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

Patient Name: 김현칠
Gender: Male
Sample ID: N26-53

Primary Tumor Site: Brain
Collection Date: 2026.01.06

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

Report Highlights
6 Relevant Biomarkers
3 Therapies Available
26 Clinical Trials

Relevant Glioblastoma IDH-wildtype (Grade 4) Findings

Gene	Finding	Gene	Finding
BRAF	None detected	NTRK1	None detected
EGFR	None detected	NTRK2	None detected
FGFR1	None detected	NTRK3	None detected
FGFR2	None detected	RET	None detected
FGFR3	None detected	TERT	None detected

Genomic Alteration	Finding
Tumor Mutational Burden	***19.88 Mut/Mb measured***

Relevant Biomarkers

Tier	Genomic Alteration	Relevant Therapies (In this cancer type)	Relevant Therapies (In other cancer type)	Clinical Trials
IIC	*PIK3CA p.(M1043V) c.3127A>G* phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha Allele Frequency: 45.30% Locus: chr3:178952072 Transcript: NM_006218.4	None*	**inavolisib + palbociclib + hormone therapy** [1, 2 / I] **capivasertib + hormone therapy** [1, 2 / II +] aspirin [II+]	4
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

*** 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	*ATM p.(C1286*) c.3858C>A* ATM serine/threonine kinase Allele Frequency: 42.38% Locus: chr11:108155065 Transcript: NM_000051.4	None*	None*	2
IIC	*PDGFRA p.(V561D) c.1682T>A* platelet derived growth factor receptor alpha Allele Frequency: 39.27% Locus: chr4:55141036 Transcript: NM_006206.6	None*	None*	2
IIC	*MSH2 deletion* mutS homolog 2 Locus: chr2:47630288	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

CDKN2A p.(W110) c.330G>A, CDKN2C p.(D17Gfs*7) c.49_50insG, CDKN2C p.(D17Tfs*2) c.49delG, JAK2 deletion, MUTYH p.(R19*) c.55C>T, Microsatellite stable, POLE p.(R1371*) c.4111C>T, SETD2 p.(R456*) c.1366C>T, EPHA2 p.(E911Sfs*20) c.2730_2757delCGAGTGGCTGGAGTCCATCAAGATGCAG, CUL3 p.(E220Vfs*10) c.658_659insT, HLA-A deletion, HLA-A p.(L180*) c.539T>A, NOTCH3 p.(T101Hfs*16) c.301_303delACCinsCACT, Tumor Mutational Burden*

Variant Details

DNA Sequence Variants

Gene	Amino Acid Change	Coding	Variant ID	Locus	Allele Frequency	Transcript	Variant Effect
PIK3CA	p.(M1043V)	c.3127A>G	COSM12591	chr3:178952072	45.30%	NM_006218.4	missense
ATM	p.(C1286*)	c.3858C>A	.	chr11:108155065	42.38%	NM_000051.4	nonsense
PDGFRA	p.(V561D)	c.1682T>A	COSM739	chr4:55141036	39.27%	NM_006206.6	missense
CDKN2A	p.(W110*)	c.330G>A	COSM12547	chr9:21971028	76.02%	NM_001195132.2	nonsense
CDKN2C	p.(D17Gfs*7)	c.49_50insG	.	chr1:51436083	44.78%	NM_078626.3	frameshift Insertion
CDKN2C	p.(D17Tfs*2)	c.49delG	.	chr1:51436083	42.09%	NM_078626.3	frameshift Deletion
MUTYH	p.(R19*)	c.55C>T	.	chr1:45800165	48.77%	NM_001128425.2	nonsense
POLE	p.(R1371*)	c.4111C>T	.	chr12:133225553	43.27%	NM_006231.4	nonsense
SETD2	p.(R456*)	c.1366C>T	.	chr3:47164760	42.44%	NM_014159.7	nonsense
EPHA2	p.(E911Sfs*20)	c.2730_2757delCGAGTGGCTGGAGTCCATCAAGATGCAG	.	chr1:16455996	20.69%	NM_004431.5	frameshift Deletion
CUL3	p.(E220Vfs*10)	c.658_659insT	.	chr2:225376295	8.42%	NM_003590.5	frameshift Insertion

Variant Details (continued)

DNA Sequence Variants (continued)

Gene	Amino Acid Change	Coding	Variant ID	Locus	Allele Frequency	Transcript	Variant Effect
HLA-A	p.(L180*)	c.539T>A	.	chr6:29911240	73.17%	NM_001242758.1	nonsense
NOTCH3	p.(T101Hfs*16)	c.301_303delACCinsCACT	.	chr19:15303225	29.72%	NM_000435.3	frameshift Block Substitution
ARID1A	p.(P1651L)	c.4952C>T	.	chr1:27101670	49.35%	NM_006015.6	missense
LRRC7	p.(E686D)	c.2058G>T	.	chr1:70501866	39.46%	NM_001370785.2	missense
MAP3K1	p.(E1286del)	c.3857_3859delAAG	.	chr5:56180521	48.01%	NM_005921.2	nonframeshift Deletion
RASA1	p.(A908V)	c.2723C>T	.	chr5:86679562	41.65%	NM_002890.3	missense
CELF2	p.(?)	c.977-5_977-2delinsGCTTTTTCATC	.	chr10:11356097	2.57%	NM_006561.3	unknown
FANCM	p.(R1204H)	c.3611G>A	.	chr14:45645568	41.45%	NM_020937.4	missense
RAD51B	p.(P128S)	c.382C>T	.	chr14:68331786	48.53%	NM_133509.4	missense
BLM	p.(A875S)	c.2623G>T	.	chr15:91326119	48.15%	NM_000057.4	missense
NF1	p.(R873H)	c.2618G>A	.	chr17:29556251	37.90%	NM_001042492.3	missense
MAP2K2	p.(R53Q)	c.158G>A	.	chr19:4117562	42.75%	NM_030662.4	missense
KEAP1	p.(R483C)	c.1447C>T	.	chr19:10600408	39.49%	NM_203500.2	missense
SMARCA4	p.(R539H)	c.1616G>A	.	chr19:11106911	44.10%	NM_001128849.3	missense
SMARCA4	p.(R906H)	c.2717G>A	.	chr19:11132501	43.80%	NM_001128849.3	missense
KMT2B	p.(A178P)	c.532G>C	.	chr19:36210781	7.24%	NM_014727.3	missense
PPP2R1A	p.(S219L)	c.656C>T	.	chr19:52716212	16.87%	NM_014225.6	missense
MPPED1	p.(E127K)	c.379G>A	.	chr22:43831108	46.77%	NM_001044370.2	missense

Copy Number Variations

Gene	Locus	Copy Number	CNV Ratio
MTAP	chr9:21802646	0.85	0.57
CDKN2A	chr9:21968178	0.81	0.55
MSH2	chr2:47630288	1.13	0.67
JAK2	chr9:5021954	0.85	0.57
HLA-A	chr6:29910229	0.85	0.57
PRDM9	chr5:23509577	0.91	0.59
CD274	chr9:5456050	0.79	0.54
PDCD1LG2	chr9:5522530	0.87	0.58

Biomarker Descriptions

PIK3CA p.(M1043V) c.3127A>G

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[143]. PI3K is a heterodimer that contains a p85 regulatory subunit, which couples one of four p110 catalytic subunits to activated tyrosine protein kinases[144,145]. The p110 catalytic subunits include p110α, β, δ, γ and are encoded by genes PIK3CA, PIK3CB, PIK3CD, and PIK3CG, respectively[144]. 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[146,147]. The reversible phosphorylation of inositol lipids regulates diverse aspects of cell growth and metabolism[146,147,148,149]. 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[150,151,152].

Alterations and prevalence: 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)[153,154]. 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[155,156,157]. Somatic mutations in PIK3CA are observed in 50% of uterine corpus endometrial carcinoma, 35% of uterine carcinosarcoma, 32% of breast invasive carcinoma, 29% of cervical squamous cell carcinoma, 28% of colorectal adenocarcinoma, 22% of bladder urothelial carcinoma, 17% of head and neck squamous cell carcinoma, 16% of stomach adenocarcinoma, 11% of lung squamous cell carcinoma, 9% of esophageal adenocarcinoma, 8% of brain lower grade glioma, 6% of cholangiocarcinoma, 5% of skin cutaneous melanoma and lung adenocarcinoma, 4% of liver hepatocellular carcinoma, 3% of pancreatic adenocarcinoma and sarcoma, and 2% of mesothelioma, prostate adenocarcinoma, testicular germ cell tumors, and ovarian serous cystadenocarcinoma[18,19]. PIK3CA is amplified in 38% of lung squamous cell carcinoma, 20% of ovarian serous cystadenocarcinoma, 18% of esophageal adenocarcinoma, 16% of head and neck squamous cell carcinoma, 15% of cervical squamous cell carcinoma, 11% of uterine carcinosarcoma, 7% of uterine corpus endometrial carcinoma, 5% of stomach adenocarcinoma, 4% of bladder urothelial carcinoma, 3% of breast invasive carcinoma and pancreatic adenocarcinoma, and 2% of prostate adenocarcinoma, lung adenocarcinoma, and kidney renal clear cell carcinoma[18,19]. Alterations in PIK3CA are also observed in pediatric cancers[19]. Somatic mutations in PIK3CA are observed in 6% of non-Hodgkin Lymphoma (1 in 17 cases), 4% of glioma (11 in 297 cases), 3% of soft tissue sarcoma (1 in 38 patients), 2% of embryonal tumors (6 in 332 cases), 1% of leukemia (5 in 354 cases), and less than 1% of bone cancer (3 in 327 cases), B-lymphoblastic leukemia/lymphoma (2 in 252 cases), and peripheral nervous system tumors (1 in 1158 cases)[19].

Potential relevance: The PI3K inhibitor, alpelisib[158], 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. Specifically, exon 21 H1047R mutations were associated with more durable clinical responses in comparison to exon 10 E545K mutations[159]. However, alpelisib did not improve response when administered with letrozole in patients with ER + early breast cancer with PIK3CA mutations[160]. The FDA also approved the kinase inhibitor, capivasertib (2023)[161] 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[162], 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[163,164]. In colorectal cancers, PIK3CA mutations predict significantly improved survival and reduced disease recurrence with adjuvant aspirin therapy, compared to no benefit in wild-type PIK3CA tumors[132,138,165,166]. In 2025, the FDA granted fast track designation to the PI3Kα inhibitor and degrader, ETX-636[167], for the treatment of PIK3CA-mutant, HR-positive/HER-negative advanced breast cancer.

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[39,40]. 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[40].

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[40,41]. 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,

Biomarker Descriptions (continued)

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, CDKN2A p.(W110*) c.330G>A

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)[44]. The INK4 family regulates cell cycle progression by inhibiting CDK4 or CDK6, thereby preventing the phosphorylation of Rb[45,46,47]. CDKN2A encodes two alternative transcript variants, namely p16 and p14ARF, both of which exhibit differential tumor suppressor functions[48]. 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[1,48,49]. CDKN2A aberrations commonly co-occur with CDKN2B[44]. Loss of CDKN2A/p16 results in downstream inactivation of the Rb and p53 pathways, leading to uncontrolled cell proliferation[50]. Germline mutations of CDKN2A are known to confer a predisposition to melanoma and pancreatic cancer[51,52].

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[53]. 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% 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[54,55,56]. Additionally, deletion of CDKN2B is a molecular marker used in staging Grade 4 pediatric IDH-mutant astrocytoma[57]. 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[58,59,60]. Alternatively, CDKN2A expression and Rb inactivation demonstrate resistance to palbociclib in cases of glioblastoma multiforme[61]. 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[62,63,64,65].

ATM p.(C1286*) c.3858C>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)[85]. 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[86]. ATM is recruited to the DNA damage site by the MRE11/RAD50/NBN (MRN) complex that senses DSB[86,87]. Upon activation, ATM phosphorylates several downstream proteins such as the NBN, MDC1, BRCA1, CHK2 and TP53BP1 proteins[88]. 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[89,90]. 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[91].

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[18,19].

Potential relevance: The PARP inhibitor, olaparib[92] 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[93] in

Biomarker Descriptions (continued)

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[89,94,95]. 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[96]. However, gene-level analyses from the phase III PROfound trial indicate that ATM-mutated tumors do not experience meaningful radiographic progression-free survival (rPFS) or overall survival (OS) benefit from olaparib, and that the observed survival advantage in the broader HRR-altered population is largely driven by BRCA1/2 alterations rather than ATM[97,98]. In 2022, the FDA granted fast track designation to the small molecule inhibitor, pidnarulex[99], for BRCA1/2, PALB2, or other homologous recombination deficiency (HRD) mutations in breast and ovarian cancers.

PDGFRA p.(V561D) c.1682T>A

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[168,169]. PDGFRA is a receptor for platelet derived growth factors, which are mitogens for cells of mesenchymal origin[170]. PDGFRA may function as a homodimer or heterodimer with PDGFRB depending on the ligand[171]. The PDGFRA gene is physically adjacent to KIT and KDR on chromosome 4q12, and all 3 tyrosine kinases are often co-amplified in cancer[172]. 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[173].

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[174,175,176,177]. 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[178,179,180]. 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[181] (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[182] (2017) for harboring PDGFRA D842V mutation. Imatinib[183] (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[184]. Amplification of PDGFRA is a diagnostic marker of H3-wildtype and IDH-wildtype diffuse pediatric-type high-grade glioma[185,186]. PDGFRA rearrangements are associated with poor risk in pediatric acute lymphoblastic leukemia[187,188].

MSH2 deletion

mutS homolog 2

Background: The MSH2 gene encodes the mutS homolog 2 protein[1]. MSH2 is a tumor suppressor gene that heterodimerizes with MSH6 to form the MutSα complex or with MSH3 to form the MutSβ complex[110]. Both MutS complexes function in DNA damage recognition of base-base mismatches or insertion/deletion (indels) mispairs[110]. Specifically, the MutSα complex recognizes 1-2 nucleotide indels while MutSβ recognizes longer indel mispairs[110]. DNA damage recognition initiates the mismatch repair (MMR) process that repairs mismatch errors which typically occur during DNA replication[110]. Mutations in MSH2 result in the degradation of MSH6[111]. Loss of MSH2 protein expression correlates with mutations in the genes and are used to pre-screen colorectal cancer or endometrial hyperplasia[112]. MSH2, along with MLH1, MSH6, and PMS2, form the core components of the MMR pathway[113]. Deficiency in MMR (dMMR) is characterized by mutations and loss of expression in these genes[114]. dMMR is associated with microsatellite instability (MSI), which is defined as a change in the length of a microsatellite in a tumor as compared to normal tissue[113,115,116]. 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[113,117]. LS is associated with an increased risk of developing colorectal cancer, as well as other

Biomarker Descriptions (continued)

cancers, including endometrial and stomach cancer.[115,117,118,119]. Specifically, MSH2 mutations are associated with an increased risk of ovarian and pancreatic cancer[120,121,122,123].

Alterations and prevalence: Somatic mutations in MSH2 are observed in 8% of uterine corpus endometrial carcinoma, as well as 2-3% of bladder urothelial carcinoma, melanoma, and colorectal adenocarcinoma[18,19]. Alterations in MSH2 are observed in pediatric cancers[18,19]. Somatic mutations are observed in 3% of soft tissue sarcoma, 1% of embryonal tumor, and less than 1% of B-lymphoblastic leukemia/lymphoma (2 in 252 cases), glioma (2 in 297 cases), leukemia (2 in 311 cases), bone cancer (2 in 327 cases), and peripheral nervous system tumors (1 in 1158 cases)[18,19].

Potential relevance: Pembrolizumab (2014) is an anti-PD-1 immune checkpoint inhibitor that is approved for patients with dMMR solid tumors that have progressed on prior therapies[124]. 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[125,126]. MSH2 mutations are consistent with high grade in pediatric diffuse gliomas[127,128].

CDKN2C p.(D17Gfs*7) c.49_50insG, CDKN2C p.(D17Tfs*2) c.49delG

cyclin dependent kinase inhibitor 2C

Background: CDKN2C encodes the cyclin-dependent kinase inhibitor 2C protein, a cell cycle regulator that controls G1/S progression[1]. CDKN2C, also known as p18/INK4C, belongs to a family of INK4 cyclin-dependent kinase inhibitors, which includes CDKN2A (p16/INK4A), CDKN2B (p15/INK4B), and CDKN2D (p19/INK4D). The INK4 family regulates cell cycle progression by inhibiting CDK4 or CDK6, thereby preventing the phosphorylation of Rb[45,46,47]. Unlike CDKN2A and CDKN2B, inactivation of CDKN2C is not frequently observed in cancer[66].

Alterations and prevalence: Somatic mutations in CDKN2C are observed in 2% of uterine corpus endometrial carcinoma and glioblastoma. Biallelic deletion of CDKN2C is observed in 3% of glioblastoma and 2% of pheochromocytoma, paraganglioma, brain lower grade glioma, kidney chromophobe, and sarcoma[18,19]. Deletion of chromosome 1p32, where CDKN2C resides, is observed to be recurrent in multiple myeloma with variable frequency (7%-20%), depending on the study[67,68,69].

Potential relevance: Currently, no therapies are approved for CDKN2C 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 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

Biomarker Descriptions (continued)

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].

MUTYH p.(R19*) c.55C>T

mutY DNA glycosylase

Background: The MUTYH gene encodes the mutY DNA glycosylase protein[1]. DNA glycosylases are structurally specific enzymes that function in base excision repair (BER) by removing damaged or incorrect bases in DNA[29]. MUTYH functions by removing adenine residues that have been misincorporated opposite of 8-oxoG (7,8-dihydro-8-oxoguanine) and FapyG (2,6-diamino-4-hydroxy-5-formamidopyrimidine)[29]. Germline biallelic MUTYH pathogenic variants are associated with MUTYH-Associated Polyposis (MAP), a hereditary condition that confers a predisposition to colorectal cancer[30,31].

Alterations and prevalence: Somatic mutations in MUTYH are observed in 4% of skin cutaneous melanoma and uterine corpus endometrial carcinoma, 2% of lung squamous cell carcinoma, stomach adenocarcinoma, and colorectal adenocarcinoma[18,19]. Biallelic deletions in MUTYH are observed in 2% of pheochromocytoma and paraganglioma[18,19].

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

Microsatellite stable

Background: Microsatellites are short tandem repeats (STR) of 1 to 6 bases of DNA between 5 to 50 repeat units in length. There are approximately 0.5 million STRs that occupy 3% of the human genome[129]. Microsatellite instability (MSI) is defined as a change in the length of a microsatellite in a tumor as compared to normal tissue[115,117]. 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[116]. 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[130]. 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)[130]. Tumors classified as MSI-L are often phenotypically indistinguishable from MSS tumors and tend to be grouped with MSS[118,131,132,133,134]. 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[117]. LS is associated with an increased risk of developing colorectal cancer, as well as other cancers, including endometrial and stomach cancer[115,117,118,119].

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[115,117,135,136]. 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[135,136].

Potential relevance: Anti-PD-1 immune checkpoint inhibitors including pembrolizumab[124] (2014) and nivolumab[125] (2015) are approved for patients with MSI-H or dMMR colorectal cancer who have progressed following chemotherapy. Pembrolizumab[124] 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[124]. Dostarlimab[137] (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[132,138]. The cytotoxic T-lymphocyte antigen 4 (CTLA-4) blocking antibody, ipilimumab[126] (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[132,139,140]. 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[140]. 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[141,142]. However, checkpoint blockade with the addition of chemotherapy or targeted therapies have demonstrated response in MSS or pMMR cancers[141,142].

POLE p.(R1371*) c.4111C>T

DNA polymerase epsilon, catalytic subunit

Background: The POLE gene encodes the DNA polymerase epsilon, catalytic subunit protein[1]. POLE is one of the four-subunits in the DNA polymerase epsilon complex that also includes POLE2, POLE3, and POLE4[100,101]. The DNA polymerase epsilon complex mediates DNA repair, chromosomal replication, and genomic stability[100,101]. Specifically, POLE is the largest subunit in the complex and contains the catalytic and proofreading exonuclease active sites proposed to function in leading strand synthesis during homologous recombination repair (HRR)[101,102]. Mutations in POLE lead to increased mutation rates and subsequent tumor formation thereby

Biomarker Descriptions (continued)

impacting genomic stability[101,102]. Somatic POLE mutations are characterized by a hypermutated phenotype due to the increase in single-nucleotide substitutions[103]. Monoallelic POLE variants have also been associated with adenomatous polyposis and may confer an increased risk in colorectal cancer (CRC)[104,105,106,107,108]. Germline mutations in POLE exonuclease domains are associated with a predisposition to polymerase proofreading-associated polyposis[103].

Alterations and prevalence: Recurrent somatic mutations occur in 15% of uterine corpus endometrial carcinoma, 9% of skin cutaneous melanoma, 6% of colorectal adenocarcinoma, stomach adenocarcinoma, and bladder urothelial carcinoma, as well as 5% of lung squamous cell carcinoma and lung adenocarcinoma[18,19]. Specifically, mutations in the proofreading domain of POLE occur in 7-12% of endometrial cancer and 1-2% of colorectal cancer[101,103]. POLE mutations are associated with high tumor mutational burden (TMB)[101,103,109].

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

SETD2 p.(R456*) c.1366C>T

SET domain containing 2

Background: The SETD2 gene encodes the SET domain containing 2 histone lysine methyltransferase, a protein responsible for the trimethylation of lysine-36 on histone H3 (H3K36)[70,71]. Methylation of H3K36 is a hallmark of active transcription and can be either mono-, di-, or tri-methylated where di- and tri-methylation are thought to be responsible for transcriptional regulation[72]. Trimethylation of H3K36 by SETD2 promotes post-transcriptional gene silencing and prevents aberrant transcriptional initiation[73,74]. SETD2 trimethylation activity is also observed to be involved in DNA repair through the recruitment of DNA repair machinery[71]. Specifically, H3K36 tri-methylation by SETD2 has been shown to regulate mismatch repair (MMR) in vivo, wherein the loss of SETD2 results in MMR deficiency (dMMR) and consequent microsatellite instability (MSI)[75]. Both copy number deletion and mutations resulting in SETD2 loss of function have been observed in a variety of cancers, suggesting a tumor suppressor role for SETD2[71,76].

Alterations and prevalence: Inactivating somatic mutations in SETD2 were first described in clear cell renal cell carcinoma (ccRCC) and are observed to be predominantly missense or truncating[18,76,77]. Mutations at codon R1625 are observed to be the most recurrent with R1625C having been identified to result in loss of SETD2 H3K36 trimethylase activity[18,70]. SETD2 mutation is observed in about 14% of uterine cancer, 12% of ccRCC, 9% of mesothelioma, and 6-7% of melanoma, lung adenocarcinoma, papillary renal cell carcinoma (pRCC), colorectal and bladder cancers[70]. Biallelic loss of SETD2 is observed in about 6% of diffuse large B-cell lymphoma, and about 3% of ccRCC and mesothelioma[70].

Potential relevance: Currently, no therapies are approved for SETD2 aberrations. Mutations in SETD2 can be used to support diagnosis of hepatosplenic T-cell lymphoma (HSTCL)[78].

EPHA2 p.(E911Sfs*20) c.2730_2757delCGAGTGGCTGGAGTCCATCAAGATGCAG

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[42,43]. 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[43]. 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[42,43].

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.

CUL3 p.(E220Vfs*10) c.658_659insT

cullin 3

Background: The CUL3 gene encodes cullin 3, a member of the cullin family, which includes CUL1, CUL2, CUL4a, CUL4b, CUL5, CUL7, and Parc[1,25]. Cullin proteins share a conserved cullin homology domain and act as molecular scaffolds for RING E3 ubiquitin ligases to assemble into cullin-RING ligase complexes (CRLs)[25]. CRLs are involved in diverse biological processes including cell cycle control, DNA replication and repair, and chromatin remodeling[26]. CUL3 is part of the CRL3 complex which is responsible for ubiquitination and degradation of a variety of substrates[26,27,28]. Substrate specificity is dependent on the proteins recruited by CUL3 that have BTB domains, such as KEAP1 and SPOP[26,27,28]. CRL3 substrates include various oncoproteins, tumor suppressors, cell cycle promoters,

Biomarker Descriptions (continued)

apoptosis regulators, and signaling molecules, thereby impacting various processes critical to cancer progression and supporting a complex role of CUL3 in oncogenesis[28].

Alterations and prevalence: Somatic mutations in CUL3 are observed in 8% of uterine corpus endometrial carcinoma, 5% of lung squamous cell carcinoma, 4% of kidney renal papillary cell carcinoma, 3% of head and neck squamous cell carcinoma, cholangiocarcinoma, and skin cutaneous melanoma, and 2% of lung adenocarcinoma, bladder urothelial carcinoma, colorectal adenocarcinoma, and stomach adenocarcinoma[18,19]. Biallelic loss of CUL3 is observed in 2% of sarcoma, cervical squamous cell carcinoma, head and neck squamous cell carcinoma, bladder urothelial carcinoma, lung squamous cell carcinoma, and thymoma[18,19]. Amplification of CUL3 is observed in 3% of pancreatic adenocarcinoma and 2% of uterine carcinosarcoma[18,19].

Potential relevance: Currently, no therapies are approved for CUL3 aberrations.

HLA-A deletion, HLA-A p.(L180*) c.539T>A

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[79]. MHC class I molecules are heterodimers composed of two polypeptide chains, α and B2M[80]. 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[81,82,83]. Downregulation of MHC class I promotes tumor evasion of the immune system, suggesting a tumor suppressor role for HLA-A[84].

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[18,19]. Biallelic loss of HLA-A is observed in 4% of DLBCL[18,19].

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

NOTCH3 p.(T101Hfs*16) c.301_303delACCinsCACT

notch 3

Background: The NOTCH3 gene encodes the notch receptor 3 protein, a type 1 transmembrane protein and member of the NOTCH family of genes, which also includes NOTCH1, NOTCH2, and NOTCH4. NOTCH proteins contain multiple epidermal growth factor (EGF)-like repeats in their extracellular domain, which are responsible for ligand binding and homodimerization, thereby promoting NOTCH signaling[32]. Following ligand binding, the NOTCH intracellular domain is released, which activates the transcription of several genes involved in regulation of cell proliferation, differentiation, growth, and metabolism[33,34]. In cancer, depending on the tumor type, aberrations in the NOTCH family can be gain of function or loss of function suggesting both oncogenic and tumor suppressor roles for NOTCH family members[35,36,37,38].

Alterations and prevalence: Somatic mutations observed in NOTCH3 are primarily missense or truncating and are found in about 12% of melanoma and uterine cancer, as well as 3-6% of diffuse large B-cell lymphoma (DLBCL), adrenocortical carcinoma, esophageal, colorectal, cervical, squamous lung, bladder, and head and neck cancers[18].

Potential relevance: Currently, no therapies are approved for NOTCH3 aberrations.

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

PIK3CA p.(M1043V) c.3127A>G

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
capivasertib + fulvestrant	○	○	○	✖	✖
inavolisib + palbociclib + fulvestrant	○	○	○	✖	✖
aspirin	✖	○	✖	✖	✖
ETX-636	✖	✖	✖	✖	● (I/II)
HTL-0039732, atezolizumab	✖	✖	✖	✖	● (I/II)
JS-105	✖	✖	✖	✖	● (I)
SNV-4818, hormone therapy	✖	✖	✖	✖	● (I)

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)

* 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

CDKN2A deletion (continued)

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
CID-078	✖	✖	✖	✖	● (I)

ATM p.(C1286*) c.3858C>A

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

PDGFRA p.(V561D) c.1682T>A

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

MSH2 deletion

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

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

HRR Details

Gene/Genomic Alteration	Finding
LOH percentage	***1.08%***
RAD51B	***SNV, P128S, AF:0.49***

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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