carcinoma, 6% of skin cutaneous melanoma, 5% of diffuse large B-cell lymphoma, 4% of stomach adenocarcinoma[18,19]. Biallelic loss of ARID5B is observed in 1% of kidney chromophobe, lung squamous cell carcinoma, and skin cutaneous melanoma[18,19].

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

CYP2C9 deletion

cytochrome P450 family 2 subfamily C member 9

Background: The CYP2C9 gene encodes cytochrome P450 family 2 subfamily C member 9, a member of the cytochrome P450 superfamily of proteins[1]. The cytochrome P450 proteins are monooxygenases that play important roles in the biotransformation of xenobiotics and carcinogens, and the synthesis of cholesterol, steroids and other lipids[1,35]. CYP2C9 catalyzes the oxidation of arachidonic acid to epoxyeicosatrienoic acids (EETs) and also inactivates several NSAIDs, including cyclooxygenase inhibitors and chemopreventive agents[36,37]. EETs are mitogenic and pro-angiogenic signaling molecules that have been shown to promote cancer cell growth and metastasis in vitro[36,37,38]. CYPC29 overexpression is found in several cancers supporting the role of EETs in vascularization and tumorigenesis[35,36,37,38]. Inherited CYP2C9 polymorphisms, including CYP2C9*2 and CYP2C9*3, can result in attenuated catalytic efficiency and reduced EETs leading to reduced proliferation and migration of cancer cells and less vascularized tumors[36]. Depending on the cancer type and treatment, individuals with these polymorphisms may have slower drug metabolism and therefore, altered drug responses which may make them more protected or more at risk of disease[36].

Alterations and prevalence: Somatic mutations in CYP2C9 are observed in 12% of skin cutaneous melanoma, 3% of uterine corpus endometrial carcinoma, and 2% of cervical squamous cell carcinoma, esophageal adenocarcinoma, lung adenocarcinoma, and kidney chromophobe[18,19]. Biallelic loss of CYP2C9 is observed in 2% diffuse large B-cell lymphoma and prostate adenocarcinoma[18,19]. Amplification of CYP2C9 is observed in 1% of pheochromocytoma, paraganglioma, and ovarian serous cystadenocarcinoma[18,19].

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

Biomarker Descriptions (continued)

SUFU deletion

SUFU negative regulator of hedgehog signaling

Background: SUFU encodes the SUFU negative regulator of hedgehog signaling protein, a protein integrally involved in inhibition of hedgehog pathway signaling[1]. During early human development, hedgehog pathway activation of the Gli/Ci family of zinc finger transcription factors is known to drive both cell proliferation and differentiation[207]. SUFU is capable of interacting and complexing with GLI1 and GLI2, thereby regulating transactivation of GLI1 and GLI2 target genes and inhibiting hedgehog pathway signaling[208,209]. Aberrant activation of the hedgehog signaling pathway has been implicated in several cancer types, supporting a tumor suppressor role for SUFU[210]. Germline mutations in SUFU confer a strong predisposition to medulloblastoma, particularly the desmoplastic/nodular subtype, and are observed almost exclusively in children less than 3 years of age[211].

Alterations and prevalence: Somatic mutations are observed in 4% uterine corpus endometrial carcinoma and 2% esophageal adenocarcinoma and stomach adenocarcinoma[19]. Biallelic deletion of SUFU is observed in 2% of mesothelioma, diffuse large cell B-cell lymphoma, and prostate adenocarcinoma[19]. Alterations in SUFU are also observed in pediatric cancers[19]. Somatic mutations in SUFU are observed in 1% of embryonal tumors (4 in 332 cases) and less than 1% of glioma (2 in 297 cases), bone cancer (1 in 327 cases), and peripheral nervous system cancers (1 in 1158 cases)[19]. Biallelic deletion of SUFU is observed in less than 1% of leukemia (2 in 250 cases) and B-lymphoblastic leukemia/lymphoma (2 in 731 cases)[19].

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

PDIA3 deletion

protein disulfide isomerase family A member 3

Background: The PDIA3 gene encodes the protein disulfide isomerase family A member 3[1]. PDIA3 is a member of the protein disulfide isomerase (PDI) gene family, and acts as an enzymatic chaperone for reconstructing misfolded proteins[39]. PDIA3 has also been identified as being involved EGFR regulation, mTOR signaling, and associated with the major histocompatibility complex (MHC) protein loading complex (PLC)[40]. 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[40,41,42].

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[18,19]. 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[18,19].

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[39]. Conversely, PDIA3 loss is correlated with aggressive disease and poor survival in gastric cancer and head and neck cancer[41,42].

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[248]. MHC class I molecules are located on the cell surface and present antigens from within the cell for recognition by cytotoxic T cells[65]. Peptide antigen presentation by MHC class I requires B2M, and mutation or loss of B2M prevents presentation and results in escape from immune recognition[249]. 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[249].

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[18,19]. Biallelic loss of B2M is observed in 8% of DLBCL 5% of mesothelioma, and 2% of lung adenocarcinoma and skin cutaneous melanoma[18,19].

Potential relevance: Currently, no therapies are approved for B2M aberrations. Loss of B2M has been implicated in resistance to immunotherapy in melanoma[249,250]. However, B2M mutations in microsatellite instability-high colorectal carcinomas show response to immune checkpoint inhibitors[251].

Biomarker Descriptions (continued)

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[266,267]. 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[268,269]. Along with transcriptional coactivation, EP300 also functions in the formation of the transcription pre-initiation complex[268]. Inherited EP300 mutations result in Rubinstein-Taybi syndrome (RTS), a developmental disorder with an increased susceptibility to solid tumors[270].

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[18,19]. Inactivating EP300 mutations are associated with lack of acetylation activity of EP300, resulting in altered expression of protein targets[271].

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

PHF6 p.(T170Nfs*2) c.508_509insA

PHD finger protein 6

Background: The PHF6 gene encodes the plant homeodomain (PHD) finger protein 6 which contains four nuclear localization signals and two imperfect PHD zinc finger domains. PHF6 is a tumor suppressor that interacts with the nucleosome remodeling deacetylase (NuRD) complex, which regulates nucleosome positioning and transcription of genes involved in development and cell-cycle progression[43,44].

Alterations and prevalence: The majority of PHF6 aberrations are nonsense, frameshift (70%), or missense (30%) mutations, which result in complete loss of protein expression[43,45,46,47]. Truncating or missense mutations in PHF6 are observed in 38% of adult and 16% of pediatric T-cell acute lymphoblastic leukemia (T-ALL), 20-25% of mixed phenotype acute leukemias (MPAL), and 3% of AML, and 2.6% of hepatocellular carcinoma (HCC)[45,47]. Missense mutations recurrently involve codon C215 and the second zinc finger domain of PHF6[45]. PHF6 mutations are frequently observed in hematologic malignancies from male patients[43,45].

Potential relevance: Somatic mutations in PHF6 are associated with reduced overall survival in AML patients treated with high-dose induction chemotherapy[48].

Alerts Informed By Public Data Sources

Current FDA Information

🚫 Contraindicated   ⊖ Not recommended   🛡 Resistance   🚀 Breakthrough   🛣 Fast Track

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

PDGFRA p.(D842V) c.2525A>T

🛣 **crenolanib**

Cancer type: Gastrointestinal Stromal Tumor   **Variant class:** PDGFRA D842V mutation

Supporting Statement:

The FDA has granted Fast Track designation to the benzimidazole type I kinase inhibitor, crenolanib, for:

- FLT3 mutation-positive relapsed or refractory acute myeloid leukemia (AML)
- PDGFRA D842V mutated unresectable or metastatic gastrointestinal stromal tumors (GIST)

Reference:

https://www.globenewswire.com/news-release/2017/12/01/1216122/0/en/Arog-Pharmaceuticals-Receives-FDA-Fast-Track-Designation-for-Crenolanib-in-Relapsed-or-Refractory-FLT3-Positive-AML.html

Current ESMO Information

🚫 Contraindicated   ⊖ Not recommended   🛡 Resistance   🚀 Breakthrough   🛣 Fast Track

ESMO information is current as of 2025-11-03. For the most up-to-date information, search www.esmo.org.

PDGFRA p.(D842V) c.2525A>T

⊖ **imatinib**

Cancer type: Gastrointestinal Stromal Tumor   **Variant class:** PDGFRA D842V mutation

ESMO Level of Evidence/Grade of Recommendation: IV / D

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

- "PDGFRA exon 18 D842V-mutated GISTs should not be treated with adjuvant therapy [IV, D]."

Reference: ESMO Clinical Practice Guidelines - ESMO-EUROCAN-Gastrointestinal Stromal Tumours [Ann Oncol (2021), doi: https://doi.org/10.1016/j.annonc.2021.09.005.]

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,

Genes Assayed (continued)

Genes Assayed for the Detection of DNA Sequence Variants (continued)

PXDNL, RAC1, RAF1, RARA, RET, RGS7, RHEB, RHOA, RICTOR, RIT1, ROS1, RPL10, SETBP1, SF3B1, SIX1, SIX2, SLCO1B3, SMC1A, SMO, SNCAIP, SOS1, SOX2, SPOP, SRC, SRSF2, STAT3, STAT5B, STAT6, TAF1, TERT, TGFBR1, TOP1, TOP2A, TPMT, TRRAP, TSHR, U2AF1, USP8, WAS, XPO1, ZNF217, ZNF429

Genes Assayed for the Detection of Copy Number Variations

ABCB1, ABL1, ABL2, ABRAXAS1, ACVR1B, ACVR2A, ADAMTS12, ADAMTS2, AKT1, AKT2, AKT3, ALK, AMER1, APC, AR, ARAF, ARHGAP35, ARID1A, ARID1B, ARID2, ARID5B, ASXL1, ASXL2, ATM, ATR, ATRX, AURKA, AURKC, AXIN1, AXIN2, AXL, B2M, BAP1, BARD1, BCL2, BCL2L12, BCL6, BCOR, BLM, BMPR2, BRAF, BRCA1, BRCA2, BRIP1, CARD11, CASP8, CBFB, CBL, CCND1, CCND2, CCND3, CCNE1, CD274, CD276, CDC73, CDH1, CDH10, CDK12, CDK4, CDK6, CDKN1A, CDKN1B, CDKN2A, CDKN2B, CDKN2C, CHD4, CHEK1, CHEK2, CIC, CREBBP, CSMD3, CTCF, CTLA4, CTNND2, CUL3, CUL4A, CUL4B, CYLD, CYP2C9, DAXX, DDR1, DDR2, DDX3X, DICER1, DNMT3A, DOCK3, DPYD, DSC1, DSC3, EGFR, EIF1AX, ELF3, EMSY, ENO1, EP300, EPCAM, EPHA2, ERAP1, ERAP2, ERBB2, ERBB3, ERBB4, ERCC2, ERCC4, ERRFI1, ESR1, ETV6, EZH2, FAM135B, FANCA, FANCC, FANCD2, FANCE, FANCF, FANCG, FANCI, FANCL, FANCM, FAT1, FBXW7, FGF19, FGF23, FGF3, FGF4, FGF9, FGFR1, FGFR2, FGFR3, FGFR4, FLT3, FLT4, FOXA1, FUBP1, FYN, GATA2, GATA3, GLI3, GNA13, GNAS, GPS2, HDAC2, HDAC9, HLA-A, HLA-B, HNF1A, IDH2, IGF1R, IKBKB, IL7R, INPP4B, JAK1, JAK2, JAK3, KDM5C, KDM6A, KDR, KEAP1, KIT, KLF5, KMT2A, KMT2B, KMT2C, KMT2D, KRAS, LARP4B, LATS1, LATS2, MAGOH, MAP2K1, MAP2K4, MAP2K7, MAP3K1, MAP3K4, MAPK1, MAPK8, MAX, MCL1, MDM2, MDM4, MECOM, MEF2B, MEN1, MET, MGA, MITF, MLH1, MLH3, MPL, MRE11, MSH2, MSH3, MSH6, MTAP, MTOR, MUTYH, MYC, MYCL, MYCN, MYD88, NBN, NCOR1, NF1, NF2, NFE2L2, NOTCH1, NOTCH2, NOTCH3, NOTCH4, NRAS, NTRK1, NTRK3, PALB2, PARP1, PARP2, PARP3, PARP4, PBRM1, PCBP1, PDCD1, PDCD1LG2, PDGFRA, PDGFRB, PDIA3, PGD, PHF6, PIK3C2B, PIK3CA, PIK3CB, PIK3R1, PIK3R2, PIM1, PLCG1, PMS1, PMS2, POLD1, POLE, POT1, PPM1D, PPP2R1A, PPP2R2A, PPP6C, PRDM1, PRDM9, PRKACA, PRKAR1A, PTCH1, PTEN, PTPN11, PTPRT, PXDNL, RAC1, RAD50, RAD51, RAD51B, RAD51C, RAD51D, RAD52, RAD54L, RAF1, RARA, RASA1, RASA2, RB1, RBM10, RECQL4, RET, RHEB, RICTOR, RIT1, RNASEH2A, RNASEH2B, RNF43, ROS1, RPA1, RPS6KB1, RPTOR, RUNX1, SDHA, SDHB, SDHD, SETBP1, SETD2, SF3B1, SLCO1B3, SLX4, SMAD2, SMAD4, SMARCA4, SMARCB1, SMC1A, SMO, SOX9, SPEN, SPOP, SRC, STAG2, STAT3, STAT6, STK11, SUFU, TAP1, TAP2, TBX3, TCF7L2, TERT, TET2, TGFBR2, TNFAIP3, TNFRSF14, TOP1, TP53, TP63, TPMT, TPP2, TSC1, TSC2, U2AF1, USP8, USP9X, VHL, WT1, XPO1, XRCC2, XRCC3, YAP1, YES1, ZFHX3, ZMYM3, ZNF217, ZNF429, ZRSR2

Genes Assayed 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

EGFR amplification

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
bevacizumab, chemotherapy, radiation therapy	✖	✖	✖	✖	⬤ (III)
BBI-355, erlotinib	✖	✖	✖	✖	⬤ (I/II)
MCLA-129	✖	✖	✖	✖	⬤ (I/II)
ABBV-637, mirzotamab clezutoclax, ERAS-801, chemotherapy, radiation therapy	✖	✖	✖	✖	⬤ (I)
afatinib	✖	✖	✖	✖	⬤ (I)
BDTX-1535, radiation therapy, chemotherapy	✖	✖	✖	✖	⬤ (I)
ERAS-801, imaging agent	✖	✖	✖	✖	⬤ (I)
SAR-446368, pembrolizumab	✖	✖	✖	✖	⬤ (I)
TmEGFR/IL13Ra2-01	✖	✖	✖	✖	⬤ (I)
WSD-0922	✖	✖	✖	✖	⬤ (I)

TERT c.-124C>T

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
bevacizumab, chemotherapy, radiation therapy	✖	✖	✖	✖	⬤ (III)

PDGFRA p.(D842V) c.2525A>T

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
avapritinib	◯	◯	◯	◯	⬤ (II)
ripretinib	✖	◯	✖	✖	✖

SMARCB1 deletion

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

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

Relevant Therapy Summary (continued)

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

MTAP deletion

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
CTS-3497	✖	✖	✖	✖	● (I/II)
IDE397	✖	✖	✖	✖	● (I/II)
PH020-803	✖	✖	✖	✖	● (I/II)
TNG-456, abemaciclib	✖	✖	✖	✖	● (I/II)
ABSK-131	✖	✖	✖	✖	● (I)
GH-56	✖	✖	✖	✖	● (I)
GTA-182	✖	✖	✖	✖	● (I)
HSK-41959	✖	✖	✖	✖	● (I)
ISM-3412	✖	✖	✖	✖	● (I)
MRTX-1719	✖	✖	✖	✖	● (I)
SYH-2039	✖	✖	✖	✖	● (I)
TNG-462	✖	✖	✖	✖	● (I)

CDKN2A deletion

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
palbociclib	✖	✖	✖	✖	● (II)
palbociclib, abemaciclib	✖	✖	✖	✖	● (II)
ribociclib, everolimus	✖	✖	✖	✖	● (II)
ABSK-131	✖	✖	✖	✖	● (I)
CID-078	✖	✖	✖	✖	● (I)

EGFRvIII

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
CARGO-T cell	✖	✖	✖	✖	● (I)
CARv3-TEAM-E T cells	✖	✖	✖	✖	● (I)
E-SYNC T cells, chemotherapy	✖	✖	✖	✖	● (I)
WSD-0922	✖	✖	✖	✖	● (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

PTEN deletion

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
ribociclib, everolimus	✖	✖	✖	✖	⬤ (II)
amquilix	✖	✖	✖	✖	⬤ (I/II)
palbociclib, gedatolisib	✖	✖	✖	✖	⬤ (I)
temsirolimus	✖	✖	✖	✖	⬤ (I)

CHEK2 deletion

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

NF2 deletion

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

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

HRR Details

Gene/Genomic Alteration	Finding
LOH percentage	*8.93%*
BRIP1	*SNV, E675A, AF:0.54*
CHEK2	*CNV, CN:1.0*
CHEK2	*LOH, 22q12.1(29083868-29130729)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 (6.2.4 data version 2025.12(007)). The data presented here are from a curated knowledge base of publicly available information, but may not be exhaustive. FDA information was sourced from www.fda.gov and is current as of 2025-11-25. NCCN information was sourced from www.nccn.org and is current as of 2025-11-03. EMA information was sourced from www.ema.europa.eu and is current as of 2025-11-25. ESMO information was sourced from www.esmo.org and is current as of 2025-11-03. Clinical Trials information is current as of 2025-11-03. For the most up-to-date information regarding a particular trial, search www.clinicaltrials.gov by NCT ID or search local clinical trials authority website by local identifier listed in 'Other identifiers.' Variants are reported according to HGVS nomenclature and classified following AMP/ASCO/CAP guidelines (Li et al. 2017). Based on the data sources selected, variants, therapies, and trials listed in this report are listed in order of potential clinical significance but not for predicted efficacy of the therapies.

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