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Patient Name: 오복근
Gender: Male
Sample ID: N26-2

Primary Tumor Site: Brain
Collection Date: 2025.12.24

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

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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	***FGFR3 p.(K650E) c.1948A>G***	TERT	***TERT c.-146C>T***

Genomic Alteration	Finding
Tumor Mutational Burden	***5.68 Mut/Mb measured***

Relevant Biomarkers

Tier	Genomic Alteration	Relevant Therapies (In this cancer type)	Relevant Therapies (In other cancer type)	Clinical Trials
IA	*TERT c.-146C>T* telomerase reverse transcriptase Allele Frequency: 34.98% Locus: chr5:1295250 Transcript: NM_198253.3 **Diagnostic significance:** Glioblastoma IDH-wildtype (Grade 4)	None*	None*	1
IIC	*CDK4 amplification* cyclin dependent kinase 4 Locus: chr12:58142242	None*	None*	6
IIC	*FGFR3 p.(K650E) c.1948A>G* fibroblast growth factor receptor 3 Allele Frequency: 53.78% Locus: chr4:1807889 Transcript: NM_000142.5	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	*PTEN deletion* phosphatase and tensin homolog Locus: chr10:89623659	None*	None*	4

*** 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

MDM2 amplification, Microsatellite stable, TCF7L2 deletion, UGT1A1 p.(G71R) c.211G>A, HLA-A p.(L180) c.539T>A, HLA-B p.(N87Rfs*64) c.260_261delACinsG, LARP4B deletion, GATA3 deletion, MAPK8 deletion, ARID5B deletion, CYP2C9 deletion, SUFU deletion, NOTCH3 p.(R1076C) c.3226C>T, Tumor Mutational Burden*

Variant Details

DNA Sequence Variants

Gene	Amino Acid Change	Coding	Variant ID	Locus	Allele Frequency	Transcript	Variant Effect
TERT	p.(?)	c.-146C>T	COSM1716559	chr5:1295250	34.98%	NM_198253.3	unknown
FGFR3	p.(K650E)	c.1948A>G	COSM719	chr4:1807889	53.78%	NM_000142.5	missense
UGT1A1	p.(G71R)	c.211G>A	COSM4415616	chr2:234669144	50.58%	NM_000463.3	missense
HLA-A	p.(L180*)	c.539T>A	.	chr6:29911240	42.12%	NM_001242758.1	nonsense
HLA-B	p.(N87Rfs*64)	c.260_261delACinsG	.	chr6:31324547	2.00%	NM_005514.8	frameshift Block Substitution
NOTCH3	p.(R1076C)	c.3226C>T	.	chr19:15290984	25.20%	NM_000435.3	missense
MYD88	p.(L102Q)	c.305T>A	.	chr3:38180496	45.95%	NM_002468.5	missense
MUC4	p.(I428M)	c.1284A>G	.	chr3:195517167	44.30%	NM_018406.7	missense
MSH3	p.(A61_P63dup)	c.189_190insGCAGCGCCC	.	chr5:79950735	73.90%	NM_002439.5	nonframeshift Insertion
PPM1D	p.(G166R)	c.496G>C	.	chr17:58700905	26.40%	NM_003620.4	missense
NOTCH3	p.([Q505H;L506=])	c.1515_1516delGCinsTT	.	chr19:15298782	63.05%	NM_000435.3	missense, synonymous
DDX3X	p.(G303R)	c.907G>C	.	chrX:41203534	77.33%	NM_001356.5	missense

Copy Number Variations

Gene	Locus	Copy Number	CNV Ratio
CDK4	chr12:58142242	95.48	36.99
PTEN	chr10:89623659	0.65	0.48
MDM2	chr12:69202958	106.64	41.28
TCF7L2	chr10:114710485	0.88	0.57
LARP4B	chr10:858847	0.95	0.6

Variant Details (continued)

Copy Number Variations (continued)

Gene	Locus	Copy Number	CNV Ratio
GATA3	chr10:8097519	0.79	0.53
MAPK8	chr10:49609682	0.91	0.58
ARID5B	chr10:63661463	0.84	0.55
CYP2C9	chr10:96698378	0.74	0.52
SUFU	chr10:104263903	0.97	0.61
RET	chr10:43609070	0.87	0.57
FGFR2	chr10:123239426	0.97	0.61
ERBB3	chr12:56477596	0.84	0.55
STAT6	chr12:57490294	0.96	0.6

Biomarker Descriptions

TERT c.-146C>T

telomerase reverse transcriptase

Background: The TERT gene encodes telomerase reverse transcriptase, a component of the telomerase core enzyme along with the internal telomerase RNA template (TERC)[66]. TERT is repressed in most differentiated cells, resulting in telomerase silencing[66]. In cancer, telomerase reactivation is known to contribute to cellular immortalization[66,67]. Increased TERT expression results in telomerase activation, allowing for unlimited cancer cell proliferation through telomere stabilization[66]. In addition to its role in telomere maintenance, TERT has RNA-dependent RNA polymerase activity, which, when deregulated, can promote oncogenesis by facilitating mitotic progression and cancer cell stemness[66].

Alterations and prevalence: Somatic mutations are observed in 4% of skin cutaneous melanoma and uterine corpus endometrial carcinoma, 3% of kidney renal papillary cell carcinoma, and 2% of pancreatic adenocarcinoma, stomach adenocarcinoma, and sarcoma[6,7]. Additionally, TERT promoter mutations causing upregulation are observed in many cancer types, especially non-aural cutaneous melanoma (80% of cases), and glioblastoma (70% of cases)[67]. Specifically, TERT promoter mutations at C228T and C250T are recurrent and result in de novo binding sites for ETS transcription factors, leading to enhanced TERT transcription[66]. Amplification of TERT is observed in 15% of lung squamous cell carcinoma, 14% of esophageal adenocarcinoma, 13% of adrenocortical carcinoma and lung adenocarcinoma, and 10% of bladder urothelial carcinoma, 9% of ovarian serous cystadenocarcinoma, 6% of cervical squamous cell carcinoma, 5% of liver hepatocellular carcinoma, sarcoma, skin cutaneous melanoma, stomach adenocarcinoma, head and neck squamous cell carcinoma, 4% of uterine carcinosarcoma, 3% of uterine corpus endometrial carcinoma, breast invasive carcinoma, and 2% of diffuse large B-cell lymphoma[6,7]. TERT is overexpressed in over 85% of tumors and is considered a universal tumor associated antigen[68]. Alterations in TERT are rare in pediatric cancers[6,7]. Somatic mutations are observed in less than 1% of B-lymphoblastic leukemia/lymphoma (2 in 252 cases), glioma (2 in 297 cases), bone cancer (1 in 327 cases), and Wilms tumor (1 in 710 cases)[6,7]. TERT amplification is observed in 1-2% of peripheral nervous system cancers (2 in 91 cases), leukemia (2 in 250 cases), and B-lymphoblastic leukemia/lymphoma (5 in 731 cases)[6,7].

Potential relevance: Currently, no therapies are approved for TERT aberrations. TERT promoter mutations are diagnostic of oligodendroglioma IDH-mutant with 1p/19q co-deletion, while the absence of promoter mutations combined with an IDH mutation is characteristic of astrocytoma[69,70]. Due to its immunogenicity and near-universal expression on cancer cells, TERT has been a focus of immunotherapy research, including peptide, dendritic, and DNA vaccines as well as T-cell therapy[68].

CDK4 amplification

cyclin dependent kinase 4

Background: The CDK4 gene encodes the cyclin-dependent kinase 4 protein, a homologue of CDK6[1,96]. Both proteins are serine/threonine protein kinases that are involved in the regulation of the G1/S phase transition of the mitotic cell cycle[97,98]. CDK4 is activated by complex formation with D-type cyclins (e.g., CCND1, CCND2, or CCND3), which leads to the phosphorylation of retinoblastoma protein (RB), followed by E2F activation, DNA replication, and cell-cycle progression[99]. Germline mutations in CDK4 are associated with

Biomarker Descriptions (continued)

familial melanoma[100,101,102]. Overexpression of CDK4 has been observed in several cancers including epithelial cancers of endocrine tissues and mucosa, melanoma, breast cancer, gliomas, and leukemia[103].

Alterations and prevalence: Recurrent somatic mutations of CDK4 are observed in 3% of skin cutaneous melanoma and 2% of uterine corpus endometrial carcinoma[6,7]. Somatic mutations at codons K22 and R24, which are essential for binding and inhibition by p16/CDKN2A, are associated with melanoma formation and metastasis.[104,105,106,107]. CDK4 is recurrently amplified in 18% of sarcoma, 7% of adrenocortical carcinoma, 6% of cholangiocarcinoma, 5% of lung adenocarcinoma, 4% of brain lower grade glioma and skin cutaneous melanoma, and 2% of stomach adenocarcinoma, diffuse large B-cell lymphoma, and pancreatic adenocarcinoma[6,7,108,109]. Alterations in CDK4 are also observed in pediatric cancers[7]. Somatic mutations are observed in 2% of Hodgkin lymphoma[7]. CDK4 amplification is observed in 5% of bone cancer (2 in 42 cases), 2% of peripheral nervous system tumors (2 in 91 cases), and less than 1% of Wilms tumor (1 in 136 cases) and B-lymphoblastic leukemia/lymphoma (1 in 731 cases)[7].

Potential relevance: Currently, no therapies are approved for CDK4 aberrations. Amplification of region 12q14-15, which includes CDK4, is useful as an ancillary diagnostic marker of atypical lipomatous tumor/welldifferentiated liposarcoma (ALT/WDLS)[40]. Small molecule inhibitors targeting CDK4/6 including palbociclib (2015)[110], abemaciclib (2017)[111], and ribociclib (2017)[112], are FDA approved in combination with an aromatase inhibitor or fulvestrant for the treatment of hormone receptor-positive, HER2-negative advanced or metastatic breast cancer.

FGFR3 p.(K650E) c.1948A>G

fibroblast growth factor receptor 3

Background: The FGFR3 gene encodes fibroblast growth receptor 3, a member of the fibroblast growth-factor receptor (FGFR) family that also includes FGFR1, 2, and 4[1]. These proteins are single-transmembrane receptors composed of three extracellular immunoglobulin (Ig)-type domains and an intracellular kinase domain[113]. Upon FGF-mediated stimulation, FGFRs activate several oncogenic signaling pathways, including the RAS/RAF/MEK/ERK, PI3K/AKT/MTOR, PLC/PKC, and JAK/STAT pathways influencing cell proliferation, migration, and survival[114,115,116].

Alterations and prevalence: Aberrations most common to the FGFR family are amplifications, followed by mutations and fusions; the majority of these aberrations result in gain of function[117]. Missense mutations that occur in the extracellular immunoglobulin-like and transmembrane domains of FGFR3, including S249C, R248C, and Y373C, cause ligand-independent dimerization and constitutive activation of FGFR3[118,119,120]. Recurrent somatic mutations in FGFR3 are observed in 14% of bladder urothelial carcinoma, 5% of skin cutaneous melanoma, 4% of uterine corpus endometrial carcinoma, 3% of colorectal adenocarcinoma, and 2% of stomach adenocarcinoma, head and neck squamous cell carcinoma, lung squamous cell carcinoma, kidney renal papillary cell carcinoma, and uterine carcinosarcoma[6,7]. FGFR3 fusions are observed in 2% of bladder urothelial carcinoma and cervical squamous cell carcinoma[6,7]. FGFR3 amplification is observed in 14% of uterine carcinosarcoma, 5% of ovarian serous cystadenocarcinoma, 4% of bladder urothelial carcinoma, 3% of adrenocortical carcinoma, uterine corpus endometrial carcinoma, cholangiocarcinoma, and 2% of pancreatic adenocarcinoma, sarcoma, and esophageal adenocarcinoma[6,7]. Alterations in FGFR3 are also observed in the pediatric population[7]. Somatic mutations are observed in 2% of T-lymphoblastic leukemia/lymphoma (1 in 41 cases) and less than 1% of embryonal tumor (2 in 332 cases), bone cancer (1 in 327 cases), and leukemia (1 in 354 cases)[7]. FGFR3 amplification is observed in 9% of Wilms tumor (12 in 136 cases) and 1% of B-lymphoblastic leukemia/lymphoma (9 in 731 cases) and leukemia (2 in 250 cases)[7].

Potential relevance: The pan-FGFR inhibitor, erdafitinib[121], received FDA approval (2019) for the treatment of locally advanced or metastatic urothelial cancer that is positive for FGFR2 fusions, FGFR3 fusions including FGFR3::TACC3 and FGFR3::BAIAP2L1, and FGFR3 gene mutations including R248C, S249C, G370C, and Y373C. Unregulated activation of FGFR3 has been associated with resistance to tamoxifen in ER-positive breast cancer[122].

PTEN deletion

phosphatase and tensin homolog

Background: The PTEN gene encodes the phosphatase and tensin homolog, a tumor suppressor protein with lipid and protein phosphatase activities[10]. PTEN antagonizes PI3K/AKT signaling by catalyzing the dephosphorylation of phosphatidylinositol (3,4,5)-trisphosphate (PIP3) to PIP2 at the cell membrane, which inhibits the activation of AKT[11,12]. In addition, PTEN has been proposed to influence RAD51 loading at double strand breaks during homologous recombination repair (HRR) and regulate the G2/M checkpoint by influencing CHEK1 localization through AKT inhibition, thereby regulating HRR efficiency[13]. Germline mutations in PTEN are linked to hamartoma tumor syndromes, including Cowden disease, which are defined by uncontrolled cell growth and benign or malignant tumor formation[14]. PTEN germline mutations are also associated with inherited cancer risk in several cancer types[15].

Alterations and prevalence: PTEN is frequently altered in cancer by inactivating loss-of-function mutations and by gene deletion. PTEN mutations are observed in several cancers including 65% of uterine cancer, 34% of uterine corpus endometrial carcinoma, 20% of uterine carcinosarcoma, 11% of lung squamous cell carcinoma, and 5-10% of skin cutaneous melanoma, kidney chromophobe, stomach adenocarcinoma, stomach squamous cell carcinoma, and cervical squamous cell carcinoma[6,7]. Nearly half of somatic

Biomarker Descriptions (continued)

mutations in PTEN are stop-gain or frame-shift mutations that result in truncation of the protein reading frame. Recurrent missense or stop-gain mutations at codons R130, R173, and R233 result in loss of phosphatase activity and inhibition of wild-type PTEN[12,16,17,18,19]. PTEN gene deletion is observed in several cancers including 17% of prostate adenocarcinoma, 10% of lung squamous cell carcinoma and glioblastoma multiforme, 7% of skin cutaneous melanoma, 6% of diffuse large B-cell lymphoma, sarcoma, and 1-5% of breast invasive carcinoma, melanoma, sarcoma, ovarian serous cystadenocarcinoma, cervical squamous cell carcinoma, and uterine corpus endometrial carcinoma[6,7]. Alterations in PTEN are also observed in pediatric cancers[7]. Somatic mutations in PTEN are observed in 10% of T-lymphoblastic leukemia/lymphoma (4 in 41 cases), 6% of non-Hodgkin lymphoma (1 in 17 cases), 2% of glioma (7 in 297 cases), and 1% of bone cancer (4 in 327 cases) and embryonal tumors (4 in 332 cases)[7]. Biallelic deletion of PTEN is observed in 6% of glioma (1 in 16 cases), 5% of bone cancer (2 in 42 cases), 4% of B-lymphoblastic leukemia/lymphoma (10 in 250 cases), and less than 1% of embryonal tumors (5 in 731 cases)[7]. Structural alterations in PTEN are observed in less than 1% of bone cancer (1 in 150 cases)[7].

Potential relevance: Due to the role of PTEN in HRR, poly(ADP-ribose) polymerase inhibitors (PARPi) are being explored as a potential therapeutic strategy in PTEN deficient tumors[20,21]. In 2022, the FDA granted fast track designation to the small molecule inhibitor, pidnarulex[22], for BRCA1/2, PALB2, or other homologous recombination deficiency (HRD) mutations in breast and ovarian cancers. In 2023, the FDA approved the kinase inhibitor, capivasertib[23] in combination with fulvestrant for locally advanced or metastatic hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative breast cancer with one or more PIK3CA/AKT1/PTEN-alterations following progression after endocrine treatment.

MDM2 amplification

MDM2 proto-oncogene

Background: The MDM2 gene encodes the murine double minute 2 proto-oncogene[1]. MDM2 is structurally related to murine double minute 4 (MDM4), with both proteins containing an N-terminal domain that binds p53, a zinc-finger domain, and a C-terminal RING domain[35]. MDM2 and MDM4 are oncogenes that function as negative regulators of the tumor suppressor TP53, and can homo- or heterodimerize with p53 through their RING domains[35]. Specifically, the MDM2 RING domain functions as an E3 ubiquitin ligase and is responsible for the polyubiquitination and degradation of the p53 protein when MDM2 is present at high levels[36]. Alternately, low levels of MDM2 activity promote mono-ubiquitination and nuclear export of p53[36]. MDM2 amplification and overexpression disrupt the p53 protein function, thereby contributing to tumorigenesis and supporting an oncogenic role for MDM2[36].

Alterations and prevalence: MDM2 is amplified in 19% of sarcoma, 9% of bladder urothelial carcinoma, 8% of glioblastoma multiforme, 7% of adrenocortical carcinoma, 5% of uterine carcinosarcoma, lung adenocarcinoma, esophageal adenocarcinoma, and stomach adenocarcinoma, 4% of skin cutaneous melanoma, head and neck squamous cell carcinoma, and ovarian serous cystadenocarcinoma, 3% of breast invasive carcinoma, cholangiocarcinoma, pancreatic adenocarcinoma, testicular germ cell tumors, and lung squamous cell carcinoma, and 2% of diffuse large B-cell lymphoma[6,7]. MDM2 overexpression is observed in lung, breast, liver, esophagogastric, and colorectal cancers[37]. The most common co-occuring aberrations with MDM2 amplification or overexpression are CDK4 amplification and TP53 mutation[38,39]. Somatic mutations in MDM2 are observed in 2% of uterine corpus endometrial carcinoma, adrenocortical carcinoma, and sarcoma[6,7]. Alterations in MDM2 are also observed in pediatric cancers[7]. Amplification of MDM2 is observed in 2% of bone cancer (1 in 42 cases), 1% of Wilms tumor (2 in 136 cases) and peripheral nervous system tumors (1 in 91 cases), and less than 1% of B-lymphoblastic leukemia/lymphoma (1 in 731 cases)[7]. Somatic mutations in MDM2 are observed in 2% of non-Hodgkin lymphoma (1 in 17 cases) and less than 1% of bone cancer (3 in 327 cases) and embryonal tumors (1 in 332 cases)[7].

Potential relevance: Currently, no therapies are approved for MDM2 aberrations. Amplification of region 12q13-15, which includes MDM2, is useful as an ancillary diagnostic marker of atypical lipomatous tumor/well differentiated liposarcoma (ALT/WDLS) and dedifferentiated liposarcoma[40].

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[71]. Microsatellite instability (MSI) is defined as a change in the length of a microsatellite in a tumor as compared to normal tissue[72,73]. 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[74]. 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[75]. 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)[75]. Tumors classified as MSI-L are often phenotypically indistinguishable from MSS tumors and tend to be grouped with MSS[76,77,78,79,80]. 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[73]. LS is associated with an increased risk of developing colorectal cancer, as well as other cancers, including endometrial and stomach cancer[72,73,77,81].

Biomarker Descriptions (continued)

Alterations and prevalence: The MSI-H phenotype is observed in 30% of uterine corpus endothelial carcinoma, 20% of stomach adenocarcinoma, 15-20% of colon adenocarcinoma, and 5-10% of rectal adenocarcinoma[72,73,82,83]. 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[82,83].

Potential relevance: Anti-PD-1 immune checkpoint inhibitors including pembrolizumab[84] (2014) and nivolumab[85] (2015) are approved for patients with MSI-H or dMMR colorectal cancer who have progressed following chemotherapy. Pembrolizumab[84] 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[84]. Dostarlimab[86] (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[78,87]. The cytotoxic T-lymphocyte antigen 4 (CTLA-4) blocking antibody, ipilimumab[88] (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[78,89,90]. 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[90]. 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[91,92]. However, checkpoint blockade with the addition of chemotherapy or targeted therapies have demonstrated response in MSS or pMMR cancers[91,92].

TCF7L2 deletion

transcription factor 7 like 2

Background: TCF7L2 encodes the transcription factor 7 like 2, a key component of the WNT signaling pathway[1,93]. Through its interaction with β-catenin, TCF7L2 functions as a central transcriptional regulator of the WNT pathway by modulating the expression of several genes involved in epithelial to mesenchymal transdifferentiation (EMT) and cancer progression, including MYC[93,94,95]. TCF7L2 is also responsible for the regulation of cell cycle inhibitors, including CDKN2C and CDKN2D, thereby influencing cell cycle progression[93]. Loss of TCF7L2 function is commonly observed in colorectal cancer due to mutations or copy number loss which has been correlated with increased tumor invasion and metastasis, supporting a tumor suppressor role for TCF7L2[93].

Alterations and prevalence: Somatic mutations of TCF7L2 are observed in 11% colorectal adenocarcinoma, 6% of uterine corpus endometrial carcinoma, 3% of stomach adenocarcinoma, and 2% of skin cutaneous melanoma and uterine carcinosarcoma[6,7]. Biallelic deletion of TCF7L2 is observed in 2% diffuse large B-cell lymphoma, brain lower grade glioma, and colorectal adenocarcinoma, and 1% of bladder urothelial carcinoma, mesothelioma, stomach adenocarcinoma, esophageal adenocarcinoma, liver hepatocellular carcinoma, and skin cutaneous melanoma[6,7].

Potential relevance: Currently, no therapies are approved for TCF7L2 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[1,53]. UGTs are microsomal membrane-bound enzymes that catalyze the glucuronidation of endogenous and xenobiotic compounds and transform the lipophilic molecules into excretable, hydrophilic metabolites[53,54]. 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[55]. 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[55,56,57,58]. 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[59].

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[6,7].

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

Biomarker Descriptions (continued)

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[60]. MHC class I molecules are heterodimers composed of two polypeptide chains, α and B2M[61]. 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[62,63,64]. Downregulation of MHC class I promotes tumor evasion of the immune system, suggesting a tumor suppressor role for HLA-A[65].

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[6,7]. Biallelic loss of HLA-A is observed in 4% of DLBCL[6,7].

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

HLA-B p.(N87Rfs*64) c.260_261delACinsG

major histocompatibility complex, class I, B

Background: The HLA-B gene encodes the major histocompatibility complex, class I, B[1]. MHC (major histocompatibility complex) class I molecules are located on the cell surface of nucleated cells and present antigens from within the cell for recognition by cytotoxic T cells[60]. MHC class I molecules are heterodimers composed of two polypeptide chains, α and B2M[61]. 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[62,63,64]. Downregulation of MHC class I promotes tumor evasion of the immune system, suggesting a tumor suppressor role for HLA-B[65].

Alterations and prevalence: Somatic mutations in HLA-B are observed in 10% of diffuse large B-cell lymphoma (DLBCL), 5% of cervical squamous cell carcinoma and stomach adenocarcinoma, 4% of head and neck squamous cell carcinoma and colorectal adenocarcinoma, 3% of uterine cancer, and 2% of esophageal adenocarcinoma and skin cutaneous melanoma[6,7]. Biallelic loss of HLA-B is observed in 5% of DLBCL[6,7].

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

LARP4B deletion

La ribonucleoprotein domain family member 4B

Background: The LARP4B gene encodes the La ribonucleoprotein 4B protein[1]. La-related proteins (LARPs) are RNA binding proteins and can be split into 5 families, LARP1, La, LARP4, LARP6, and LARP7[24]. Along with LARP4, LARP4B is part of the LARP4 family and is observed to bind AU-rich regions in the 3' untranslated regions of mRNAs[24]. In glioma, LARP4B has been observed to induce mitotic arrest and apoptosis in vitro, supporting a tumor suppressor role for LARP4B[25].

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

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

GATA3 deletion

GATA binding protein 3

Background: The GATA3 gene encodes GATA binding protein 3, a member of the GATA family of zinc-finger transcription factors, which also includes GATA1, GATA2, and GATA4-6[1,41,42]. The GATA family regulates transcription of many genes by binding to the DNA consensus sequence T/A(GATA)A/G[42]. GATA3 functions in the differentiation of immune cells and tissue development[43,44]. As GATA3 also functions in luminal cell development and cell function, it is a common marker of the gene expression profile in luminal breast cancer[43].

Biomarker Descriptions (continued)

Alterations and prevalence: Somatic mutations in GATA3 are observed in 12% of breast invasive carcinoma, 4% of uterine corpus endometrial carcinoma and stomach adenocarcinoma, and 3% of colorectal adenocarcinoma and skin cutaneous melanoma[6,7]. Biallelic loss of GATA3 is observed in 2% of diffuse large B-cell lymphoma (DLBCL)[6,7]. Alterations in GATA3 are also observed in the pediatric population[7]. Somatic mutations are observed in 6% of non-Hodgkin lymphoma (1 in 17 cases), 3% of soft tissue sarcoma (1 in 38 cases), 2% of T-lymphoblastic leukemia/lymphoma (1 in 41 cases) and Hodgkin lymphoma (1 in 61 cases), and less than 1% of bone cancer (3 in 327 cases), embryonal tumor (3 in 332 cases), and leukemia (1 in 311 cases)[7]. Biallelic deletion is observed in 1% of peripheral nervous system cancers (1 in 91 cases), less than 1% of leukemia (1 in 250 cases) and B-lymphoblastic leukemia/lymphoma (1 in 731 cases)[7].

Potential relevance: Currently, no therapies are approved for GATA3 aberrations. Low GATA3 expression is associated with invasion and poor prognosis in breast cancer[43,45].

MAPK8 deletion

mitogen-activated protein kinase 8

Background: The MAPK8 gene encodes the mitogen-activated protein kinase 8, also known as JNK1[1]. MAPK8 is involved in the JNK signaling pathway along with MAP3K4, MAP3K12, MAP2K4, MAP2K7, MAPK9, and MAPK10[2,3,4]. Activation of MAPK proteins occurs through a kinase signaling cascade[2,3,5]. Specifically, MAP3Ks are responsible for phosphorylation of MAP2K family members[2,3,5]. 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[2,3,5].

Alterations and prevalence: Somatic mutations in MAPK8 are observed in 4% of uterine corpus endometrial carcinoma, 3% of skin cutaneous melanoma, and 2% of colorectal adenocarcinoma[6,7]. Biallelic deletions are observed in 1% of bladder urothelial carcinoma, esophageal adenocarcinoma, adrenocortical carcinoma, and skin cutaneous melanoma[6,7].

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

ARID5B deletion

AT-rich interaction domain 5B

Background: The ARID5B gene encodes the AT-rich interaction domain 5B protein[1]. ARID5B, also known as MRF2, belongs to the ARID superfamily that also includes ARID1A, ARID1B, and ARID2[8,9]. ARID5B forms a complex with PHF2, which is capable of histone demethylation leading to transcriptional activation of target genes[9]. ARID5B is known to be essential for the development of hematopoietic cells[9]. Several single-nucleotide polymorphisms (SNPs) in ARID5B have been associated with susceptibility of acute lymphoblastic leukemia (ALL)[9].

Alterations and prevalence: Somatic mutations in ARID5B are observed in 15% of uterine corpus endometrial carcinoma, 6% of skin cutaneous melanoma, 5% of diffuse large B-cell lymphoma, 4% of stomach adenocarcinoma[6,7]. Biallelic loss of ARID5B is observed in 1% of kidney chromophobe, lung squamous cell carcinoma, and skin cutaneous melanoma[6,7].

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

CYP2C9 deletion

cytochrome P450 family 2 subfamily C member 9

Background: The CYP2C9 gene encodes cytochrome P450 family 2 subfamily C member 9, a member of the cytochrome P450 superfamily of proteins[1]. The cytochrome P450 proteins are monooxygenases that play important roles in the biotransformation of xenobiotics and carcinogens, and the synthesis of cholesterol, steroids and other lipids[1,26]. CYP2C9 catalyzes the oxidation of arachidonic acid to epoxyeicosatrienoic acids (EETs) and also inactivates several NSAIDs, including cyclooxygenase inhibitors and chemopreventive agents[27,28]. EETs are mitogenic and pro-angiogenic signaling molecules that have been shown to promote cancer cell growth and metastasis in vitro[27,28,29]. CYPC29 overexpression is found in several cancers supporting the role of EETs in vascularization and tumorigenesis[26,27,28,29]. Inherited CYP2C9 polymorphisms, including CYP2C9*2 and CYP2C9*3, can result in attenuated catalytic efficiency and reduced EETs leading to reduced proliferation and migration of cancer cells and less vascularized tumors[27]. Depending on the cancer type and treatment, individuals with these polymorphisms may have slower drug metabolism and therefore, altered drug responses which may make them more protected or more at risk of disease[27].

Alterations and prevalence: Somatic mutations in CYP2C9 are observed in 12% of skin cutaneous melanoma, 3% of uterine corpus endometrial carcinoma, and 2% of cervical squamous cell carcinoma, esophageal adenocarcinoma, lung adenocarcinoma, and

Biomarker Descriptions (continued)

kidney chromophobe[6,7]. Biallelic loss of CYP2C9 is observed in 2% diffuse large B-cell lymphoma and prostate adenocarcinoma[6,7]. Amplification of CYP2C9 is observed in 1% of pheochromocytoma, paraganglioma, and ovarian serous cystadenocarcinoma[6,7].

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

SUFU deletion

SUFU negative regulator of hedgehog signaling

Background: SUFU encodes the SUFU negative regulator of hedgehog signaling protein, a protein integrally involved in inhibition of hedgehog pathway signaling[1]. During early human development, hedgehog pathway activation of the Gli/Ci family of zinc finger transcription factors is known to drive both cell proliferation and differentiation[30]. SUFU is capable of interacting and complexing with GLI1 and GLI2, thereby regulating transactivation of GLI1 and GLI2 target genes and inhibiting hedgehog pathway signaling[31,32]. Aberrant activation of the hedgehog signaling pathway has been implicated in several cancer types, supporting a tumor suppressor role for SUFU[33]. Germline mutations in SUFU confer a strong predisposition to medulloblastoma, particularly the desmoplastic/nodular subtype, and are observed almost exclusively in children less than 3 years of age[34].

Alterations and prevalence: Somatic mutations are observed in 4% uterine corpus endometrial carcinoma and 2% esophageal adenocarcinoma and stomach adenocarcinoma[7]. Biallelic deletion of SUFU is observed in 2% of mesothelioma, diffuse large cell B-cell lymphoma, and prostate adenocarcinoma[7]. Alterations in SUFU are also observed in pediatric cancers[7]. Somatic mutations in SUFU are observed in 1% of embryonal tumors (4 in 332 cases) and less than 1% of glioma (2 in 297 cases), bone cancer (1 in 327 cases), and peripheral nervous system cancers (1 in 1158 cases)[7]. Biallelic deletion of SUFU is observed in less than 1% of leukemia (2 in 250 cases) and B-lymphoblastic leukemia/lymphoma (2 in 731 cases)[7].

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

NOTCH3 p.(R1076C) c.3226C>T

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[46]. 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[47,48]. 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[49,50,51,52].

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[6].

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

Genes Assayed (continued)

Genes Assayed for the Detection of Copy Number Variations

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

Genes Assayed for the Detection of Fusions

AKT2, ALK, AR, AXL, BRAF, BRCA1, BRCA2, CDKN2A, EGFR, ERBB2, ERBB4, ERG, ESR1, ETV1, ETV4, ETV5, FGFR1, FGFR2, FGFR3, FGR, FLT3, JAK2, KRAS, MDM4, MET, MYB, MYBL1, NF1, NOTCH1, NOTCH4, NRG1, NTRK1, NTRK2, NTRK3, NUTM1, PDGFRA, PDGFRB, PIK3CA, PPARG, PRKACA, PRKACB, PTEN, RAD51B, RAF1, RB1, RELA, RET, ROS1, RSPO2, RSPO3, TERT

Genes Assayed with Full Exon Coverage

ABRAXAS1, ACVR1B, ACVR2A, ADAMTS12, ADAMTS2, AMER1, APC, ARHGAP35, ARID1A, ARID1B, ARID2, ARID5B, ASXL1, ASXL2, ATM, ATR, ATRX, AXIN1, AXIN2, B2M, BAP1, BARD1, BCOR, BLM, BMPR2, BRCA1, BRCA2, BRIP1, CALR, CASP8, CBFB, CD274, CD276, CDC73, CDH1, CDH10, CDK12, CDKN1A, CDKN1B, CDKN2A, CDKN2B, CDKN2C, CHEK1, CHEK2, CIC, CIITA, CREBBP, CSMD3, CTCF, CTLA4, CUL3, CUL4A, CUL4B, CYLD, CYP2C9, CYP2D6, DAXX, DDX3X, DICER1, DNMT3A, DOCK3, DPYD, DSC1, DSC3, ELF3, ENO1, EP300, EPCAM, EPHA2, ERAP1, ERAP2, ERCC2, ERCC4, ERCC5, ERRFI1, ETV6, FANCA, FANCC, FANCD2, FANCE, FANCF, FANCG, FANCI, FANCL, FANCM, FAS, FAT1, FBXW7, FUBP1, GATA3, GNA13, GPS2, HDAC2, HDAC9, HLA-A, HLA-B, HNF1A, ID3, INPP4B, JAK1, JAK2, JAK3, KDM5C, KDM6A, KEAP1, KLHL13, KMT2A, KMT2B, KMT2C, KMT2D, LARP4B, LATS1, LATS2, MAP2K4, MAP2K7, MAP3K1, MAP3K4, MAPK8, MEN1, MGA, MLH1, MLH3, MRE11, MSH2, MSH3, MSH6, MTAP, MTUS2, MUTYH, NBN, NCOR1, NF1, NF2, NOTCH1, NOTCH2, NOTCH3, NOTCH4, PALB2, PARP1, PARP2, PARP3, PARP4, PBRM1, PDCD1, PDCD1LG2, PDIA3, PGD, PHF6, PIK3R1, PMS1, PMS2, POLD1, POLE, POT1, PPM1D, PPP2R2A, PRDM1, PRDM9, PRKAR1A, PSMB10, PSMB8, PSMB9, PTCH1, PTEN, PTPRT, RAD50, RAD51, RAD51B, RAD51C, RAD51D, RAD52, RAD54L, RASA1, RASA2, RB1, RBM10, RECQL4, RNASEH2A, RNASEH2B, RNASEH2C, RNF43, RPA1, RPL22, RPL5, RUNX1, RUNX1T1, SDHA, SDHB, SDHC, SDHD, SETD2, SLX4, SMAD2, SMAD4, SMARCA4, SMARCB1, SOCS1, SOX9, SPEN, STAG2, STAT1, STK11, SUFU, TAP1, TAP2, TBX3, TCF7L2, TET2, TGFBR2, TMEM132D, TNFAIP3, TNFRSF14, TP53, TP63, TPP2, TSC1, TSC2, UGT1A1, USP9X, VHL, WT1, XRCC2, XRCC3, ZBTB20, ZFHX3, ZMYM3, ZRSR2

Relevant Therapy Summary

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

TERT c.-146C>T

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

CDK4 amplification

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

FGFR3 p.(K650E) c.1948A>G

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
ABSK061, ABSK-043	✖	✖	✖	✖	● (II)
TYRA-300	✖	✖	✖	✖	● (I/II)
afatinib, pemigatinib	✖	✖	✖	✖	● (I)
LOXO-435	✖	✖	✖	✖	● (I)
TYRA-430	✖	✖	✖	✖	● (I)

PTEN deletion

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
ribociclib, everolimus	✖	✖	✖	✖	● (II)
amquilix	✖	✖	✖	✖	● (I/II)
palbociclib, gedatolisib	✖	✖	✖	✖	● (I)
temsirolimus	✖	✖	✖	✖	● (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	***5.15%***
Not Detected	***Not Applicable***

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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