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Patient Name: 박분자
Gender: F
Sample ID: N25-34

Primary Tumor Site: brain
Collection Date: 2025.05.19

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

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Relevant Glioblastoma IDH-wildtype (Grade 4) Findings

Gene	Finding
BRAF	None detected
EGFR	None detected
NTRK1	None detected
NTRK2	None detected
NTRK3	None detected
RET	None detected
TERT	None detected

Genomic Alteration	Finding
Tumor Mutational Burden	***1.9 Mut/Mb measured***

Relevant Biomarkers

Tier	Genomic Alteration	Relevant Therapies (In this cancer type)	Relevant Therapies (In other cancer type)	Clinical Trials
IIC	*BAP1 deletion* BRCA1 associated protein 1 Locus: chr3:52436290	None*	None*	1
IIC	*CDKN2C deletion* cyclin dependent kinase inhibitor 2C Locus: chr1:51434849	None*	None*	1
IIC	*FANCM deletion* FA complementation group M Locus: chr14:45605157	None*	None*	1
IIC	*LATS1 deletion* large tumor suppressor kinase 1 Locus: chr6:149982844	None*	None*	1

*** Public data sources included in relevant therapies: FDA**[1], NCCN, **EMA**[2], 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

*ARID1B deletion, CIC p.(S1104T) c.3310T>A, ERCC2 deletion, FANCD2 deletion, MAP2K4 deletion, MLH1 deletion, MLH3 deletion, Microsatellite stable, PARP3 deletion, POLD1 deletion, RAD51B deletion, SETD2 deletion, SETD2 p.(K1355Nfs*18) c.4065delA, XRCC3 deletion, UGT1A1 p.(G71R) c.211G>A, TGFBR2 deletion, DOCK3 deletion, PBRM1 deletion, PRDM1 deletion, HDAC2 deletion, TNFAIP3 deletion, MAP3K4 deletion, DICER1 deletion, NQO1 p.(P187S) c.559C>T, GPS2 deletion, NCOR1 deletion, KMT2B deletion, CIC deletion, ARHGAP35 deletion, Tumor Mutational Burden*

Variant Details

DNA Sequence Variants

Gene	Amino Acid Change	Coding	Variant ID	Locus	Allele Frequency	Transcript	Variant Effect
UGT1A1	p.(G71R)	c.211G>A	COSM4415616	chr2:234669144	52.90%	NM_000463.3	missense
SETD2	p.(K1355Nfs*18)	c.4065delA	.	chr3:47162060	71.92%	NM_014159.7	frameshift Deletion
NQO1	p.(P187S)	c.559C>T	.	chr16:69745145	49.27%	NM_000903.3	missense
CIC	p.(S1104T)	c.3310T>A	.	chr19:42796852	84.46%	NM_015125.5	missense
TP53	p.(S121P)	c.361T>C	.	chr17:7579326	68.26%	NM_000546.6	missense

Copy Number Variations

Gene	Locus	Copy Number	CNV Ratio
CDKN2C	chr1:51434849	0.01	0.19
FANCD2	chr3:10070306	1.09	0.63
TGFBR2	chr3:30648337	1.14	0.65
MLH1	chr3:37034957	1.14	0.65
SETD2	chr3:47058542	1.19	0.67
DOCK3	chr3:51101879	0.98	0.59
PARP3	chr3:51976651	1.21	0.68
BAP1	chr3:52436290	1.19	0.67
PBRM1	chr3:52582040	1.06	0.62
PRDM1	chr6:106534408	0.99	0.59
HDAC2	chr6:114262171	0.89	0.55
TNFAIP3	chr6:138192315	1.04	0.61
LATS1	chr6:149982844	1.04	0.61
ARID1B	chr6:157099057	1.06	0.62
MAP3K4	chr6:161412931	1.1	0.63
FANCM	chr14:45605157	1.05	0.62
RAD51B	chr14:68290164	1	0.59
MLH3	chr14:75483761	1.01	0.6
DICER1	chr14:95556791	1.04	0.61

Variant Details (continued)

Copy Number Variations (continued)

Gene	Locus	Copy Number	CNV Ratio
XRCC3	chr14:104165043	0.96	0.58
GPS2	chr17:7216071	1.1	0.64
MAP2K4	chr17:11924164	1.19	0.67
NCOR1	chr17:15935586	0.95	0.58
KMT2B	chr19:36209128	1.04	0.61
CIC	chr19:42775916	0.96	0.58
ERCC2	chr19:45854865	1.05	0.61
ARHGAP35	chr19:47421913	0.98	0.59
POLD1	chr19:50902079	1	0.59
RAF1	chr3:12625930	1.19	0.67
MITF	chr3:69788729	1.01	0.6
FYN	chr6:111982890	1.05	0.62
ROS1	chr6:117622071	0.96	0.58
ESR1	chr6:152163831	0.96	0.58
FOXA1	chr14:38060550	0.99	0.59
MAX	chr14:65472833	1.16	0.66
AKT1	chr14:105236628	0.84	0.53
CCNE1	chr19:30303647	0.94	0.57
AKT2	chr19:40739751	1.07	0.62
AXL	chr19:41725295	1.01	0.6
BCL2L12	chr19:50169053	1.12	0.64
PPP2R1A	chr19:52693246	1.19	0.67
AURKC	chr19:57742416	0.89	0.55

Biomarker Descriptions

FANCM deletion

FA complementation group M

Background: The FANCM gene encodes the FA complementation group M protein, a member of the Fanconi Anemia (FA) family, which also includes FANCA, FANCB, FANCC, FANCD1 (BRCA2), FANCD2, FANCE, FANCF, FANCG, FANCI, FANCJ (BRIP1), FANCL, and FANCN (PALB2)[1]. FA genes are tumor suppressors that are responsible for the maintenance of replication fork stability, DNA damage repair through the removal of interstrand cross-links (ICL), and subsequent initiation of the homologous recombination repair (HRR) pathway[2,3]. In response to DNA damage, FANCA, FANCB, FANCC, FANCE, FANCF, FANCG, FANCL, and FANCM assemble to form the FA core complex which is responsible for the monoubiquitination of the FANCI-FANCD2 (ID2) complex[2]. Monoubiquitination of the ID2 complex promotes co-localization with BRCA1/2, which is critical in BRCA mediated DNA repair[4,5]. Loss of function mutations in the FA family and HRR pathway can result in the BRCAness phenotype, characterized by a defect in the HRR pathway, mimicking BRCA1 or BRCA2 loss[6,7]. Germline mutations in FA genes lead to Fanconi Anemia, a condition characterized by chromosomal instability and congenital abnormalities, including bone marrow failure and cancer predisposition[8,9].

Biomarker Descriptions (continued)

Alterations and prevalence: Somatic mutations in FANCM are observed in 11% of uterine corpus endometrial carcinoma, 8% of skin cutaneous melanoma, 7% of lung adenocarcinoma, 6% of stomach adenocarcinoma, 5% colorectal adenocarcinoma, uterine carcinosarcoma, and bladder urothelial carcinoma[10,11].

Potential relevance: Currently, no therapies are approved for FANCM aberrations. Consistent with other genes that contribute to the BRCAness phenotype, mutations in FANCM are shown to confer enhanced sensitivity in vitro to PARP inhibitors such as olaparib[12].

TGFBR2 deletion

transforming growth factor beta receptor 2

Background: TGFBR2 encodes transforming growth factor beta receptor 2[1]. Along with TGFBR1 and TGFBR3, TGFBR2 is a member of the TGF-beta receptor family[13]. Both TGFBR1 and TGFBR2 function as serine/threonine and tyrosine kinases, whereas TGFBR3 does not possess any kinase activity[13]. TGFBR1 heterodimerizes with TGFBR2 and activates ligand binding of TGF-beta cytokines namely TGFB1, TGFB2, and TGFB3[13]. Heterodimerization with TGFBR2 enables TGFBR1 to phosphorylate downstream SMAD2/3, which leads to activation of SMAD4[14]. This process regulates various signaling pathways implicated in cancer initiation and progression, including epithelial to mesenchymal transition (EMT) and apoptosis[15,16,17].

Alterations and prevalence: Somatic mutations in TGFBR2 are observed in 5% of esophageal adenocarcinoma, and head and neck squamous cell carcinoma, 4% of pancreatic adenocarcinoma, stomach adenocarcinoma, uterine corpus endometrial carcinoma, colorectal adenocarcinoma, and cholangiocarcinoma[10,11]. Biallelic deletion of TGFRB2 is observed in 3% of kidney renal clear cell carcinoma and 2% of stomach adenocarcinoma and head and neck squamous cell carcinoma[10,11].

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

MLH3 deletion

mutL homolog 3

Background: The MLH3 gene encodes the mutL homolog 3 protein[1]. MLH3 heterodimerizes with MLH1 to form the MutLγ complex which functions as an endonuclease during meiosis, specifically in meiotic recombination[18]. MLH3 is considered a mismatch repair (MMR) gene due to its functional role in yeast, however, its exact MMR role in humans is less clear[18,19,20]. Low expression of MMR genes, including MLH3, have been associated with high levels of microsatellite instability (MSI-H) in colorectal cancer[21].

Alterations and prevalence: Somatic mutations in MLH3 are observed in 9% of uterine corpus endometrial carcinoma, 4% of colorectal adenocarcinoma, skin cutaneous melanoma, and stomach adenocarcinoma[10,11]. Biallelic deletions are observed in 2% of kidney chromophobe[10,11].

Potential relevance: Currently, no therapies are approved for MLH3 aberrations.

FANCD2 deletion

Fanconi anemia complementation group D2

Background: The FANCD2 gene encodes the FA complementation group D2 protein, a member of the Fanconi Anemia (FA) family, which also includes FANCA, FANCB, FANCC, FANCD1 (BRCA2), FANCE, FANCF, FANCG, FANCI, FANCJ (BRIP1), FANCL, FANCM and FANCN (PALB2)[1]. FA genes are tumor suppressors that are responsible for the maintenance of replication fork stability, DNA damage repair through the removal of interstrand cross-links (ICL), and subsequent initiation of the homologous recombination repair (HRR) pathway[2,3]. In response to DNA damage, FANCA, FANCB, FANCC, FANCE, FANCF, FANCG, FANCL, and FANCM assemble to form the FA core complex which is responsible for the monoubiquitination of the FANCI-FANCD2 (ID2) complex[2]. Monoubiquitination of the ID2 complex promotes co-localization with BRCA1/2, which is critical in BRCA mediated DNA repair[4,5]. Loss of function mutations in the FA family and HRR pathway, including FANCD2, can result in the BRCAness phenotype, characterized by a defect in the HRR pathway, mimicking BRCA1 or BRCA2 loss[6,7]. Germline mutations in FA genes lead to Fanconi Anemia, a condition characterized by chromosomal instability and congenital abnormalities, including bone marrow failure and cancer predisposition[8,9].

Alterations and prevalence: Somatic mutations in FANCD2 are observed in 4-8% of diffuse large B-cell lymphoma (DLBCL), melanoma, bladder, and uterine cancer[10].

Potential relevance: Currently, no therapies are approved for FANCD2 aberrations. Consistent with other genes that contribute to the BRCAness phenotype, FANCD2 deficiency or loss of function has been shown to confer enhanced sensitivity to PARP inhibitors in vitro[22,23,24].

Biomarker Descriptions (continued)

LATS1 deletion

large tumor suppressor kinase 1

Background: The LATS1 gene encodes the large tumor suppressor kinase 1[1]. LATS1 is a serine/threonine protein kinase and, along with LATS2, is a member of the AGC kinase family comprised of more than 60 members[25,26]. LATS1 and LATS2 are downstream phosphorylation targets of the Hippo pathway, and when activated, mediate the phosphorylation of transcriptional co-activators YAP and TAZ[27]. Phosphorylation of YAP and TAZ results in their cytoplasmic retention and inhibition of nuclear translocation, thereby inhibiting YAP and TAZ mediated transcription of target genes[27]. Mutations in LATS1 and LATS2 are suggested to result in kinase inactivation and loss of function, supporting a tumor suppressor role for LATS1[28].

Alterations and prevalence: Somatic mutations in LATS1 are observed in 9% of uterine corpus endometrial carcinoma, 4% of cervical squamous cell carcinoma, bladder urothelial carcinoma, colorectal adenocarcinoma, lung squamous cell carcinoma, and skin cutaneous melanoma, and 3% of stomach adenocarcinoma and lung adenocarcinoma[10,11]. Biallelic deletion of LATS1 is observed in 8% of uveal melanoma, 6% of diffuse large B-cell lymphoma, and 2% liver hepatocellular carcinoma, ovarian serous cystadenocarcinoma, and thymoma[10,11].

Potential relevance: Currently, no therapies are approved for LATS1 aberrations.

PARP3 deletion

poly(ADP-ribose) polymerase family member 3

Background: The PARP3 gene encodes the poly(ADP-ribose) polymerase 3 protein[1]. PARP3 belongs to the large PARP protein family that also includes PARP1, PARP2, and PARP4[29]. PARP enzymes are responsible for the transfer of ADP-ribose, known as poly(ADP-ribosyl)ation or PARylation, to a variety of protein targets resulting in the recruitment of proteins involved in DNA repair, DNA synthesis, nucleic acid metabolism, and regulation of chromatin structure[29,30]. PARP enzymes are involved in several DNA repair pathways[29,30]. Although the functional role of PARP3 is not well understood, PARP3 may serve a role in double-strand break (DSB) repair by facilitating selection for either non-homologous end joining (NHEJ) or homologous recombination repair (HRR)[31,32]. Specifically, PARP3 is proposed to accelerate DSB repair by NHEJ by targeting APLF to chromosomal DSBs[31].

Alterations and prevalence: Somatic mutations in PARP3 are observed in 4% of uterine corpus endometrial carcinoma, and 2% of skin cutaneous melanoma, lung adenocarcinoma, and stomach adenocarcinoma[10,11]. Biallelic deletions in PARP3 are observed in 4% of diffuse large B-cell lymphoma (DLBCL), 3% of kidney renal clear cell carcinoma, 2% of esophageal adenocarcinoma and sarcoma[10,11].

Potential relevance: Currently, no therapies are approved for PARP3 aberrations. However, PARP inhibition is known to induce synthetic lethality in certain cancer types that are HRR deficient (HRD) due to mutations in the HRR pathway. This is achieved from PARP inhibitors (PARPi) by promoting the accumulation of DNA damage in cells with HRD, consequently resulting in cell death[33,34]. Although not indicated for specific alterations in PARP3, several PARPis including olaparib, rucaparib, talazoparib, and niraparib have been approved in various cancer types with HRD. Olaparib[35] (2014) was the first PARPi to be approved by the FDA for BRCA1/2 aberrations. Originally approved for the treatment of germline variants, olaparib is now indicated (2018) for the maintenance treatment of both germline BRCA1/2-mutated (gBRCAm) and somatic BRCA1/2-mutated (sBRCAm) epithelial ovarian, fallopian tube, or primary peritoneal cancers that are responsive to platinum-based chemotherapy. Olaparib is also indicated for the treatment of patients with gBRCAm HER2-negative metastatic breast cancer and metastatic pancreatic adenocarcinoma. Additionally, olaparib[35] is approved (2020) for metastatic castration-resistant prostate cancer (mCRPC) with deleterious or suspected deleterious germline or somatic mutations in HRR genes that includes BRCA1. Rucaparib[36] (2016) was the first PARPi approved for the treatment of patients with either gBRCAm or sBRCAm epithelial ovarian, fallopian tube, or primary peritoneal cancers and is also approved (2020) for deleterious gBRCAm or sBRCAm mCRPC. Talazoparib[37] (2018) is indicated for the treatment of gBRCAm HER2-negative locally advanced or metastatic breast cancer. Niraparib[38] (2017) is another PARPi approved for the treatment of epithelial ovarian, fallopian tube, or primary peritoneal cancers with a deleterious or suspected deleterious BRCA mutation.

PBRM1 deletion

polybromo 1

Background: The PBRM1 gene encodes polybromo 1 protein[1]. PBRM1, also known as BAF180, is a member of the PBAF complex, a SWI/SNF chromatin-remodeling complex[39]. The PBAF complex is a multisubunit protein complex that consists of ARID2, SMARCA4A/BRG1, BRD7, ACTL6A/BAF53A, PHF10/BAF45A, PBRM1/BAF180, SMARCC2/BAF170, SMARCC1/BAF155, SMARCB1/BAF47, SMARCD1/BAF60A, and SMARCE1/BAF57[39,40]. PBRM1 is proposed to facilitate localization of PBAF complexes to specific loci for chromatin remodeling[39,41]. PBRM1 also promotes centromere cohesion in order to maintain genomic stability and prevent aneuploidy by silencing transcription near double-stranded DNA breaks (DSBs), supporting a tumor suppressor role for PBRM1[42,43].

Biomarker Descriptions (continued)

Alterations and prevalence: Somatic mutations in PBRM1 are observed in 38% of kidney renal clear cell carcinoma, 22% of cholangiocarcinoma, 10% of uterine corpus endometrial carcinoma, and 8% of skin cutaneous melanoma[10,11]. Biallelic deletion of PBRM1 is observed in 5% of mesothelioma, 4% of diffuse large B-cell lymphoma (DLBCL), 3% of kidney renal clear cell carcinoma, and 2% of esophageal adenocarcinoma, uterine carcinosarcoma, stomach adenocarcinoma, and sarcoma[10,11].

Potential relevance: Currently, no therapies are approved for PBRM1 aberrations.

DICER1 deletion

dicer 1, ribonuclease III

Background: The DICER1 gene encodes the dicer 1, ribonuclease III protein[1]. DICER1 is a member of the ribonuclease (RNase) III family that also includes DROSHA[44]. Both DICER and DROSHA are responsible for the processing of precursor non-coding RNA (primary miRNA) into micro-RNA (miRNA)[44,45]. Following primary miRNA processing to hairpin precursor miRNA (pre-miRNA) by DROSHA and DGCR8, pre-miRNA is then cleaved by DICER1 resulting in the production of mature miRNA[44]. Once processed, mature miRNA is capable of post-transcriptional gene repression by recognizing complimentary target sites on messenger RNA (mRNA)[44,45]. miRNAs are frequently dysregulated in cancer, potentially through DGCR8, DICER1, or DROSHA aberrations that impact miRNA processing[45,46,47,48]. Germline DICER1 mutations result in DICER1 syndrome, a rare genetic disorder that predisposes affected individuals to tumor development[49].

Alterations and prevalence: Somatic mutations in DICER1 are observed in 13% of uterine corpus endometrial carcinoma, 11% of skin cutaneous melanoma, and 4% of colorectal adenocarcinoma, bladder urothelial carcinoma, and uterine carcinosarcoma[10,11]. Biallelic loss of DICER1 is observed in 3% of cholangiocarcinoma and 2% kidney chromophobe[10,11].

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

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

UDP glucuronosyltransferase family 1 member A1

Background: The UGT1A1 gene encodes UDP glucuronosyltransferase family 1 member A1, a member of the UDP-glucuronosyltransferase 1A (UGT1A) subfamily of the UGT protein superfamily[1,50]. UGTs are microsomal membrane-bound enzymes that catalyze the glucuronidation of endogenous and xenobiotic compounds and transform the lipophilic molecules into excretable, hydrophilic metabolites[50,51]. UGTs play an important role in drug metabolism, detoxification, and metabolite homeostasis. Differential expression of UGTs can promote cancer development, disease progression, as well as drug resistance[52]. Specifically, elevated expression of UGT1As are associated with resistance to many anti-cancer drugs due to drug inactivation and lower active drug concentrations. However, reduced expression and downregulation of UGT1As are implicated in bladder and hepatocellular tumorigenesis and progression due to toxin accumulation[52,53,54,55]. Furthermore, UGT1A1 polymorphisms, such as UGT1A1*28, UGT1A1*93, and UGT1A1*6, confer an increased risk of severe toxicity to irinotecan-based chemotherapy treatment of solid tumors, due to reduced glucuronidation of the irinotecan metabolite, SN-38[56].

Alterations and prevalence: Biallelic deletion of UGT1A1 has been observed in 6% of sarcoma, 3% of brain lower grade glioma and uveal melanoma, and 2% of thymoma, cervical squamous cell carcinoma, bladder urothelial carcinoma, head and neck squamous cell carcinoma, and esophageal adenocarcinoma[10,11].

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

MLH1 deletion

mutL homolog 1

Background: The MLH1 gene encodes the mutL homolog 1 protein[1]. MLH1 is a tumor suppressor gene that heterodimerizes with PMS2 to form the MutLα complex, PMS1 to form the MutLβ complex, and MLH3 to form the MutLγ complex[18]. 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[18,57]. Loss of MLH1 protein expression and MLH1 promoter hypermethylation correlates to mutations in these genes and are used to pre-screen colorectal cancer or endometrial hyperplasia[58,59]. MLH1, along with MSH6, MSH2, and PMS2 form the core components of the MMR pathway[18]. The MMR pathway is critical to the repair of mismatch errors which typically occur during DNA replication. Deficiency in MMR (dMMR) is characterized by mutations and loss of expression in these genes. 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[60,61,62]. 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[60,63]. LS is associated with an increased risk of developing

Biomarker Descriptions (continued)

colorectal cancer, as well as other cancers, including endometrial and stomach cancer[61,63,64,65]. Specifically, MLH1 mutations are associated with increased risk of ovarian and pancreatic cancer[66,67,68,69].

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[10,11].

Potential relevance: The PARP inhibitor, talazoparib[37] 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[70]. 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[71,72].

MAP2K4 deletion

mitogen-activated protein kinase kinase 4

Background: The MAP2K4 gene encodes the mitogen-activated protein kinase kinase 4, also known as MEK4[1]. MAP2K4 is a member of the mitogen-activated protein kinase 2 (MAP2K) subfamily which also includes MAP2K1, MAP2K2, MAP2K3, MAP2K5, and MAP2K6[73]. Activation of MAPK proteins occurs through a kinase signaling cascade[73,74,75]. Specifically, MAP3Ks are responsible for phosphorylation of MAP2K family members[73,74,75]. 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[73,74,75]. Mutations observed in MAP2K4 were have been observed to impair kinase activity and promote tumorigenesis in vitro, supporting a possible tumor suppressor role for MAP2K4[76].

Alterations and prevalence: Somatic mutations in MAP2K4 have been observed in 5% of uterine carcinoma and colorectal cancer, and 4% of breast invasive carcinoma[10,11]. Biallelic deletions have been observed in 3% of stomach cancer, and 2% of breast invasive carcinoma, diffuse large B-cell lymphoma (DLBCL), colorectal, pancreatic, and ovarian cancer[10,11]. Nonsense, frameshift, and missense mutations in MAP2K4 generally inactivate the kinase activity, and lost expression has been identified in prostate, ovarian, brain, and pancreatic cancer models[77,78].

Potential relevance: Currently, no therapies are approved for MA2PK4 aberrations.

RAD51B deletion

RAD51 paralog B

Background: The RAD51B gene encodes the RAD51 paralog B protein, a member of the RAD51 recombinase family that also includes RAD51, RAD51C (RAD51L2), RAD51D (RAD51L3), XRCC2, and XRCC3 paralogs. The RAD51 family of proteins are involved in homologous recombination repair (HRR) and DNA repair of double-strand breaks (DSB)[79]. RAD51B associates with other RAD51 paralogs to form RAD51B-RAD51C-RAD51D-XRCC2 (BCDX2) complex[80]. The BCDX2 complex binds single- and double-stranded DNA to hydrolyze ATP[81]. RAD51B is a tumor suppressor gene. Loss of function mutations in RAD51B are implicated in the BRCAness phenotype, which is characterized by a defect in HRR mimicking BRCA1 or BRCA2 loss[6,82]. Biallelic expression of RAD51B is required for chromosomal integrity and haploinsufficiency leads to aberrant HRR resulting in centrosome fragmentation, aneuploidy, and mild hypersensitivity to DNA-damaging agents[83]. Genetic variation within the RAD51B locus on 14q24.1 is significantly associated with familial breast cancer risk[84].

Alterations and prevalence: Somatic mutations in RAD51B are observed in up to 3% of uterine cancer[10,11]. Loss of function mutations in RAD51B are rare, but variation within the RAD51B locus is significantly associated with familial breast cancer risk[84].

Potential relevance: The PARP inhibitor, olaparib[35] is approved (2020) for metastatic castration-resistant prostate cancer (mCRPC) with deleterious or suspected deleterious, germline or somatic mutations in HRR genes that includes RAD51B. In 2022, the FDA granted fast track designation to the small molecule inhibitor, pidnarulex[85], for BRCA1/2, PALB2, or other homologous recombination deficiency (HRD) mutations in breast and ovarian cancers.

ERCC2 deletion

ERCC excision repair 2, TFIIH core complex helicase subunit

Background: The ERCC2 gene encodes ERCC excision repair 2, TFIIH core complex helicase subunit, also known as XPD[1]. ERCC2 is a protein involved in the nucleotide excision repair (NER) pathway responsible for repairing bulky DNA lesions caused by UV radiation, environmental mutagens, chemical agents, and cyclopurines generated by reactive oxygen species[86]. ERCC2 functions as a helicase along with ERCC3/XPB in the TFIIH core complex[86]. During repair of bulky lesions by NER, the TFIIH core complex binds

Biomarker Descriptions (continued)

to the lesion, followed by DNA damage verification by ERCC2, which is essential for NER[86]. Following lesion binding and verification, ERCC2 unwinds DNA in the 5'-3' direction[86]. Mutations in ERCC2 lead to stalled RNA polymerase, resulting in persistent block of transcription[86]. Germline ERCC2 mutations can lead to hereditary disorders including: Cockayne syndrome, characterized by skin cancer susceptibility and neurodegerneration; xeroderma pigmentosum (XP), characterized by neurodegeneration and developmental defects; and trichothiodystrophy (TTD), characterized by brittle hair due to sulfur deficiency as well as other developmental defects[86,87].

Alterations and prevalence: Somatic mutations in ERCC2 are predominantly missense and occur in 9% of bladder urothelial carcinoma, 4% of skin cutaneous melanoma, 3% of uterine corpus endometrial carcinoma, stomach adenocarcinoma, and cholangiocarcinoma, and 2% of lung squamous cell carcinoma[10,11]. The missense mutation, N238S, is observed to be recurrent in bladder urothelial carcinoma and is predicted to result in ERCC2 loss of function[10,11,88]. Biallelic loss of ERCC2 is observed in 2% of brain lower grade glioma and diffuse large B-cell lymphoma, as well as 1% of sarcoma and ovarian serous cystadenocarcinoma[10,11].

Potential relevance: Currently, no therapies are approved for ERCC2 aberrations. In one study, ERCC2 mutations correlated with enhanced response to cisplatin based chemotherapy compared to wild-type ERCC2 in patients with muscle-invasive urothelial carcinoma[89].

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[90]. Microsatellite instability (MSI) is defined as a change in the length of a microsatellite in a tumor as compared to normal tissue[61,63]. 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[62]. 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[91]. 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)[91]. Tumors classified as MSI-L are often phenotypically indistinguishable from MSS tumors and tend to be grouped with MSS[64,92,93,94,95]. 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[63]. LS is associated with an increased risk of developing colorectal cancer, as well as other cancers, including endometrial and stomach cancer[61,63,64,65].

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[61,63,96,97]. 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[96,97].

Potential relevance: Anti-PD-1 immune checkpoint inhibitors including pembrolizumab[70] (2014) and nivolumab[71] (2015) are approved for patients with MSI-H or dMMR colorectal cancer who have progressed following chemotherapy. Pembrolizumab[70] 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[70]. Dostarlimab[98] (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[93,99]. The cytotoxic T-lymphocyte antigen 4 (CTLA-4) blocking antibody, ipilimumab[72] (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[93,100,101]. 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[101]. 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[102,103]. However, checkpoint blockade with the addition of chemotherapy or targeted therapies have demonstrated response in MSS or pMMR cancers[102,103].

PRDM1 deletion

PR/SET domain 1

Background: The PRDM1 gene encodes the PR/SET domain 1 protein, also known as BLIMP1[1]. PRDM1 is a transcriptional repressor that regulates B- and T-cell differentiation[104,105,106]. PRDM1 drives the differentiation of mature B-cells to antibody-secreting cells (ASCs) and is commonly expressed in ASCs[107]. PRDM1, along with other transcription factors, also regulates the expression of IL-2, IL-21, and IL-10 in effector T-cells, resulting in T-cell mediated immunosuppression through IL repression[106]. Dysregulation of B-cell terminal differentiation, as a result of PRDM1 mutations, has been observed to contribute to lymphoma development, supporting a tumor suppressor role for PRDM1[107].

Biomarker Descriptions (continued)

Alterations and prevalence: Somatic mutations in PRDM1 are observed in 7% of skin cutaneous melanoma, 6% of uterine corpus endometrial carcinoma, 5% diffuse large B-cell lymphoma (DLBCL), and 3% of cholangiocarcinoma[10,11]. Additionally, PRDM1 mutations have been reported in 25% of activated B-cell phenotype diffuse large B-cell lymphoma (ABC-DLBCL)[107]. PRDM1 biallelic deletions are observed in 10% of DLBCL, 9% of prostate adenocarcinoma, and 6% of uveal melanoma[10,11].

Potential relevance: Currently, no therapies are approved for PRDM1 aberrations.

CIC p.(S1104T) c.3310T>A, CIC deletion

capicua transcriptional repressor

Background: The CIC gene encodes the capicua transcriptional repressor, a member of the high mobility group (HMG)-box superfamily[1,108]. The HMG-box domain mediates CIC binding to an octameric consensus sequence at the promoters of target genes[1,108]. CIC interacts with the HDAC complex and SWI/SNF to transcriptionally repress target genes, which include members of the E-Twenty Six (ETS) oncogene family ETV1, ETV4 and ETV5[108]. CIC aberrations lead to increased RTK/MAPK signaling and oncogenesis, supporting a tumor suppressor role for CIC[108].

Alterations and prevalence: Somatic mutations in CIC are observed in 21% of brain lower grade glioma, 11% of uterine corpus endometrial carcinoma, 8% of skin cutaneous melanoma, 7% of stomach adenocarcinoma, and 6% of colorectal adenocarcinoma[10,11]. Biallelic loss of CIC is observed 2% of prostate adenocarcinoma and diffuse large B-cell lymphoma (DLBCL)[10,11]. Recurrent CIC fusions are found in Ewing-like sarcoma (ELS) (CIC::DUX4 and CIC::FOXO4), angiosarcoma (CIC::LEUTX), peripheral neuroectodermal tumors (CIC::NUTM1) and oligodendroglioma[108,109].

Potential relevance: Currently, no therapies are approved for CIC aberrations. CIC fusions, including CIC::DUX4 fusion, t(10;19)(q26;q13) and t(4;19)(q35;q13), are ancillary diagnostic markers for CIC-Rearranged Sarcoma[110,111].

POLD1 deletion

DNA polymerase delta 1, catalytic subunit

Background: The POLD1 gene encodes the DNA polymerase delta 1, catalytic subunit protein[1]. POLD1 is one of four subunits that make up the DNA polymerase delta (Polδ) enzyme along with POLD2, POLD3, and POLD4[112,113]. Specifically, POLD1 is responsible for the polymerase and 3'-5' exonuclease activity of Polδ in the synthesis of DNA during DNA replication and repair observed in homologous recombination repair (HRR), mismatch repair (MMR), and nucleotide excision repair (NER)[18,86,112,113]. Independent of Polδ, POLD1 associates with γ-tubulin ring complexes to control cytoplasmic microtubule growth[112]. Germline mutations in POLD1 are associated with polymerase proofreading-associated polyposis, which confers predisposition to colorectal adenomas and carcinomas[114,115,116,117,118].

Alterations and prevalence: Somatic mutations in POLD1 are observed in 8% of uterine corpus endometrial carcinoma, 5% of colorectal adenocarcinoma, 4% of skin cutaneous melanoma, and 3% of stomach adenocarcinoma[10,11].

Potential relevance: Currently, no therapies are approved for POLD1 aberrations.

XRCC3 deletion

X-ray repair cross complementing 3

Background: The XRCC3 gene encodes the X-ray cross complementing 3 protein, a member of the RAD51 recombinase family that also includes RAD51, RAD51C, RAD51D, and XRCC2 paralogs[1,119]. XRCC3 complexes with RAD51C to form the CX3 complex, which functions in strand exchange and Holliday junction resolution during homologous recombination repair (HRR)[119,120]. XRCC3 may complex with BRCA2, FANCD2, and FANCG to maintain chromosome stability[121].

Alterations and prevalence: Somatic mutations in XRCC3 are observed in 1% of uveal melanoma, colorectal adenocarcinoma, and cervical squamous cell carcinoma[10,11]. Biallelic deletions in XRCC3 are observed in 3% of cholangiocarcinoma and 2% of diffuse large B-cell lymphoma (DLBCL) and bladder urothelial carcinoma[10,11].

Potential relevance: Currently, no therapies are approved for XRCC3 aberrations. Pre-clinical evidence suggests that XRCC3 mutations may demonstrate sensitivity to cisplatin[121].

Biomarker Descriptions (continued)

NCOR1 deletion

nuclear receptor corepressor 1

Background: NCOR1 encodes nuclear receptor corepressor 1, which serves as a scaffold protein for large corepressor including transducin beta like 1 X-linked (TBL1X), TBL1X/Y related 1 (TBL1XR1), the G-protein-pathway suppressor 2 (GPS2), and protein deacetylases such as histone deacetylase 3 (HDAC3)[1,122,123]. NCOR1 plays a key role in several processes including embryonal development, metabolism, glucose homeostasis, inflammation, cell fate, chromatin structure and genomic stability[122,123,124,125]. NCOR1 has been shown exhibit a tumor suppressor role by inhibiting invasion and metastasis in various cancer models[123]. Inactivation of NCOR1 through mutation or deletion is observed in several cancer types including colorectal cancer, bladder cancer, hepatocellular carcinomas, lung cancer, and breast cancer[123,126].

Alterations and prevalence: Somatic mutations in NCOR1 are observed in 13% of uterine corpus endometrial carcinoma, 11% of skin cutaneous melanoma, 8% of bladder urothelial carcinoma, 7% of stomach adenocarcinoma, 6% of colorectal adenocarcinoma, 5% of lung squamous cell carcinoma and breast invasive carcinoma, 4% of cervical squamous cell carcinoma and lung adenocarcinoma, 3% of mesothelioma, head and neck squamous cell carcinoma, cholangiocarcinoma, and kidney renal papillary cell carcinoma, and 2% of esophageal adenocarcinoma, glioblastoma multiforme, and ovarian serous cystadenocarcinoma[10,11]. Biallelic loss of NCOR1 are observed in 3% of liver hepatocellular carcinoma, and 2% of uterine carcinosarcoma, stomach adenocarcinoma, diffuse large B-cell lymphoma, and bladder urothelial carcinoma[10,11]. Structural variants of NCOR1 are observed in 3% of cholangiocarcinoma and 2% of uterine carcinosarcoma[10,11].

Potential relevance: Currently, no therapies are approved for NCOR1 aberrations.

ARHGAP35 deletion

Rho GTPase activating protein 35

Background: ARHGAP35 encodes Rho GTPase activating protein 35, human glucocorticoid receptor DNA binding factor. ARHGAP35 functions as a repressor of glucocorticoid receptor transcription[1]. Rho GTPases regulate various cellular processes such as cell adhesion, cell migration and play a critical role in metastasis through the negative regulation of RhoA which is localized to the cell membrane[127,128]. Aberrations in ARHGAP35, including mutations, have been observed to result in both loss and gain of function thereby promoting tumor growth and metastasis[129,130].

Alterations and prevalence: Somatic mutations of AHGAP35 are observed in 20% of uterine corpus endometrial carcinoma, 11% of uterine carcinosarcoma, 6% of skin cutaneous melanoma, bladder urothelial carcinoma, and lung squamous cell carcinoma, 5% of colorectal adenocarcinoma, and 4% of stomach adenocarcinoma and lung adenocarcinoma[10,11]. In endometrial cancer, R997* has been observed to be recurrent and has been observed to confer loss of RhoGAP activity due to protein truncation and loss of its RhoGAP domain[131]. Amplification of AHGAP35 is observed in 4% of uterine carcinosarcoma, 2% of adrenocortical carcinoma, and diffuse large B-cell lymphoma[10,11]. Biallelic loss of AHGAP35 has been observed in 2% of sarcoma[10,11].

Potential relevance: Currently, no therapies are approved for ARHGAP35 aberrations.

KMT2B deletion

lysine methyltransferase 2B

Background: The KMT2B gene encodes the lysine methyltransferase 2B protein, a transcriptional coactivator and histone H3 lysine K (H3K4) methyltransferase[1]. KMT2B belongs to the SET domain protein methyltransferase superfamily[132]. Specifically, KMT2B along with KDM6A promotes the transcription of the oncogene MYC by H3K4 methylation[133].

Alterations and prevalence: Somatic mutations in KMT2B are observed in 22% of uterine corpus endometrial carcinoma, 13% of skin cutaneous melanoma, 11% colorectal adenocarcinoma, 10% of stomach adenocarcinoma, 7% of adrenocortical carcinoma, and 5% of bladder urothelial carcinoma and lung squamous cell carcinoma[10,11].

Potential relevance: Currently, no therapies are approved for KMT2B aberrations.

HDAC2 deletion

histone deacetylase 2

Background: The HDAC2 gene encodes the histone deacetylase 2 protein[1]. HDAC2 is part of the histone deacetylase (HDAC) family consisting of 18 different isoforms categorized into four classes (I-IV)[134]. Specifically, HDAC2 is a member of class I, along with HDAC1, HDAC3, and HDAC8[134]. HDACs, including HDAC2, function by removing acetyl groups on histone lysines resulting in chromatin

Biomarker Descriptions (continued)

condensation, transcriptional repression, and regulation of cell proliferation and differentiation[134,135]. HDAC2 negatively regulates antigen presentation by inhibiting CIITA, which regulates MHC class II genes[134]. Further, HDAC2 and HDAC1 are essential for B-cell proliferation during development and antigen stimulation in mature B-cells[134]. HDAC deregulation, including overexpression, is observed in a variety of tumor types, which is proposed to affect the expression of genes involved in cellular regulation and promote tumor development[134,136].

Alterations and prevalence: Somatic mutations in HDAC2 are observed in 4% of uterine corpus endometrial carcinoma, 2% of diffuse large B-cell lymphoma (DLBCL) and colorectal adenocarcinoma[10,11]. Biallelic deletions in HDAC2 are observed in 8% of prostate adenocarcinoma and DLBCL, and 6% of uveal melanoma[10,11].

Potential relevance: Currently, no therapies are approved for HDAC2 aberrations. Although not approved for specific HDAC2 alterations, the pan-HDAC inhibitor vorinostat (2006) is approved for the treatment of progressive, persistent, or recurrent cutaneous T-cell lymphoma (CTCL) following treatment with two systemic therapies[137]. The pan-HDAC inhibitor, romidepsin (2009), is approved for the treatment of CTCL and peripheral T-cell lymphoma (PTCL) having received at least one prior systemic therapy[138]. The pan-HDAC inhibitor, belinostat (2014), is approved for the treatment of relapsed or refractory PTCL[139]. The pan-HDAC inhibitor, panobinostat (2015), is approved for the treatment of multiple myeloma in combination of bortezomib and dexamethasone having received at least 2 prior regimens[140].

MAP3K4 deletion

mitogen-activated protein kinase kinase kinase 4

Background: The MAP3K4 gene encodes the mitogen-activated protein kinase kinase kinase 4, also known as MEKK4[1]. MAP3K4 is involved in the JNK signaling pathway along with MAP3K12, MAP2K4, MAP2K7, MAPK8, MAPK9, and MAPK10[73]. Activation of MAPK proteins occurs through a kinase signaling cascade[73,74,75]. Specifically, MAP3Ks are responsible for phosphorylation of MAP2K family members[73,74,75]. 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[73,74,75]. In intrahepatic cholangiocarcinoma, mutations leading to lack of MAP3K4 activity result in vascular invasion and poor survival, supporting a tumor suppressor role for MAP3K4[141].

Alterations and prevalence: Somatic mutations in MAP3K4 are observed in 10% of uterine corpus endometrial carcinoma, 9% of skin cutaneous melanoma, 7% of uterine carcinosarcoma, and 6% of colorectal adenocarcinoma[10,11]. Biallelic deletions are observed in 6% of uveal melanoma, 3% of ovarian serous cystadenocarcinoma, and 2% of diffuse large B-cell lymphoma (DLBCL)[10,11].

Potential relevance: Currently, no therapies are approved for MAP3K4 aberrations.

GPS2 deletion

G protein pathway suppressor 2

Background: GPS2 encodes G protein pathway suppressor 2[1]. GPS2 is a core subunit regulating transcription and suppresses G protein-activated MAPK signaling[142]. GPS2 plays a role in several cellular processes including transcriptional regulation, cell cycle regulation, metabolism, proliferation, apoptosis, cytoskeleton architecture, DNA repair, and brain development[142,143]. Dysregulation of GPS2 through decreased expression, somatic mutation, and deletion is associated with oncogenic pathway activation and tumorigenesis, supporting a tumor suppressor role for GPS2[144,145,146].

Alterations and prevalence: Somatic mutations in GPS2 are predominantly splice site or truncating mutations and have been observed in 3% of cholangiocarcinoma, and 2% of uterine corpus endometrial carcinoma, bladder urothelial carcinoma, and colorectal adenocarcinoma[10,11]. Biallelic loss of GPS2 is observed in 4% of prostate adenocarcinoma, and 2% of liver hepatocellular carcinoma and diffuse large B-cell lymphoma[10,11]. Isolated GSP2 fusions have been reported in cancer with various fusion partners[10,11,147]. In one case, MLL4::GPS2 fusion was observed to drive anchorage independent growth in a spindle cell sarcoma[147].

Potential relevance: Currently, no therapies are approved for GPS2 aberrations.

CDKN2C deletion

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,

Biomarker Descriptions (continued)

thereby preventing the phosphorylation of Rb[148,149,150]. Unlike CDKN2A and CDKN2B, inactivation of CDKN2C is not frequently observed in cancer[151].

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[10,11]. Deletion of chromosome 1p32, where CDKN2C resides, is observed to be recurrent in multiple myeloma with variable frequency (7%-20%), depending on the study[152,153,154].

Potential relevance: Currently, no therapies are approved for CDKN2C aberrations.

SETD2 deletion, SETD2 p.(K1355Nfs*18) c.4065delA

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)[155,156]. 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[157]. Trimethylation of H3K36 by SETD2 promotes post-transcriptional gene silencing and prevents aberrant transcriptional initiation[158,159]. SETD2 trimethylation activity is also observed to be involved in DNA repair through the recruitment of DNA repair machinery[156]. 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)[160]. 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[156,161].

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[10,161,162]. 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[10,155]. 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[155]. Biallelic loss of SETD2 is observed in about 6% of diffuse large B-cell lymphoma, and about 3% of ccRCC and mesothelioma[155].

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)[163].

ARID1B deletion

AT-rich interaction domain 1B

Background: The ARID1B gene encodes the AT-rich interaction domain 1B tumor suppressor protein[1]. ARID1B, also known as BAF250B, belongs to the ARID1 subfamily that also includes ARID1A[1,164]. ARID1A and ARID1B are mutually exclusive subunits of the BAF variant of the SWI/SNF chromatin remodeling complex[39,164].The BAF complex is a multisubunit protein that consists of SMARCB1/IN1, SMARCC1/BAF155, SMARCC2/BAF170, SMARCA4/BRG1 or SMARCA2/BRM, and ARID1A or ARID1B[39]. The BAF complex remodels chromatin at promoter and enhancer elements to alter and regulate gene expression[39,165]. Recurrent inactivating mutations in BAF complex subunits, including ARID1B, lead to transcriptional dysfunction, suggesting ARID2B functions as a tumor suppressor[164].

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[165]. Somatic mutations in ARID1B are observed in 9% of uterine corpus endometrial carcinoma, 8% of cholangiocarcinoma, 7% of skin cutaneous melanoma, and 6% of stomach adenocarcinoma, bladder urothelial carcinoma, and colorectal adenocarcinoma[10,11]. Biallelic loss of ARID1B is observed in 6% of uveal melanoma, 1% of bladder urothelial carcinoma, stomach adenocarcinoma, skin cutaneous melanoma, and colorectal adenocarcinoma[10,11].

Potential relevance: Currently, no therapies are approved for ARID1B aberrations. Mutations in chromatin modifying genes, including ARID1B, are considered to be characteristic genetic features of hepatosplenic T-cell lymphoma (HSTL), as they have been observed in up to 62% of cases[163,166].

BAP1 deletion

BRCA1 associated protein 1

Background: The BAP1 gene encodes the BRCA1 associated protein 1 that belongs to the ubiquitin C-terminal hydrolase subfamily of deubiquitinating enzymes[1]. BAP1 is a tumor suppressor deubiquitinase that is involved in chromatin modification, transcription, and cell cycle regulation[167]. BAP1 deubiquitylation targets include HCF-1, which modulates chromatin structure[167]. Germline mutations in

Biomarker Descriptions (continued)

BAP1 are associated with BAP1-tumor predisposition syndrome (BAP1-TPDS), a heritable condition which confers an elevated risk of developing uveal melanoma, malignant mesothelioma, and renal cell carcinoma[168,169,170,171,172,173].

Alterations and prevalence: Recurrent somatic mutations in BAP1 are observed in 21% of mesothelioma, 19% of cholangiocarcinoma, 16% of uveal melanoma, and 7% of kidney renal clear cell carcinoma[10,11]. BAP1 biallelic deletions are observed in 11% of mesothelioma[10,11].

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

TNFAIP3 deletion

TNF alpha induced protein 3

Background: The TNFAIP3 gene encodes the TNF alpha induced protein 3[1]. TNFAIP3, also known as A20, is a ubiquitin modifying protein that possesses deubiquitination, E3 ligase, and ubiquitin binding activity[174]. TNFAIP3 is known to negatively regulate the NF-κB pathway by means of its ubiquitin modifying ability, thus impacting inflammatory and immune responses[174,175]. Specifically, TNFAIP3 is known to function as a cysteine protease with deubiquitination (DUB) capability and possesses seven zinc finger motifs that mediate binding to K63- and M1- polyubiquitin chains, thereby altering protein degradation and other protein-protein interactions[174]. TNFAIP3 deficient cells are observed to promote aberrant NF-κB signaling, deregulation of which is proposed to contribute to lymphoma pathogenesis[174,176].

Alterations and prevalence: Somatic mutations in TNFAIP3 are observed in 12% of diffuse large B-cell lymphoma (DLBCL), 4% of uterine corpus endometrial carcinoma, 3% of skin cutaneous melanoma, and 2% of colorectal adenocarcinoma and bladder urothelial carcinoma[10,11]. Biallelic loss of TNFAIP3 is observed in 30% of human B-cell lymphoma, 12% of DLBCL and 8% of uveal melanoma[10,11,174].

Potential relevance: Currently, no therapies are approved for TNFAIP3 aberrations.

DOCK3 deletion

dedicator of cytokinesis 3

Background: The DOCK3 gene encodes dedicator of cytokinesis 3, a member of the DOCK (dedicator of cytokinesis) family of guanine nucleotide exchange factors (GEFs)[1]. As a GEF, DOCK3 functions by catalyzing the exchange of GDP for GTP, and activates the G protein, Rac1, thereby facilitating RAC1 mediated signaling[177]. Consequently, DOCK3 has been observed to facilitate the regulation of several cellular processes including axonal outgrowth, cytoskeletal organization, and cell adhesion[1,178,179]. Unlike other GEFs found to be altered in cancer, DOCK3 has been shown to exhibit tumor suppressor like properties through inhibition of β-catenin/WNT signaling[180,181]. Additionally knockdown of DOCK3 has been observed to inhibit tumor cell adhesion, migration, and invasion in non-small cell lung cancer cell lines, further supporting a tumor suppressive role for DOCK3[179].

Alterations and prevalence: Somatic mutations in DOCK3 are observed in 21% of skin cutaneous melanoma, 16% of uterine corpus endometrial carcinoma, 12% of stomach adenocarcinoma, 9% of colorectal adenocarcinoma, 6% of esophageal adenocarcinoma, 4% of sarcoma, and lung adenocarcinoma, 3% of bladder urothelial carcinoma, lung squamous cell carcinoma, cervical squamous cell carcinoma, and 2% of diffuse large B-cell lymphoma, pancreatic adenocarcinoma, head and neck squamous cell carcinoma, kidney renal papillary cell carcinoma, ovarian serous cystadenocarcinoma, liver hepatocellular carcinoma, and kidney chromophobe[10,11]. Biallelic loss of DOCK3 is observed in 4% of diffuse large B-cell lymphoma, 3% of esophageal adenocarcinoma and kidney renal clear cell carcinoma, and 2% of sarcoma[10,11].

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

Genes Assayed (continued)

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

IRS4, KCNJ5, KDR, KIT, KLF4, KLF5, KNSTRN, KRAS, MAGOH, MAP2K1, MAP2K2, MAPK1, MAX, MDM4, MECOM, MED12, MEF2B, MET, MITF, MPL, MTOR, MYC, MYCN, MYD88, MYOD1, NFE2L2, NRAS, NSD2, NT5C2, NTRK1, NTRK2, NTRK3, NUP93, PAX5, PCBP1, PDGFRA, PDGFRB, PIK3C2B, PIK3CA, PIK3CB, PIK3CD, PIK3CG, PIK3R2, PIM1, PLCG1, PPP2R1A, PPP6C, PRKACA, PTPN11, PTPRD, PXDNL, RAC1, RAF1, RARA, RET, RGS7, RHEB, RHOA, RICTOR, RIT1, ROS1, RPL10, SETBP1, SF3B1, SIX1, SIX2, SLCO1B3, SMC1A, SMO, SNCAIP, SOS1, SOX2, SPOP, SRC, SRSF2, STAT3, STAT5B, STAT6, TAF1, TERT, TGFBR1, TOP1, TOP2A, TPMT, TRRAP, TSHR, U2AF1, USP8, WAS, XPO1, ZNF217, ZNF429

Genes Assayed for the Detection of Copy Number Variations

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

Genes Assayed 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

BAP1 deletion

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

CDKN2C deletion

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
ribociclib, everolimus	✖	✖	✖	✖	● (II)

FANCM deletion

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

LATS1 deletion

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
IAG-933	✖	✖	✖	✖	● (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	***14.54%***
RAD51B	***CNV, CN:1.0***
RAD51B	***LOH, 14q24.1(68290164-69061406)x1***
RAD54L	***LOH, 1p34.1(46714017-46743978)x2***

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 (6.0.2 data version 2025.04(004)). 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 2025-03-19. NCCN information was sourced from www.nccn.org and is current as of 2025-03-03. EMA information was sourced from www.ema.europa.eu and is current as of 2025-03-19. ESMO information was sourced from www.esmo.org and is current as of 2025-03-03. Clinical Trials information is current as of 2025-03-03. 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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