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Patient Name: 최인철 Gender: M Sample ID: N25-227 Primary Tumor Site: lung
Collection Date: 2025.09.16

# Sample Cancer Type: Lung Cancer

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# **Relevant Lung Cancer Findings**

Gene	Finding		Gene	Finding
ALK	None detected		NTRK1	None detected
BRAF	None detected		NTRK2	None detected
EGFR	None detected		NTRK3	None detected
ERBB2	None detected		RET	None detected
KRAS	None detected		ROS1	None detected
MET	None detected			
Genomic Alt	eration	Finding		
Tumor Mu	ıtational Burden	19.93 Mut/Mb measured		

### **Relevant Biomarkers**

Tier	Genomic Alteration	Relevant Therapies (In this cancer type)	Relevant Therapies (In other cancer type)	Clinical Trials
IB	FGFR3::TACC3 fusion fibroblast growth factor receptor 3 - transforming acidic coiled-coil containing protein 3 Locus: chr4:1808661 - chr4:1741429	erdafitinib	erdafitinib 1,2/l, II+	13
IIC	MTAP deletion methylthioadenosine phosphorylase Locus: chr9:21802646	None*	None*	10
IIC	CCND1 amplification cyclin D1 Locus: chr11:69455949	None*	None*	3

<sup>\*</sup> Public data sources included in relevant therapies: FDA1, NCCN, EMA2, 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.

<sup>\*</sup> Public data sources included in prognostic and diagnostic significance: NCCN, ESMO

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# **Relevant Biomarkers (continued)**

Tier	Genomic Alteration	Relevant Therapies (In this cancer type)	Relevant Therapies (In other cancer type)	Clinical Trials
IIC	CDKN2A deletion cyclin dependent kinase inhibitor 2A Locus: chr9:21968178	None*	None*	3
IIC	ARID1A p.(E2098*) c.6292G>T  AT-rich interaction domain 1A  Allele Frequency: 27.77%  Locus: chr1:27106681  Transcript: NM_006015.6	None*	None*	1
IIC	CDKN2B deletion cyclin dependent kinase inhibitor 2B Locus: chr9:22005728	None*	None*	1
IIC	FGF19 amplification fibroblast growth factor 19 Locus: chr11:69513948	None*	None*	1

<sup>\*</sup> Public data sources included in relevant therapies: FDA1, NCCN, EMA2, 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 p.(Q660\*) c.1978C>T, CDKN2A p.(D84N) c.250G>A, FGF3 amplification, FGF4 amplification, Microsatellite stable, PIK3CA p.(E726K) c.2176G>A, TP53 p.(R280T) c.839G>C, ELF3 deletion, CDKN1A p.(W65\*) c.194G>A, PIM1 amplification, KMT2C p.(Q569\*) c.1705C>T, NQ01 p.(P187S) c.559C>T, NCOR1 p.(Q978\*) c.2932C>T, Tumor Mutational Burden

### **Variant Details**

					Allele		
Gene	Amino Acid Change	Coding	Variant ID	Locus	Frequency	Transcript	Variant Effect
ARID1A	p.(E2098*)	c.6292G>T		chr1:27106681	27.77%	NM_006015.6	nonsense
ARID1B	p.(Q660*)	c.1978C>T		chr6:157150547	55.19%	NM_001371656.1	nonsense
CDKN2A	p.(D84N)	c.250G>A	COSM13488	chr9:21971108	45.86%	NM_001195132.2	missense
PIK3CA	p.(E726K)	c.2176G>A	COSM87306	chr3:178938934	62.82%	NM_006218.4	missense
TP53	p.(R280T)	c.839G>C	COSM10724	chr17:7577099	64.20%	NM_000546.6	missense
CDKN1A	p.(W65*)	c.194G>A		chr6:36652072	25.70%	NM_078467.3	nonsense
KMT2C	p.(Q569*)	c.1705C>T		chr7:151947968	38.07%	NM_170606.3	nonsense
NQ01	p.(P187S)	c.559C>T		chr16:69745145	48.97%	NM_000903.3	missense
NCOR1	p.(Q978*)	c.2932C>T		chr17:15995261	66.43%	NM_006311.4	nonsense
ARID1A	p.(S1248L)	c.3743C>T		chr1:27099864	24.02%	NM_006015.6	missense
ARID1A	p.(S1623L)	c.4868C>T		chr1:27101586	21.58%	NM_006015.6	missense
ARID1A	p.(?)	c.4994-3C>A		chr1:27102065	25.13%	NM_006015.6	unknown
ARID1A	p.(D2157N)	c.6469G>A		chr1:27106858	25.48%	NM_006015.6	missense
	1						

<sup>\*</sup> Public data sources included in prognostic and diagnostic significance: NCCN, ESMO

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# **Variant Details (continued)**

# **DNA Sequence Variants (continued)**

Gene	Amino Acid Change	Coding	Variant ID	Locus	Allele Frequency	Transcript	Variant Effect
ARID1A	p.(E2250K)	c.6748G>A		chr1:27107137	29.59%	NM_006015.6	missense
MYCL	p.(S329L)	c.986C>T		chr1:40363243	48.57%	NM_001033082.3	missense
TRIM31	p.(E209K)	c.625G>A		chr6:30078344	23.76%	NM_007028.5	missense
FAM135B	p.(L1116V)	c.3346T>G		chr8:139160865	35.00%	NM_015912.4	missense
TSC1	p.(N859I)	c.2576A>T		chr9:135776151	72.95%	NM_000368.5	missense
ETV6	p.(S321F)	c.962C>T		chr12:12022856	50.00%	NM_001987.5	missense
STAT6	p.(?)	c.1213-3C>T		chr12:57496707	12.08%	NM_003153.5	unknown
TP53	p.(D259N)	c.775G>A		chr17:7577506	63.82%	NM_000546.6	missense
SMARCA4	p.(I1229M)	c.3687C>G		chr19:11144106	23.49%	NM_001128849.3	missense
ZNF626	p.(R60K)	c.179G>A		chr19:20828537	19.35%	NM_001076675.3	missense
ZNF217	p.(G317R)	c.949G>C		chr20:52198417	49.07%	NM_006526.3	missense
DDX3X	p.(L272F)	c.816A>C		chrX:41203333	78.23%	NM_001356.5	missense

	ions

Genes	Variant ID	Locus
FGFR3::TACC3	FGFR3-TACC3.F17T11.COSF1348.1	chr4:1808661 - chr4:1741429
FGFR3::TACC3	FGFR3-TACC3.F18T10.1	chr4:1808924 - chr4:1739413
FGFR3::TACC3	FGFR3-TACC3.F18T11.Non-Targeted	chr4:1808950 - chr4:1741429
FGFR3::TACC3	FGFR3-TACC3.F18Int136T11.1	chr4:1808979 - chr4:1741429

Conv	Mumbar'	Variations
CODY	Mullipel	variations

Gene	Locus	Copy Number	CNV Ratio
MTAP	chr9:21802646	0.98	0.67
CCND1	chr11:69455949	6.08	2.3
CDKN2A	chr9:21968178	0.5	0.52
CDKN2B	chr9:22005728	0.88	0.64
FGF19	chr11:69513948	7.08	2.62
FGF3	chr11:69625020	7.48	2.76
FGF4	chr11:69588019	6.55	2.45
ELF3	chr1:201980251	0.78	0.61
PIM1	chr6:37138341	5.67	2.18
CD274	chr9:5456050	1	0.68

# **Biomarker Descriptions**

FGFR3::TACC3 fusion

fibroblast growth factor receptor 3, transforming acidic coiled-coil containing protein 3

<u>Background:</u> 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. These proteins are single-transmembrane receptors composed of three extracellular immunoglobulin (Ig)-type domains and an intracellular kinase domain. 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<sup>56,57,58</sup>.

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<sup>153</sup>. FGFR3 amplification is observed in up to 19% of uterine carcinoma, with somatic mutations occurring in 10-20% of bladder cancer<sup>4,5,154</sup>. Missense mutations that occur in the extracellular immunoglobulin-like and transmembrane domains of FGFR3, including S249C, R248C, and Y375C, cause ligand-independent dimerization and constitutive activation of FGFR3<sup>155,156,157</sup>.

Potential relevance: The pan-FGFR inhibitor, erdafitinib<sup>158</sup>, 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. The FGFR3 monoclonal antibody, vofatamab<sup>159</sup> was granted fast-track designation (2019) by the FDA, for the treatment of advanced or metastatic bladder urothelial cell carcinoma that harbors FGFR3 mutations or fusions. The FDA also granted fast track designation (2018) to Debio 1347<sup>160</sup> for solid tumors harboring FGFR1, FGFR2, or FGFR3 aberrations. Unregulated activation of FGFR3 has been associated with resistance to tamoxifen in ER-positive breast cancer<sup>161</sup>.

#### MTAP deletion

methylthioadenosine phosphorylase

<u>Background:</u> The MTAP gene encodes methylthioadenosine phosphorylase<sup>1</sup>. Methylthioadenosine phosphorylase, a key enzyme in polyamine biosynthesis and methionine salvage pathways, catalyzes the reversible phosphorylation of S-methyl-5'-thioadenosine (MTA) to adenine and 5-methylthioribose-1-phosphate<sup>11,12</sup>. Loss of MTAP function is commonly observed in cancer due to deletion or promotor methylation which results in the loss of MTA phosphorylation and sensitivity of MTAP-deficient cells to purine synthesis inhibitors and to methionine deprivation<sup>12</sup>.

Alterations and prevalence: MTAP is flanked by CDKN2A tumor suppressor on chromosome 9p21 and is frequently found to be codeleted with CDKN2A in numerous solid and hematological cancers<sup>12,13</sup>. Consequently, biallelic loss of MTAP has been observed in 42% of glioblastoma multiforme, 32% of mesothelioma, 26% of bladder urothelial carcinoma, 22% of pancreatic adenocarcinoma, 21% of esophageal adenocarcinoma, 20% of lung squamous cell carcinoma and skin cutaneous melanoma, 15% of diffuse large B-cell lymphoma and head and neck squamous cell carcinoma, 12% of lung adenocarcinoma, 11% of cholangiocarcinoma, 9% of sarcoma, stomach adenocarcinoma and brain lower grade glioma, and 3% of ovarian serous cystadenocarcinoma, breast invasive carcinoma, adrenocortical carcinoma, thymoma and liver hepatocellular carcinoma<sup>4,5</sup>. Somatic mutations in MTAP have been found in 3% of uterine corpus endometrial carcinoma<sup>4,5</sup>.

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

#### **CCND1** amplification

cyclin D1

Background: The CCND1 gene encodes the cyclin D1 protein, a member of the highly conserved D-cyclin family that also includes CCND2 and CCND3<sup>140,141,142</sup>. D-type cyclins are known to regulate cell cycle progression by binding to and activating cyclin dependent kinases (CDKs), specifically CDK4 and CDK6, which leads to the phosphorylation and inactivation of the retinoblastoma (RB1) protein<sup>140,141</sup>. Consequently, RB1 inactivation results in E2F transcription factor activation and cellular G1/S phase transition thereby resulting in cell cycle progression, a common event observed in tumorigenesis<sup>140,141,143</sup>. Aberrations in the D-type cyclins have been observed to promote tumor progression suggesting an oncogenic role for CCND1<sup>142,144</sup>.

Alterations and prevalence: Recurrent somatic alterations to CCND1, including mutations, amplifications, and chromosomal translocations, are observed in many cancer types. A common mechanism of these alterations is to increase the expression and nuclear localization of the cyclin D1 protein. Recurrent somatic mutations include missense mutations at codons T286 and P287 and c-terminal truncating mutations that are enriched in about 33% of uterine cancer, and missense mutations at Y44 that are enriched in about 50% of Mantle cell lymphoma (MCL)<sup>4,5,145,146</sup>. These mutations block phosphorylation-dependent nuclear export and proteolysis<sup>147,148,149,150</sup>. CCND1 is recurrently amplified in many cancer types, including up to 35% of esophageal cancer, 20-30% of head and neck cancer, and 10-20% of breast, squamous lung, and bladder cancers<sup>4,5,68</sup>. MCL is genetically characterized by the t(11;14)

# **Biomarker Descriptions (continued)**

(q13;q13) translocation, a rearrangement that juxtaposes CCND1 to the immunoglobulin heavy (lgH) chain gene. This rearrangement leads to constitutive expression of cyclin D1 and plays an important role in MCL pathogenesis<sup>151,152</sup>.

Potential relevance: Currently, no therapies are approved for CCND1 aberrations. The t(11;14) translocation involving CCND1 can be used to help diagnose some lymphoma subtypes including non-gastric MALT lymphoma, splenic marginal cell lymphoma, and mantle cell lymphoma<sup>87</sup>.

#### CDKN2A deletion, CDKN2A p.(D84N) c.250G>A

cyclin dependent kinase inhibitor 2A

Background: CDKN2A encodes cyclin dependent kinase inhibitor 2A, a cell cycle regulator that controls G1/S progression¹. CDKN2A, also known as p16/INK4A, belongs to a family of INK4 cyclin-dependent kinase inhibitors, which also includes CDKN2B (p15/INK4B), CDKN2C (p18/INK4C), and CDKN2D (p19/INK4D)²0. The INK4 family regulates cell cycle progression by inhibiting CDK4 or CDK6, thereby preventing the phosphorylation of Rb²¹,²²²,²³. CDKN2A encodes two alternative transcript variants, namely p16 and p14ARF, both of which exhibit differential tumor suppressor functions²⁴. Specifically, the CDKN2A/p16 transcript inhibits cell cycle kinases CDK4 and CDK6, whereas the CDKN2A/p14ARF transcript stabilizes the tumor suppressor protein p53 to prevent its degradation¹,²²⁴,²⁵. CDKN2A aberrations commonly co-occur with CDKN2B²0. Loss of CDKN2A/p16 results in downstream inactivation of the Rb and p53 pathways, leading to uncontrolled cell proliferation²6. Germline mutations of CDKN2A are known to confer a predisposition to melanoma and pancreatic cancer²7,²²8.

Alterations and prevalence: Somatic alterations in CDKN2A often result in loss of function (LOF) which is attributed to copy number loss, truncating, or missense mutations<sup>29</sup>. Somatic mutations in CDKN2A are observed in 20% of head and neck squamous cell carcinoma and pancreatic adenocarcinoma, 15% of lung squamous cell carcinoma, 13% of skin cutaneous melanoma, 8% of esophageal adenocarcinoma, 7% of bladder urothelial carcinoma, 6% of cholangiocarcinoma, 4% of lung adenocarcinoma and stomach adenocarcinoma, and 2% of liver hepatocellular carcinoma, uterine carcinosarcoma, and cervical squamous cell carcinoma<sup>4,5</sup>. Biallelic deletion of CDKN2A is observed in 56% of glioblastoma multiforme, 45% of mesothelioma, 39% of esophageal adenocarcinoma, 32% of bladder urothelial carcinoma, 31% of skin cutaneous melanoma and head and neck squamous cell carcinoma, 28% of pancreatic adenocarcinoma, 27% of diffuse large B-cell lymphoma, 26% of lung squamous cell carcinoma, 17% of lung adenocarcinoma and cholangiocarcinoma, 15% of sarcoma, 11% of stomach adenocarcinoma and of brain lower grade glioma, 7% of adrenocortical carcinoma, 6% of liver hepatocellular carcinoma, 4% of breast invasive carcinoma, kidney renal papillary cell carcinoma and thymoma, 3% of ovarian serous cystadenocarcinoma and kidney renal clear cell carcinoma, and 2% of uterine carcinosarcoma and kidney chromophobe<sup>4,5</sup>. Alterations in CDKN2A are also observed in pediatric cancers<sup>5</sup>. Biallelic deletion of CDKN2A is observed in 68% of T-lymphoblastic leukemia/lymphoma, 40% of B-lymphoblastic leukemia/lymphoma, 25% of glioma, 19% of bone cancer, and 6% of embryonal tumors<sup>5</sup>. Somatic mutations in CDKN2A are observed in less that 1.5% of bone cancer (5 in 327 cases), B-lymphoblastic leukemia/lymphoma (3 in 252 cases), and leukemia (1 in 354 cases)<sup>5</sup>.

Potential relevance: Loss of CDKN2A can be useful in the diagnosis of mesothelioma, and mutations in CDKN2A are ancillary diagnostic markers of malignant peripheral nerve sheath tumors<sup>30,31,32</sup>. Additionally, deletion of CDKN2B is a molecular marker used in staging Grade 4 pediatric IDH-mutant astrocytoma<sup>33</sup>. Currently, no therapies are approved for CDKN2A aberrations. However, CDKN2A LOF leading to CDK4/6 activation may confer sensitivity to CDK inhibitors such as palbociclib and abemaciclib<sup>34,35,36</sup>. Alternatively, CDKN2A expression and Rb inactivation demonstrate resistance to palbociclib in cases of glioblastoma multiforme<sup>37</sup>. CDKN2A (p16) expression is associated with a favorable prognosis for progression-free survival (PFS) and overall survival (OS) in p16/HPV positive head and neck cancer<sup>38,39,40,41</sup>.

#### ARID1A p.(E2098\*) c.6292G>T

AT-rich interaction domain 1A

Background: The ARID1A gene encodes the AT-rich interaction domain 1A tumor suppressor protein<sup>1</sup>. ARID1A, also known as BAF250A, belongs to the ARID1 subfamily that also includes AR1D1B<sup>1,14</sup>. ARID1A and ARID1B are mutually exclusive subunits of the BAF variant of the SWI/SNF chromatin-remodeling complex<sup>14,15</sup>. 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<sup>15</sup>. The BAF complex remodels chromatin at promoter and enhancer elements to alter and regulate gene expression<sup>15,16</sup>. ARID1A binds to transcription factors and coactivator/corepressor complexes to alter transcription<sup>14</sup>. Recurrent inactivating mutations in BAF complex subunits, including ARID1A, lead to transcriptional dysfunction thereby, altering its tumor suppressor function<sup>14</sup>.

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<sup>16</sup>. The majority of ARID1A inactivating mutations are nonsense or frameshift mutations<sup>14</sup>. Somatic mutations in ARID1A have been identified in 50% of ovarian clear cell carcinoma, 30% of endometrioid carcinoma, and 24-43% of uterine corpus endometrial carcinoma, bladder urothelial carcinoma, and stomach adenocarcinoma<sup>4,5,15</sup>. In microsatellite stable

# **Biomarker Descriptions (continued)**

(MSS) colorectal cancer, mutations in ARID1A have been observed to correlate with increased tumor mutational burden (TMB) and expression of genes involved in the immune response<sup>17</sup>.

Potential relevance: Currently, no therapies are approved for ARID1A aberrations. However, the FDA has granted fast track designation (2022) to HSF1 pathway inhibitor, NXP-800<sup>18</sup>, for the treatment of platinum resistant ARID1A-mutated ovarian carcinoma. Tulmimetostat<sup>19</sup>, dual inhibitor of EZH2 and EZH1, was also granted a fast track designation (2023) for the treatment of patients with advanced, recurrent or metastatic endometrial cancer harboring ARID1A mutations and who have progressed on at least one prior line of treatment.

#### **CDKN2B** deletion

cyclin dependent kinase inhibitor 2B

<u>Background</u>: CDKN2B encodes cyclin dependent kinase inhibitor 2B, a cell cycle regulator that controls G1/S progression<sup>1,20</sup>. CDKN2B, also known as p15/INK4B, belongs to a family of INK4 cyclin-dependent kinase inhibitors, which also includes CDKN2A (p16/INK4A), CDKN2C (p18/INK4C), and CDKN2D (p19/INK4D)<sup>20</sup>. The INK4 family regulates cell cycle progression by inhibiting CDK4 or CDK6, thereby preventing the phosphorylation of Rb<sup>21,22,23</sup>. CDKN2B is a tumor suppressor and aberrations in this gene commonly co-occur with CDKN2A<sup>20</sup>. Germline mutations in CDKN2B are linked to pancreatic cancer predisposition and familial renal cell carcinoma<sup>1,45,46</sup>.

Alterations and prevalence: CDKN2B copy number loss is a frequently occurring somatic aberration that is observed in 55% of glioblastoma multiforme, 43% of mesothelioma, 35% of esophageal adenocarcinoma, 31% of bladder urothelial carcinoma, 29% of skin cutaneous melanoma, 28% of head and neck squamous cell carcinoma, 27% of pancreatic adenocarcinoma, 26% of lung squamous cell carcinoma, 25% of diffuse large B -cell lymphoma, 16% of lung adenocarcinoma, 15% of sarcoma, 14% of cholangiocarcinoma, 11% of stomach adenocarcinoma and brain lower grade glioma, 5% of liver hepatocellular carcinoma, 4% of adrenocortical carcinoma, breast invasive carcinoma, thymoma, and kidney renal papillary cell carcinoma, 3% of kidney renal clear cell carcinoma and ovarian serous cystadenocarcinoma, and 2% of uterine carcinosarcoma and kidney chromophobe<sup>4,5</sup>. Somatic mutations in CDKN2B are observed in 2% of uterine carcinosarcoma<sup>4,5</sup>. CDKN2B copy number loss is also observed in pediatric cancers, including 64% of childhood T-lymphoblastic leukemia/lymphoma, 37% of pediatric B-lymphoblastic leukemia/lymphoma, 25% of pediatric gliomas, 14% of pediatric bone cancers, 6% of embryonal tumors, and 2% of peripheral nervous system cancers<sup>4,5</sup>. Somatic mutations in CDKN2B are observed in less than 1% of bone cancer (1 in 327 cases)<sup>4,5</sup>.

Potential relevance: Currently, no therapies are approved for CDKN2B aberrations. Homozygous deletion of CDKN2B is a molecular marker used in staging grade 4 pediatric IDH-mutant astrocytoma<sup>33</sup>.

### FGF19 amplification

fibroblast growth factor 19

Background: The FGF19 gene encodes the fibroblast growth factor 19 protein, a member of the FGF protein family composed of twenty-two members<sup>54,55</sup>. With the exception of four non-signaling FGF memebers (FGF11-14), FGF proteins function as ligands and mediate the activation of the fibroblast growth factor receptor (FGFR) family of tyrosine kinases<sup>54,55</sup>. 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 thereby influencing cell proliferation, migration, and survival<sup>56,57,58</sup>. FGF19 is specifically observed to bind FGFR4 with increased affinity in the presence of the transmembrane protein klotho beta (KLB) which functions as a cofactor in FGF19 mediated FGFR4 activation<sup>89,90</sup>. FGF19-mediated aberrant signaling has been identified as an oncogenic driver in hepatocellular carcinoma<sup>89,91</sup>.

Alterations and prevalence: FGF19 amplification is observed in about 35% of esophageal cancer, 23% of head and neck cancer, 10-15% of invasive breast carcinoma, cholangiocarcinoma, squamous lung, and bladder cancers as well as 5-7% of melanoma, liver, ovarian, and stomach cancers<sup>4</sup>. FGF19 overexpression is correlated with the development and tumor progression in hepatocellular carcinoma<sup>92</sup>.

Potential relevance: Currently, no therapies are approved for FGF19 aberrations. Selective, irreversible FGFR4 inhibitors, including fisogatinib (BLU-554), are under current clinical trial evaluation. In a phase-I clinical study of fisogatinib in patients with advanced hepatocellular carcinoma, 63% of the 115 patients enrolled were FGF19-positive by IHC<sup>93</sup>. Additionally, in 53 patients with tissue available for evaluation, 96% also exhibited mRNA-expression of FGFR4 and KLB. The total overall response rate observed for fisogatinib in FGF19-positive patients evaluable for response was 17% (11/66)<sup>93</sup>.

#### ARID1B p.(Q660\*) c.1978C>T

AT-rich interaction domain 1B

<u>Background:</u> The ARID1B gene encodes the AT-rich interaction domain 1B tumor suppressor protein<sup>1</sup>. ARID1B, also known as BAF250B, belongs to the ARID1 subfamily that also includes ARID1A<sup>1,14</sup>. ARID1A and ARID1B are mutually exclusive subunits of the

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# **Biomarker Descriptions (continued)**

BAF variant of the SWI/SNF chromatin remodeling complex<sup>14,15</sup>. 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<sup>15</sup>. The BAF complex remodels chromatin at promoter and enhancer elements to alter and regulate gene expression<sup>15,16</sup>. Recurrent inactivating mutations in BAF complex subunits, including ARID1B, lead to transcriptional dysfunction, suggesting ARID2B functions as a tumor suppressor<sup>14</sup>.

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 <sup>16</sup>. 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<sup>4,5</sup>. Biallelic loss of ARID1B is observed in 6% of uveal melanoma, 1% of bladder urothelial carcinoma, stomach adenocarcinoma, skin cutaneous melanoma, and colorectal adenocarcinoma<sup>4,5</sup>.

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<sup>51,52</sup>.

#### **FGF3** amplification

fibroblast growth factor 3

Background: The FGF3 gene encodes the fibroblast growth factor 3 protein, a member of the FGF protein family composed of twenty-two members<sup>54,55</sup>. With the exception of four non-signaling FGF members (FGF11-14), FGF proteins function as ligands and mediate the activation of the fibroblast growth factor receptor (FGFR) family of tyrosine kinases<sup>54,55</sup>. 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 thereby influencing cell proliferation, migration, and survival<sup>56,57,58</sup>. Specifically, FGF3 has been shown to bind to both FGFR1 and FGFR2<sup>59,60</sup>. Overexpression of FGF3 has been associated with certain tumor types including lung and liver cancers<sup>61,62</sup>. Additionally, constitutive ectopic expression has been suggested to promote tumorigenesis in vitro, supporting an oncogenic role for FGF3<sup>60</sup>.

Alterations and prevalence: FGF3 amplification is observed in about 35% of esophageal cancer, 24% of head and neck cancer, 10-15% of invasive breast carcinoma, squamous lung, and bladder cancers as well as 5-10% of cholangiocarcinoma, melanoma, liver, ovarian and stomach cancers<sup>4</sup>. FGF3 overexpression is correlated with non-small cell lung cancer (NSCLC) development as well as tumor metastasis and recurrence in hepatocellular carcinoma<sup>61,62</sup>.

Potential relevance: Currently, no therapies are approved for FGF3 aberrations.

### FGF4 amplification

fibroblast growth factor 4

Background: The FGF4 gene encodes the fibroblast growth factor 4 protein, a member of the FGF protein family, which is composed of 22 members<sup>1,55</sup>. With the exception of four non-signaling FGF members (FGF11-14), FGF proteins function as ligands and mediate the activation of the fibroblast growth factor receptor (FGFR) family of tyrosine kinases<sup>54,55</sup>. 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, thereby influencing cell proliferation, migration, and survival<sup>56,57,58</sup>.

Alterations and prevalence: Amplifications in FGF4 are observed in various tumor types, but most frequently are found in up to 35% of esophageal adenocarcinoma, 24% of head and neck squamous cell carcinoma, 14% of breast invasive carcinoma, 12% of lung squamous cell carcinoma, 11% of cholangiocarcinoma, 10% of bladder urothelial carcinoma, 7% of stomach adenocarcinoma, and 5% of liver hepatocellular carcinoma<sup>4,5</sup>. FGF4 overexpression has been associated with Kaposi sarcoma lesions as well as testicular cancer<sup>94,95</sup>.

Potential relevance: Currently, no therapies are approved for FGF4 aberrations.

#### Microsatellite stable

Background: Microsatellites are short tandem repeats (STR) of 1 to 6 bases of DNA between 5 to 50 repeat units in length. There are approximately 0.5 million STRs that occupy 3% of the human genome<sup>96</sup>. Microsatellite instability (MSI) is defined as a change in the length of a microsatellite in a tumor as compared to normal tissue<sup>97,98</sup>. 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<sup>99</sup>. 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<sup>100</sup>. 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)<sup>100</sup>. Tumors classified as MSI-L are often phenotypically indistinguishable from MSS tumors and tend to be grouped with MSS<sup>101,102,103,104,105</sup>. MSI-H is a hallmark of Lynch

# **Biomarker Descriptions (continued)**

syndrome (LS), also known as hereditary non-polyposis colorectal cancer, which is caused by germline mutations in the MMR genes<sup>98</sup>. LS is associated with an increased risk of developing colorectal cancer, as well as other cancers, including endometrial and stomach cancer <sup>97,98,102,106</sup>.

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<sup>97,98,107,108</sup>. 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<sup>107,108</sup>.

Potential relevance: Anti-PD-1 immune checkpoint inhibitors including pembrolizumab<sup>109</sup> (2014) and nivolumab<sup>110</sup> (2015) are approved for patients with MSI-H or dMMR colorectal cancer who have progressed following chemotherapy. Pembrolizumab<sup>109</sup> 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<sup>109</sup>. Dostarlimab<sup>111</sup> (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<sup>103,112</sup>. The cytotoxic T-lymphocyte antigen 4 (CTLA-4) blocking antibody, ipilimumab<sup>113</sup> (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<sup>103,114,115</sup>. 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<sup>115</sup>. 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<sup>116,117</sup>. However, checkpoint blockade with the addition of chemotherapy or targeted therapies have demonstrated response in MSS or pMMR cancers<sup>116,117</sup>.

#### PIK3CA p.(E726K) c.2176G>A

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

Background: The PIK3CA gene encodes the phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha of the class I phosphatidylinositol 3-kinase (PI3K) enzyme<sup>118</sup>. PI3K is a heterodimer that contains a p85 regulatory subunit, which couples one of four p110 catalytic subunits to activated tyrosine protein kinases<sup>119,120</sup>. The p110 catalytic subunits include p110α, β, δ, γ and are encoded by genes PIK3CA, PIK3CB, PIK3CD, and PIK3CG, respectively<sup>119</sup>. PI3K catalyzes the conversion of phosphatidylinositol (4,5)-bisphosphate (PI(4,5)P2) into phosphatidylinositol (3,4,5)-trisphosphate (PI(3,4,5)P3) while the phosphatase and tensin homolog (PTEN) catalyzes the reverse reaction<sup>121,122</sup>. The reversible phosphorylation of inositol lipids regulates diverse aspects of cell growth and metabolism<sup>121,122,123,124</sup>. Recurrent somatic alterations in PIK3CA are frequent in cancer and result in the activation of PI3K/AKT/MTOR pathway, which can influence several hallmarks of cancer including cell proliferation, apoptosis, cancer cell metabolism and invasion, and genetic instability<sup>125,126,127</sup>.

Alterations and prevalence: Recurrent somatic activating mutations in PIK3CA are common in diverse cancers and are observed in 20-30% of breast, cervical, and uterine cancers and 10-20% of bladder, gastric, head and neck, and colorectal cancers<sup>4,5</sup>. Activating mutations in PIK3CA commonly occur in exons 10 and 21 (previously referred to as exons 9 and 20 due to exon 1 being untranslated)<sup>128,129</sup>. These mutations typically cluster in the exon 10 helical (codons E542/E545) and exon 21 kinase (codon H1047) domains, each having distinct mechanisms of activation<sup>130,131,132</sup>. PIK3CA resides in the 3q26 cytoband, a region frequently amplified (10-30%) in diverse cancers including squamous carcinomas of the lung, cervix, head and neck, and esophagus, and in serous ovarian and uterine cancers<sup>4,5</sup>.

Potential relevance: The PI3K inhibitor, alpelisib¹³³, is FDA-approved (2019) in combination with fulvestrant for the treatment of patients with PIK3CA-mutated, hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative, advanced or metastatic breast cancer. Additionally, a phase lb study of alpelisib with letrozole in patients with metastatic estrogen receptor (ER)-positive breast cancer showed the clinical benefit rate, defined as lack of disease progression ≥ 6 months, was 44% (7/16) in PIK3CA-mutated tumors and 20% (2/20) in PIK3CA wild-type tumors¹³⁴. Specifically, exon 20 H1047R mutations were associated with more durable clinical responses in comparison to exon 9 E545K mutations¹³⁴. However, alpelisib did not improve response when administered with letrozole in patients with ER+ early breast cancer with PIK3CA mutations¹³⁵. The FDA also approved the kinase inhibitor, capivasertib (2023)¹³⁶ in combination with fulvestrant for locally advanced or metastatic HR-positive, HER2-negative breast cancer with one or more PIK3CA/AKT1/PTEN-alterations following progression after endocrine treatment. The kinase inhibitor, inavolisib¹³³, is also FDA-approved (2024) in combination with palbociclib and fulvestrant for the treatment of adults with endocrine-resistant, PIK3CA-mutated, HR-positive, and HER2-negative breast cancer. Case studies with mTOR inhibitors sirolimus and temsirolimus report isolated cases of clinical response in PIK3CA mutated refractory cancers¹³³.

# **Biomarker Descriptions (continued)**

#### TP53 p.(R280T) c.839G>C

tumor protein p53

<u>Background</u>: The TP53 gene encodes the tumor suppressor protein p53, which binds to DNA and activates transcription in response to diverse cellular stresses to induce cell cycle arrest, apoptosis, or DNA repair<sup>1</sup>. In unstressed cells, TP53 is kept inactive by targeted degradation via MDM2, a substrate recognition factor for ubiquitin-dependent proteolysis<sup>63</sup>. Alterations in TP53 are required for oncogenesis as they result in loss of protein function and gain of transforming potential<sup>64</sup>. Germline mutations in TP53 are the underlying cause of Li-Fraumeni syndrome, a complex hereditary cancer predisposition disorder associated with early-onset cancers<sup>65,66</sup>.

Alterations and prevalence: TP53 is the most frequently mutated gene in the cancer genome with approximately half of all cancers experiencing TP53 mutations. Ovarian, head and neck, esophageal, and lung squamous cancers have particularly high TP53 mutation rates (60-90%)<sup>4,5,67,68,69,70</sup>. Approximately two-thirds of TP53 mutations are missense mutations and several recurrent missense mutations are common, including substitutions at codons R158, R175, Y220, R248, R273, and R282<sup>4,5</sup>. Invariably, recurrent missense mutations in TP53 inactivate its ability to bind DNA and activate transcription of target genes<sup>71,72,73,74</sup>. Alterations in TP53 are also observed in pediatric cancers<sup>4,5</sup>. Somatic mutations are observed in 53% of non-Hodgkin lymphoma, 24% of soft tissue sarcoma, 19% of glioma, 13% of bone cancer, 9% of B-lymphoblastic leukemia/lymphoma, 4% of embryonal tumors, 3% of Wilms tumor and leukemia, 2% of T-lymphoblastic leukemia/lymphoma, and less than 1% of peripheral nervous system cancers (5 in 1158 cases)<sup>4,5</sup>. Biallelic loss of TP53 is observed in 10% of bone cancer, 2% of Wilms tumor, and less than 1% of B-lymphoblastic leukemia/lymphoma (2 in 731 cases) and leukemia (1 in 250 cases)<sup>4,5</sup>.

Potential relevance: The small molecule p53 reactivator, PC14586<sup>75</sup> (2020), received a fast track designation by the FDA for advanced tumors harboring a TP53 Y220C mutation. The FDA has granted fast track designation to the p53 reactivator, eprenetapopt<sup>76</sup>, (2019) and breakthrough designation<sup>77</sup> (2020) in combination with azacitidine or azacitidine and venetoclax for acute myeloid leukemia patients (AML) and myelodysplastic syndrome (MDS) harboring a TP53 mutation, respectively. In addition to investigational therapies aimed at restoring wild-type TP53 activity, compounds that induce synthetic lethality are also under clinical evaluation<sup>78,79</sup>. TP53 mutation are a diagnostic marker of SHH-activated, TP53-mutant medulloblastoma<sup>80</sup>. TP53 mutations confer poor prognosis and poor risk in multiple blood cancers including AML, MDS, myeloproliferative neoplasms (MPN), and chronic lymphocytic leukemia (CLL), and acute lymphoblastic leukemia (ALL)<sup>81,82,83,84,85,86</sup>. In mantle cell lymphoma, TP53 mutations are associated with poor prognosis when treated with conventional therapy including hematopoietic cell transplant<sup>87</sup>. Mono- and bi-allelic mutations in TP53 confer unique characteristics in MDS, with multi-hit patients also experiencing associations with complex karyotype, few co-occurring mutations, and high-risk disease presentation as well as predicted death and leukemic transformation independent of the IPSS-R staging system<sup>88</sup>.

#### **ELF3** deletion

E74 like ETS transcription factor 3

Background: The ELF3 gene encodes the E74 like ETS transcription factor 3 protein<sup>1</sup>. ELF3 is a transcription factor that has been observed to function as a negative regulator of the epithelial-mesenchymal transition (EMT) process, specifically in ovarian cancer cells<sup>2</sup>. ELF3 has also been proposed to act as an antagonist of oncogenic-signaling induced ZEB1 expression in colorectal cancer, supporting a tumor suppressor role for ELF3<sup>2,3</sup>.

Alterations and prevalence: Somatic mutations in ELF3 are observed in 13% of bladder urothelial carcinoma, 6% of cholangiocarcinoma, 3% of stomach adenocarcinoma and skin cutaneous melanoma, and 2% of colorectal adenocarcinoma, uterine corpus endometrial carcinoma, and cervical squamous cell carcinoma<sup>4,5</sup>.

Potential relevance: Currently, no therapies are approved for ELF3 aberrations.

### CDKN1A p.(W65\*) c.194G>A

cyclin dependent kinase inhibitor 1A

Background: The CDKN1A gene encodes the cyclin-dependent kinase inhibitor 1A protein, also known as p21 or WAF1<sup>1,42</sup>. CDKN1A belongs to a family of CIP/KIP family of CDK inhibitor (CKI) genes that also includes CDKN1B (also known as KIP/p27) and CDKN2C (also known as KIP2/p57)<sup>42,43</sup>. Through inhibition of cyclin dependent kinases, including CDK1 and CDK2, CDKN1A impacts several biological processes, including cell cycle arrest, differentiation, gene transcription, apoptosis, and DNA repair<sup>44</sup>. CDKN1A is also capable of binding to proliferating cell nuclear antigen (PCNA) and inhibiting PCNA-dependent DNA polymerase activity<sup>44</sup>. Deregulation of CDKN1A, including loss of expression, is observed in several tumor types, supporting a tumor suppressor role for CDKN1A<sup>44</sup>.

# **Biomarker Descriptions (continued)**

Alterations and prevalence: Somatic mutations in CDKN1A are observed in 10% of bladder urothelial carcinoma, 3% of kidney chromophobe, and 2% of skin cutaneous melanoma, uterine corpus endometrial carcinoma, and liver hepatocellular carcinoma<sup>4,5</sup>. Biallelic deletion of CDKN1A is observed in 2% of kidney chromophobe and 1% of sarcoma<sup>4,5</sup>.

Potential relevance: Currently, no therapies are approved for CDKN1A aberrations.

#### PIM1 amplification

Pim-1 proto-oncogene, serine/threonine kinase

Background: The PIM1 gene encodes the PIM-1 proto-oncogene, serine/threonine kinase protein<sup>1</sup>. PIM1, also known as PIM, is an oncogene that belongs to the PIM family of serine threonine kinases, which includes PIM2 and PIM3<sup>53</sup>. PIM1 is capable of phosphorylating CDC25A and CDC25C, which promotes G1 and S phase cell cycle progression, and G2/M phase progression, respectively<sup>53</sup>. PIM1 also targets proteins involved in cell survival, proliferation and apoptosis, including activation of MYC and BAD<sup>53</sup>.

Alterations and prevalence: Somatic mutations in PIM1 are observed in 20% of diffuse large B-cell lymphoma (DLBCL)<sup>4,5</sup>. PIM1 amplification is observed in 5% of ovarian serous cystadenocarcinoma, 3% of skin cutaneous melanoma, cholangiocarcinoma, esophageal adenocarcinoma, 2% of DLBCL and liver hepatocellular carcinoma<sup>4,5</sup>.

Potential relevance: Currently, no therapies are approved for PIM1 aberrations.

#### KMT2C p.(Q569\*) c.1705C>T

lysine methyltransferase 2C

Background: The KMT2C gene encodes the lysine methyltransferase 2C protein, a transcriptional coactivator and histone H3 lysine 4 (H3K4) methyltransferase¹. KMT2C belongs to the SET domain protein methyltransferase superfamily⁴7. KMT2C is capable of di- and tri-methylation of histone 3 lysine 4 (H3K4) at select transcriptional enhancers depending on the cell type⁴8. KMT2C is also found to interact with BAP1 to control ubiquitin-mediated gene silencing of H2A by Polycomb group (PcG) complexes⁴9,50. Specifically, KMT2C interaction with BAP1 promotes KMT2C histone recruitment/methyltransferase activity and, along with BAP1 deubiquitination of H2A, facilitates transcription of target genes⁴9,50. Mutations that occur within the SET domain of KMT2C are frequently observed in cancer and alter the methylation activity and target methylation states, thereby impacting gene regulation⁴8.

Alterations and prevalence: Somatic mutations in KMT2C are observed in 20% of bladder urothelial carcinoma and uterine corpus endometrial carcinoma, 19% of skin cutaneous melanoma and cervical squamous cell carcinoma, 15% of lung squamous cell carcinoma, 14% of stomach adenocarcinoma and lung adenocarcinoma, and 11% of cholangiocarcinoma<sup>4,5</sup>. Biallelic deletion of KMT2C is observed in 3% of sarcoma, stomach adenocarcinoma, 2% of esophageal adenocarcinoma, acute myeloid leukemia, uterine carcinosarcoma, and head and neck squamous cell carcinoma<sup>4,5</sup>.

Potential relevance: Currently, no therapies are approved for KMT2C aberrations.

### NCOR1 p.(Q978\*) c.2932C>T

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)<sup>1,6,7</sup>. NCOR1 plays a key role in several processes including embryonal development, metabolism, glucose homeostasis, inflammation, cell fate, chromatin structure and genomic stability<sup>6,7,8,9</sup>. NCOR1 has been shown exhibit a tumor suppressor role by inhibiting invasion and metastasis in various cancer models<sup>7</sup>. 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<sup>7,10</sup>.

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<sup>4,5</sup>. 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<sup>4,5</sup>. Structural variants of NCOR1 are observed in 3% of cholangiocarcinoma and 2% of uterine carcinosarcoma<sup>4,5</sup>.

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# **Biomarker Descriptions (continued)**

 $\underline{\hbox{Potential relevance:}} \ \hbox{Currently, no the rapies are approved for NCOR1 aberrations.}$ 

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### **Alerts Informed By Public Data Sources**

#### **Current FDA Information**

Contraindicated

Not recommended



Resistance



Fast Track

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

#### FGFR3::TACC3 fusion

#### vofatamab

Cancer type: Bladder Urothelial Carcinoma

Variant class: FGFR3 fusion

#### **Supporting Statement:**

The FDA has granted Fast Track designation to the FGFR3-targeted monoclonal antibody, vofatamab, for FGFR3 mutations or fusions in advanced or metastatic urothelial carcinoma.

#### Reference:

https://www.healio.com/news/hematology-oncology/20190107/fda-grants-fast-track-designation-to-vofatamab-for-bladdercancer-subset

### **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, PIK3CB, 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, SLC01B3, SMC1A, SMO. SNCAIP, SOS1, SOX2, SPOP, SRC, SRSF2, STAT3, STAT5B, STAT6, TAF1, TERT, TGFBR1, TOP1, TOP2A, TPMT, TRRAP, TSHR, U2AF1, USP8, WAS, XP01, 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, FANCI, FANCM, FAT1, FBXW7, FGF19, FGF23, 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,

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### **Genes Assayed (continued)**

### Genes Assayed for the Detection of Copy Number Variations (continued)

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, 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, ERRF11, ETV6, FANCA, FANCC, FANCD2, FANCE, FANCE, FANCG, FANCI, FANCI, FANCH, FA

# **Relevant Therapy Summary**

FGFR3::TACC3 fusion

In this cancer type	O In other cancer type	0	In this cancer type and other cancer types	×	No evidence
	O in ourse surrous type	•	in this surrest type and striet surrest types	-	

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
erdafitinib	0	•	0	0	×
ABSK061, ABSK-043	×	×	×	×	<b>(II)</b>
futibatinib	×	×	×	×	<b>(II)</b>
immune checkpoint inhibitor, pemigatinib	×	×	×	×	(II)
pemigatinib	×	×	×	×	(II)
sintilimab, pemigatinib	×	×	×	×	<b>(II)</b>
TYRA-300	×	×	×	×	(I/II)
ABSK-121	×	×	×	×	<b>(</b> l)
afatinib, pemigatinib	×	×	×	×	<b>(</b> I)
AMB-302	×	×	×	×	<b>(</b> 1)

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

# **Relevant Therapy Summary (continued)**

**CCND1** amplification

■ In this cancer type
O In other cancer type
In this cancer type and other cancer types
X No evidence

FGFR3::TACC3 fusion (contin	ued)				
Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
L0X0-435	×	×	×	×	<b>(</b> I)
TYRA-430	×	×	×	×	(I)

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
AMG 193	×	×	×	×	<b>(</b>  /  )
TNG-456, abemaciclib	×	×	×	×	<b>(</b>  /  )
TNG-462	×	×	×	×	<b>(</b>  /  )
AMG 193, pembrolizumab	×	×	×	×	(I)
GTA-182	×	×	×	×	(I)
ISM-3412	×	×	×	×	(I)
MRTX-1719	×	×	×	×	<b>(</b> 1)
PH020-803	×	×	×	×	(I)
S-095035	×	×	×	×	(I)
SYH-2039	×	×	×	×	(I)

·					
Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
abemaciclib	×	×	×	×	(II)
palbociclib	×	×	×	×	<b>(II)</b>
PF-07220060, midazolam	×	×	×	×	(I/II)

CDKN2A deletion					
Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
palbociclib	×	×	×	×	<b>(II)</b>
palbociclib, abemaciclib	×	×	×	×	<b>(II)</b>
AMG 193	×	×	×	×	<b>(</b> 1/11)

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

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# **Relevant Therapy Summary (continued)**

■ In this cancer type □ In other cancer type □ In this cancer type and other cancer types □ No evidence

ARIDTA p.(E2098*) c.6292G>1					
Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
talazoparib	×	×	×	×	<b>(II)</b>

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
palbociclib, abemaciclib	×	×	×	×	<b>(II)</b>

FGF19 amplification					
Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
Relevant Therapy	IDA	110011	LIVIA	LOINIO	Omnour Triulo
TYRA-430	×	×	×	×	<b>(</b> 1)

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

### **HRR Details**

CDKN2B deletion

Gene/Genomic Alteration	Finding
LOH percentage	20.25%
ATM	LOH, 11q22.3(108098341-108236285)x3
BARD1	LOH, 2q35(215593375-215674382)x2
CHEK1	LOH, 11q24.2(125496639-125525271)x3
RAD51B	LOH, 14q24.1(68290164-69061406)x3

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

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

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