

Patient Name: 박선옥  
Gender: F  
Sample ID: N25-85

Primary Tumor Site: breast  
Collection Date: 2024.03.15

## Sample Cancer Type: Breast Cancer

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## Relevant Breast Cancer Findings

Gene	Finding
BRCA1	None detected
ERBB2	None detected

Genomic Alteration	Finding
Tumor Mutational Burden	7.6 Mut/Mb measured

## Relevant Biomarkers

Tier	Genomic Alteration	Relevant Therapies (In this cancer type)	Relevant Therapies (In other cancer type)	Clinical Trials
IA	<b>PIK3CA p.(H1047R) c.3140A&gt;G</b> phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha Allele Frequency: 81.99% Locus: chr3:178952085 Transcript: NM_006218.4	<b>inavolisib + palbociclib + hormone therapy<sup>1 / I</sup></b> <b>alpelisib + hormone therapy<sup>1, 2 / II+</sup></b> <b>capivasertib + hormone therapy<sup>1, 2 / II</sup></b> +	None*	9
IIC	<b>MTAP deletion</b> methylthioadenosine phosphorylase Locus: chr9:21802646	None*	None*	8
IIC	<b>FGFR1 amplification</b> fibroblast growth factor receptor 1 Locus: chr8:38271452	None*	None*	7
IIC	<b>CDKN2A deletion</b> cyclin dependent kinase inhibitor 2A Locus: chr9:21968178	None*	None*	3
IIC	<b>KIT amplification</b> KIT proto-oncogene receptor tyrosine kinase Locus: chr4:55589693	None*	None*	3

\* Public data sources included in relevant therapies: FDA<sup>1</sup>, NCCN, EMA<sup>2</sup>, 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	<b>ARID1A p.(Q944*) c.2830C&gt;T</b> AT-rich interaction domain 1A Allele Frequency: 26.14% Locus: chr1:27092809 Transcript: NM_006015.6	None*	None*	1
	<b>CDKN2B deletion</b> cyclin dependent kinase inhibitor 2B Locus: chr9:22005728	None*	None*	1
	<b>PDGFRA amplification</b> platelet derived growth factor receptor alpha Locus: chr4:55131078	None*	None*	1
IIC	<b>TP53 p.(R273H) c.818G&gt;A</b> tumor protein p53 Allele Frequency: 67.14% Locus: chr17:7577120 Transcript: NM_000546.6	None*	None*	1

\* Public data sources included in relevant therapies: FDA<sup>1</sup>, NCCN, EMA<sup>2</sup>, 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, PPP2R2A deletion, UGT1A1 p.(G71R) c.211G>A, JAK2 deletion, NQO1 p.(P187S) c.559C>T, GNA13 amplification, Tumor Mutational Burden*

Variant Details

DNA Sequence Variants							
Gene	Amino Acid Change	Coding	Variant ID	Locus	Allele Frequency	Transcript	Variant Effect
PIK3CA	p.(H1047R)	c.3140A>G	COSM775	chr3:178952085	81.99%	NM_006218.4	missense
ARID1A	p.(Q944*)	c.2830C>T	.	chr1:27092809	26.14%	NM_006015.6	nonsense
TP53	p.(R273H)	c.818G>A	COSM10660	chr17:7577120	67.14%	NM_000546.6	missense
UGT1A1	p.(G71R)	c.211G>A	COSM4415616	chr2:234669144	99.05%	NM_000463.3	missense
NQO1	p.(P187S)	c.559C>T	.	chr16:69745145	28.08%	NM_000903.3	missense
RAF1	p.(E503Q)	c.1507G>C	.	chr3:12627209	55.02%	NM_002880.4	missense
HCN1	p.(M660I)	c.1980G>A	.	chr5:45262716	30.86%	NM_021072.4	missense
HLA-C	p.([L324=;G325R])	c.972_973delTGinsAA	.	chr6:31237785	7.27%	NM_001243042.1	synonymous, missense
KMT2C	p.(I1659S)	c.4976T>G	.	chr7:151884379	5.74%	NM_170606.3	missense
FZD6	p.(G336S)	c.1006G>A	.	chr8:104337340	26.00%	NM_001164615.2	missense
CSMD3	p.(S885T)	c.2654G>C	.	chr8:113694694	40.01%	NM_198123.2	missense
PTCH1	p.(R13G)	c.37C>G	.	chr9:98270607	80.82%	NM_000264.5	missense

Variant Details (continued)

DNA Sequence Variants (continued)							
Gene	Amino Acid Change	Coding	Variant ID	Locus	Allele Frequency	Transcript	Variant Effect
NCOR1	p.(P94T)	c.280C>A	.	chr17:16075272	69.46%	NM_006311.4	missense
USP9X	p.(?)	c.1161+3G>C	.	chrX:41000687	53.49%	NM_001039590.3	unknown
ZNF41	p.(L137P)	c.410T>C	.	chrX:47308759	32.65%	NM_153380.3	missense

Copy Number Variations			
Gene	Locus	Copy Number	CNV Ratio
MTAP	chr9:21802646	1	0.63
FGFR1	chr8:38271452	8.03	3.26
CDKN2A	chr9:21968178	0.87	0.57
KIT	chr4:55589693	4.72	2.02
CDKN2B	chr9:22005728	0.92	0.59
PDGFRA	chr4:55131078	4.77	2.04
MDM2	chr12:69202958	7.48	3.06
PPP2R2A	chr8:26149298	1.07	0.65
JAK2	chr9:5021954	0.99	0.62
GNA13	chr17:63010302	6.4	2.65
CD274	chr9:5456050	1.12	0.67
PDCD1LG2	chr9:5522530	1.07	0.65
WT1	chr11:32410528	14.12	5.54
AXIN2	chr17:63526027	7.17	2.94
PRKAR1A	chr17:66511464	4.76	2.04
SOX9	chr17:70117435	4.71	2.01
DSC3	chr18:28574139	8.84	3.56
DSC1	chr18:28710424	7.47	3.05

Biomarker Descriptions

PIK3CA p.(H1047R) c.3140A>G

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

Background: The PIK3CA gene encodes the phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha of the class I phosphatidylinositol 3-kinase (PI3K) enzyme<sup>166</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>167,168</sup>. The p110 catalytic subunits include p110α, β, δ, γ and are encoded by genes PIK3CA, PIK3CB, PIK3CD, and PIK3CG, respectively<sup>167</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>169,170</sup>. The reversible phosphorylation of inositol lipids regulates diverse aspects of cell growth and metabolism<sup>169,170,171,172</sup>. Recurrent somatic alterations in PIK3CA are frequent in cancer and result in the activation of PI3K/AKT/

## Biomarker Descriptions (continued)

MTOR pathway, which can influence several hallmarks of cancer including cell proliferation, apoptosis, cancer cell metabolism and invasion, and genetic instability<sup>173,174,175</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>18,19</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>176,177</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>178,179,180</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>18,19</sup>.

**Potential relevance:** The PI3K inhibitor, alpelisib<sup>181</sup>, 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 Ib 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  $\geq 6$  months, was 44% (7/16) in PIK3CA-mutated tumors and 20% (2/20) in PIK3CA wild-type tumors<sup>182</sup>. Specifically, exon 20 H1047R mutations were associated with more durable clinical responses in comparison to exon 9 E545K mutations<sup>182</sup>. However, alpelisib did not improve response when administered with letrozole in patients with ER+ early breast cancer with PIK3CA mutations<sup>183</sup>. The FDA also approved the kinase inhibitor, capivasertib (2023)<sup>184</sup> in combination with fulvestrant for locally advanced or metastatic HR-positive, HER2-negative breast cancer with one or more PIK3CA/AKT1/PTEN-alterations following progression after endocrine treatment. The kinase inhibitor, inavolisib<sup>185</sup>, is also FDA-approved (2024) in combination with palbociclib and fulvestrant for the treatment of adults with endocrine-resistant, PIK3CA-mutated, HR-positive, and HER2-negative breast cancer. Case studies with mTOR inhibitors sirolimus and temsirolimus report isolated cases of clinical response in PIK3CA mutated refractory cancers<sup>186,187</sup>.

### MTAP deletion

*methylthioadenosine phosphorylase*

**Background:** 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>55,56</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>56</sup>.

**Alterations and prevalence:** MTAP is flanked by CDKN2A tumor suppressor on chromosome 9p21 and is frequently found to be co-deleted with CDKN2A in numerous solid and hematological cancers<sup>56,57</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>18,19</sup>. Somatic mutations in MTAP have been found in 3% of uterine corpus endometrial carcinoma<sup>18,19</sup>.

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

### FGFR1 amplification

*fibroblast growth factor receptor 1*

**Background:** The FGFR1 gene encodes fibroblast growth factor receptor 1, a member of the fibroblast growth factor receptor (FGFR) family that also includes FGFR2, 3, and 4<sup>1</sup>. These proteins are single transmembrane receptors composed of three extracellular immunoglobulin (Ig)-type domains and an intracellular kinase domain<sup>1</sup>. Upon FGF-mediated stimulation, FGFRs activate several oncogenic signaling pathways, including the RAS/RAF/MEK/ERK, PI3K/AKT/MTOR, PLC $\gamma$ /PKC, and JAK/STAT pathways influencing cell proliferation, migration, and survival<sup>97,98,99</sup>.

**Alterations and prevalence:** Recurrent somatic alterations common to the FGFR family include gene amplification, mutation, and chromosomal translocations leading to FGFR fusions<sup>100</sup>. Amplification of FGFR1 is observed in 17% of lung squamous cell carcinoma, 11% of breast invasive carcinoma, 8% of bladder urothelial carcinoma, 7% of uterine carcinosarcoma and head and neck squamous cell carcinoma, 6% of esophageal adenocarcinoma, 5% of sarcoma, 4% of colorectal adenocarcinoma and pancreatic adenocarcinoma, 3% of prostate adenocarcinoma, ovarian serous cystadenocarcinoma, and lung adenocarcinoma, and 2% of uterine corpus endometrial carcinoma<sup>18,19,101,102,103</sup>. The most common recurrent mutations, N546K and K656E, are relatively infrequent (<1%); they activate mutations in the kinase domain and are distributed in diverse cancer types<sup>104</sup>. Somatic mutations in FGFR1 are observed in 7% of skin cutaneous melanoma, 6% of uterine corpus endometrial carcinoma, and 3% of stomach adenocarcinoma and colorectal

## Biomarker Descriptions (continued)

adenocarcinoma<sup>18,19</sup>. FGFR1 translocations giving rise to expressed fusions are common in certain hematological cancers, but are less common in solid tumors<sup>105,106,107</sup>. Alterations in FGFR1 are rare in pediatric cancers<sup>18,19</sup>. Amplification of FGFR1 is observed in less than 1% of B-lymphoblastic leukemia/lymphoma (2 in 731 cases). Somatic mutations in FGFR1 are observed in 6% of non-Hodgkin Lymphoma, 3% of soft tissue sarcoma, 2% of glioma, and less than 1% of embryonal tumors (2 in 332 cases), B-lymphoblastic leukemia/lymphoma (1 in 252 cases), Wilms tumor (2 in 710 cases), and peripheral nervous system cancers (1 in 1158 cases)<sup>18,19</sup>.

**Potential relevance:** The FGFR kinase inhibitor, pemigatinib<sup>108</sup> (2022) is approved for the treatment of adults with relapsed/refractory myeloid/lymphoid neoplasms (MLNs) with FGFR1 rearrangement. Additionally, the FDA granted fast-track designation to Debio 1347<sup>109</sup> (2018) for solid tumors harboring aberrations in FGFR1, FGFR2, or FGFR3. FDA has approved multi-kinase inhibitors, including regorafenib, ponatinib, lenvatinib, nintedanib, and pazopanib, that are known to inhibit FGFR family members<sup>110</sup>. These inhibitors have demonstrated anti-tumor activity in select cancer types with FGFR alterations<sup>111,112,113,114,115,116,117</sup>. In a phase II clinical trial, dovitinib, a multi-tyrosine kinase inhibitor (TKI), exhibited an overall response rate (ORR) of 11.5% and a disease control rate (DCR) of 50% in patients with advanced squamous cell lung cancer possessing FGFR1 amplification<sup>118</sup>. The patients had a median overall survival (OS) of 5 months and progression-free survival (PFS) of 2.9 months<sup>118</sup>. Likewise, in a phase Ib study testing the FGFR inhibitor AZD4547, the median OS was 4.9 months in patients with FGFR1-amplified advanced squamous cell lung cancer. One of 13 (8%) patients achieved a partial response, 4 (31%) exhibited stable disease, and 2 (13.3%) demonstrated PFS at 12 weeks<sup>119</sup>. Rearrangements in FGFR1 are associated with poor risk pediatric and adult acute lymphoblastic leukemia<sup>23,120,121</sup>.

### CDKN2A deletion

#### *cyclin dependent kinase inhibitor 2A*

**Background:** CDKN2A encodes cyclin dependent kinase inhibitor 2A, a cell cycle regulator that controls G1/S progression<sup>1</sup>. 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)<sup>64</sup>. The INK4 family regulates cell cycle progression by inhibiting CDK4 or CDK6, thereby preventing the phosphorylation of Rb<sup>65,66,67</sup>. CDKN2A encodes two alternative transcript variants, namely p16 and p14ARF, both of which exhibit differential tumor suppressor functions<sup>68</sup>. Specifically, the CDKN2A/p16 transcript inhibits cell cycle kinases CDK4 and CDK6, whereas the CDKN2A/p14ARF transcript stabilizes the tumor suppressor protein p53 to prevent its degradation<sup>1,68,69</sup>. CDKN2A aberrations commonly co-occur with CDKN2B<sup>64</sup>. Loss of CDKN2A/p16 results in downstream inactivation of the Rb and p53 pathways, leading to uncontrolled cell proliferation<sup>70</sup>. Germline mutations of CDKN2A are known to confer a predisposition to melanoma and pancreatic cancer<sup>71,72</sup>.

**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>73</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>18,19</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>18,19</sup>. Alterations in CDKN2A are also observed in pediatric cancers<sup>19</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>19</sup>. Somatic mutations in CDKN2A are observed in less than 1.5% of bone cancer (5 in 327 cases), B-lymphoblastic leukemia/lymphoma (3 in 252 cases), and leukemia (1 in 354 cases)<sup>19</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>54,74,75</sup>. Additionally, deletion of CDKN2B is a molecular marker used in staging Grade 4 pediatric IDH-mutant astrocytoma<sup>76</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>77,78,79</sup>. Alternatively, CDKN2A expression and Rb inactivation demonstrate resistance to palbociclib in cases of glioblastoma multiforme<sup>80</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>81,82,83,84</sup>.

### KIT amplification

#### *KIT proto-oncogene receptor tyrosine kinase*

**Background:** The KIT gene, also known as CD117, encodes the KIT proto-oncogene receptor tyrosine kinase (c-KIT), a member of the PDGF receptor type III receptor tyrosine kinase family, which includes PDGFRA, PDGFRB, CSF1R, FLT1, FLT3, FLT4 and KDR<sup>25,26</sup>. KIT

## Biomarker Descriptions (continued)

is a receptor for stem cell factor, important in regulating growth and development of hematopoietic cells<sup>27</sup>. The KIT gene is flanked by the PDGFRA and KDR genes on chromosome 4q12. Ligand binding to KIT results in kinase activation and stimulation of downstream pathways including the RAS/RAF/MEK/ERK and PI3K/AKT/MTOR pathways, promoting cell proliferation and survival<sup>28</sup>.

**Alterations and prevalence:** Recurrent somatic KIT alterations are observed in both solid and hematological cancers and include activating mutations such as single nucleotide variants, small duplications, and complex in-frame insertions or deletions (indels). Mutations in KIT exons 8, 9, 11, and 17 disrupt auto-inhibitory mechanisms and lead to constitutive activity<sup>29</sup>. Gain of function mutations are found in up to 70% of mast cell tumors, 17% of nasal T-cell lymphomas, and 9% of dysgerminoma<sup>30</sup>. Somatic mutations in exon 11 occur in 60-70% of all gastrointestinal stromal tumor (GIST), whereas alterations in exons 8 and 17 are more common in myeloid cancers<sup>19,29,30</sup>. A common kinase domain mutation that causes ligand-independent constitutive activation, D816V, occurs in 80-93% of aggressive forms of mastocytosis<sup>31,32</sup>.

**Potential relevance:** Imatinib<sup>33</sup> (2001) is approved for KIT positive unresectable or metastatic GIST and adult patients with aggressive systemic mastocytosis (SM) who do not have the D816V c-Kit mutation or whose c-Kit mutational status is unknown. Imatinib is also recommended for activating mutations, including KIT P577\_W582delinsPYD and KIT V560D in melanoma and exon 9 and 11 sensitizing mutations in GIST<sup>34,35,36,37</sup>. Mutations in exon 17 have been identified to confer resistance to imatinib and sunitinib<sup>38</sup>. Additionally, detection of activating mutations in KIT is useful as an ancillary technique in the diagnosis of GIST<sup>36</sup>. Patients with acute myeloid leukemia (AML) that harbor KIT activating mutations with t(8;21) and inv(16) have an increased risk of relapse<sup>39</sup>. KIT D816V mutation is associated with the diagnosis of SM and aggressiveness of the disease<sup>40,41</sup>.

### ARID1A p.(Q944\*) c.2830C>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 ARID1B<sup>1,58</sup>. ARID1A and ARID1B are mutually exclusive subunits of the BAF variant of the SWI/SNF chromatin-remodeling complex<sup>58,59</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>59</sup>. The BAF complex remodels chromatin at promoter and enhancer elements to alter and regulate gene expression<sup>59,60</sup>. ARID1A binds to transcription factors and coactivator/corepressor complexes to alter transcription<sup>58</sup>. Recurrent inactivating mutations in BAF complex subunits, including ARID1A, lead to transcriptional dysfunction thereby, altering its tumor suppressor function<sup>58</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>60</sup>. The majority of ARID1A inactivating mutations are nonsense or frameshift mutations<sup>58</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>18,19,59</sup>. In microsatellite stable (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>61</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>62</sup>, for the treatment of platinum resistant ARID1A-mutated ovarian carcinoma. Tulumimostat<sup>63</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*

**Background:** CDKN2B encodes cyclin dependent kinase inhibitor 2B, a cell cycle regulator that controls G1/S progression<sup>1,64</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>64</sup>. The INK4 family regulates cell cycle progression by inhibiting CDK4 or CDK6, thereby preventing the phosphorylation of Rb<sup>65,66,67</sup>. CDKN2B is a tumor suppressor and aberrations in this gene commonly co-occur with CDKN2A<sup>64</sup>. Germline mutations in CDKN2B are linked to pancreatic cancer predisposition and familial renal cell carcinoma<sup>1,85,86</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>18,19</sup>. Somatic mutations in CDKN2B are observed in 2% of uterine carcinosarcoma<sup>18,19</sup>. CDKN2B copy number loss is also observed in pediatric cancers, including 64% of



## Biomarker Descriptions (continued)

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>18,19</sup>. Somatic mutations in CDKN2B are observed in less than 1% of bone cancer (1 in 327 cases)<sup>18,19</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>76</sup>.

### PDGFRA amplification

*platelet derived growth factor receptor alpha*

**Background:** The PDGFRA gene encodes the platelet derived growth factor receptor alpha, a member of the PDGF receptor type III receptor tyrosine kinase family, which includes PDGFRB, CSF1R, FLT1, FLT3, FLT4, KDR, and KIT<sup>25,26</sup>. PDGFRA is a receptor for platelet derived growth factors, which are mitogens for cells of mesenchymal origin<sup>188</sup>. PDGFRA may function as a homodimer or heterodimer with PDGFRB depending on the ligand<sup>189</sup>. The PDGFRA gene is physically adjacent to KIT and KDR on chromosome 4q12, and all 3 tyrosine kinases are often co-amplified in cancer<sup>190</sup>. Ligand binding to PDGFRA results in kinase activation and stimulation of downstream pathways, including the RAS/RAF/MEK/ERK and PI3K/AKT/MTOR pathways, which promotes cell proliferation and survival<sup>191</sup>.

**Alterations and prevalence:** Recurrent somatic PDGFRA alterations are observed in both solid and hematological cancers and include activating mutations, gene amplification, and translocations generating PDGFRA gene fusions. Recurrent PDGFRA activating mutations, including D842V, V561D, N659K, and in-frame deletions in exon 18, are common in 30-40% of KIT negative gastrointestinal stromal tumors (GISTs) and approximately 7% overall<sup>192,193,194,195</sup>. PDGFRA recurrent mutations are also observed in 9% of skin cutaneous melanoma and uterine corpus endometrial carcinoma, 7% of lung adenocarcinoma, 5% of colorectal adenocarcinoma, 4% of lung squamous cell carcinoma, glioblastoma multiforme, and bladder urothelial carcinoma, 3% of stomach adenocarcinoma and head and neck squamous cell carcinoma, and 2% of cervical squamous cell carcinoma, liver hepatocellular carcinoma, brain lower grade glioma, and ovarian serous cystadenocarcinoma<sup>18,19</sup>. PDGFRA amplification is observed in 13% of glioblastoma multiforme, 5% of lung squamous cell carcinoma, 4% of brain lower grade glioma, 3% of sarcoma and skin cutaneous melanoma, and 2% of esophageal adenocarcinoma, testicular germ cell tumors, lung adenocarcinoma, uterine carcinosarcoma, and bladder urothelial carcinoma<sup>18,19</sup>. PDGFRA fusions are observed in gliomas and glioblastomas as well as eosinophilic leukemias, of which the FIP1L1::PDGFRA fusion defines approximately half of patients with hypereosinophilic syndrome<sup>196,197,198</sup>. Alterations of PDGFRA are rare in pediatric cancers<sup>18,19</sup>. Somatic mutations are observed in 2% of glioma, and less than 1% of embryonal tumors (3 in 332 cases), bone cancer (2 in 327 cases), and leukemia (1 in 354 cases)<sup>18,19</sup>. PDGFRA is amplified in 5% of bone cancer and less than 1% of Wilms tumor (1 in 136 cases)<sup>18,19</sup>.

**Potential relevance:** Avapritinib<sup>199</sup> (2020) is a tyrosine kinase inhibitor (TKI) that is approved by the FDA for metastatic or unresectable gastrointestinal stromal tumors (GISTs) harboring PDGFRA exon 18 mutations, including PDGFRA D842V mutation. The FDA has granted fast track designation to crenolanib<sup>200</sup> (2017) for harboring PDGFRA D842V mutation. Imatinib<sup>33</sup> (2001) is a TKI approved for patients diagnosed with chronic eosinophilic leukemia harboring the FIP1L1::PDGFRA fusion. Additionally, imatinib is recommended for the treatment of GISTs harboring PDGFRA exon 18 mutations, with the exception of D842V<sup>36</sup>. Amplification of PDGFRA is a diagnostic marker of H3-wildtype and IDH-wildtype diffuse pediatric-type high-grade glioma<sup>201,202</sup>. PDGFRA rearrangements are associated with poor risk in pediatric acute lymphoblastic leukemia<sup>120,203</sup>.

### TP53 p.(R273H) c.818G>A

*tumor protein p53*

**Background:** 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>122</sup>. Alterations in TP53 are required for oncogenesis as they result in loss of protein function and gain of transforming potential<sup>123</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>124,125</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>18,19,101,126,127,128</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>18,19</sup>. Invariably, recurrent missense mutations in TP53 inactivate its ability to bind DNA and activate transcription of target genes<sup>129,130,131,132</sup>. Alterations in TP53 are also observed in pediatric cancers<sup>18,19</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>18,19</sup>. Biallelic

## Biomarker Descriptions (continued)

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>18,19</sup>.

**Potential relevance:** The small molecule p53 reactivator, PC14586<sup>133</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, eprentapopt<sup>134</sup>, (2019) and breakthrough designation<sup>135</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>136,137</sup>. TP53 mutation are a diagnostic marker of SHH-activated, TP53-mutant medulloblastoma<sup>138</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>20,23,39,139,140,141</sup>. In mantle cell lymphoma, TP53 mutations are associated with poor prognosis when treated with conventional therapy including hematopoietic cell transplant<sup>142</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>143</sup>.

### MDM2 amplification

#### *MDM2 proto-oncogene*

**Background:** The MDM2 gene encodes the murine double minute 2 proto-oncogene. 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<sup>49</sup>. 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<sup>49</sup>. 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<sup>50</sup>. Alternately, low levels of MDM2 activity promote mono-ubiquitination and nuclear export of p53<sup>50</sup>. MDM2 amplification and overexpression disrupt the p53 protein function, thereby contributing to tumorigenesis and supporting an oncogenic role for MDM2<sup>50</sup>.

**Alterations and prevalence:** MDM2 is amplified in up to 13% of sarcoma, 8% of bladder urothelial carcinoma, glioblastoma, and 7% of adrenal cortical carcinoma<sup>18,19</sup>. MDM2 overexpression is observed in lung, breast, liver, esophagogastric, and colorectal cancers<sup>51</sup>. The most common co-occurring aberrations with MDM2 amplification or overexpression are CDK4 amplification and TP53 mutation<sup>52,53</sup>.

**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<sup>54</sup>.

### 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>144</sup>. Microsatellite instability (MSI) is defined as a change in the length of a microsatellite in a tumor as compared to normal tissue<sup>145,146</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>147</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>148</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>148</sup>. Tumors classified as MSI-L are often phenotypically indistinguishable from MSS tumors and tend to be grouped with MSS<sup>149,150,151,152,153</sup>. 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<sup>146</sup>. LS is associated with an increased risk of developing colorectal cancer, as well as other cancers, including endometrial and stomach cancer<sup>145,146,150,154</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>145,146,155,156</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>155,156</sup>.

**Potential relevance:** Anti-PD-1 immune checkpoint inhibitors including pembrolizumab<sup>157</sup> (2014) and nivolumab<sup>158</sup> (2015) are approved for patients with MSI-H or dMMR colorectal cancer who have progressed following chemotherapy. Pembrolizumab<sup>157</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>157</sup>. Dostarlimab<sup>159</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>151,160</sup>. The cytotoxic T-lymphocyte antigen 4 (CTLA-4) blocking antibody,



## Biomarker Descriptions (continued)

ipilimumab<sup>161</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>151,162,163</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>163</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>164,165</sup>. However, checkpoint blockade with the addition of chemotherapy or targeted therapies have demonstrated response in MSS or pMMR cancers<sup>164,165</sup>.

### PPP2R2A deletion

*protein phosphatase 2 regulatory subunit B alpha*

**Background:** The PPP2R2A gene encodes the protein phosphatase 2 regulatory subunit B alpha, a member of a large heterotrimeric serine/threonine phosphatase 2A (PP2A) family. Proteins of the PP2A family includes 3 subunits— the structural A subunit (includes PPP2R1A and PPP2R1B), the regulatory B subunit (includes PPP2R2A, PPP2R5, PPP2R3, and STRN), and the catalytic C subunit (PPPP2CA and PPP2CB)<sup>42,43</sup>. PPA2 proteins are essential tumor suppressor genes that regulate cell division and possess pro-apoptotic activity through negative regulation of the PI3K/AKT pathway<sup>44</sup>. Specifically, PPP2R2A modulates ATM phosphorylation which is critical in the regulation of the homologous recombination repair (HRR) pathway<sup>42</sup>.

**Alterations and prevalence:** Copy number loss and downregulation of PPP2R2A is commonly observed in solid tumors including breast and non-small cell lung cancer and define an aggressive subgroup of luminal-like breast cancer<sup>42,43,45,46</sup>. Biallelic loss of PPP2R2A is observed in 4-8% of breast invasive carcinoma, lung, colorectal, bladder, liver, and prostate cancers, as well as 4% of diffuse large B-cell lymphoma<sup>18</sup>.

**Potential relevance:** Currently no therapies are approved for PPP2R2A aberrations. However, in 2022, the FDA granted fast track designation to the small molecule inhibitor, pidnarulex<sup>47</sup>, for BRCA1/2, PALB2, or other homologous recombination deficiency (HRD) mutations in breast and ovarian cancers. Loss of PPP2R2A in pre-clinical and xenograft models have been shown to inhibit homologous recombination DNA directed repair and may predict sensitivity to PARP inhibitors such as veliparib<sup>42</sup>. Olaparib treatment in prostate cancer with PPP2R2A mutations is not recommended due to unfavorable risk benefit<sup>48</sup>.

### 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<sup>1,87</sup>. UGTs are microsomal membrane-bound enzymes that catalyze the glucuronidation of endogenous and xenobiotic compounds and transform the lipophilic molecules into excretable, hydrophilic metabolites<sup>87,88</sup>. 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<sup>89</sup>. 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<sup>89,90,91,92</sup>. 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<sup>93</sup>.

**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<sup>18,19</sup>.

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

### JAK2 deletion

*Janus kinase 2*

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

## Biomarker Descriptions (continued)

**Alterations and prevalence:** Clonal expansion of hematopoietic cells in myeloproliferative neoplasms (MPNs) is associated with loss of heterozygosity on chromosome 9p and subsequently the acquisition of a dominant somatic gain-of-function V617F mutation in the pseudokinase domain of JAK2<sup>8,9</sup>. The JAK2 V617F mutation is rarely observed in acute myeloid leukemia (AML)<sup>10,11</sup>. Mutations in the pseudokinase domain of JAK2, including R683G, have been detected in 8% of ALL<sup>12,13</sup>. JAK2 fusions are observed in myeloid and lymphoid leukemias with partner genes including TEL, PCM1, and BCR<sup>14,15,16,17</sup>. JAK2 fusions are infrequently observed in solid tumors<sup>18</sup>. As with JAK1, truncating mutations in JAK2 are common in solid tumors and particularly enriched in uterine cancers<sup>18</sup>. JAK2 is amplified in 4% of sarcoma, diffuse large B-cell lymphoma, and head and neck squamous cell carcinoma, 3% of ovarian serous cystadenocarcinoma, and 2% of esophageal adenocarcinoma, uterine corpus endometrial carcinoma, stomach adenocarcinoma, bladder urothelial carcinoma, and uterine carcinosarcoma<sup>18,19</sup>. Alterations in JAK2 are also observed in pediatric cancers<sup>18,19</sup>. Somatic mutations are observed in 6% of B-lymphoblastic leukemia/lymphoma, 3% of soft tissue sarcoma, 2% of T-lymphoblastic leukemia/lymphoma, and less than 1% of leukemia (3 in 354 cases), bone cancer (2 in 327 cases), glioma (1 in 297 cases), Wilms tumor (1 in 710 cases), and peripheral nervous system tumors (1 in 1158 cases)<sup>18,19</sup>. JAK2 fusions are observed in 10% of B-lymphoblastic leukemia/lymphoma and 1% of leukemia (1 in 107 cases)<sup>18,19</sup>. JAK2 is amplified in 1% of Wilms tumor (2 in 136 cases) and less than 1% of B-lymphoblastic leukemia/lymphoma (4 in 731 cases)<sup>18,19</sup>.

**Potential relevance:** Currently, no therapies are approved for JAK2 aberrations. JAK2 V617F and JAK2 exon 12 mutations are considered major diagnostic criteria of polycythemia vera (PV)<sup>20,21</sup>. Ruxolitinib<sup>22</sup> (2011) is a JAK1/2 inhibitor FDA approved for PMF and PV, although specific JAK2 alterations are not indicated. Other JAK inhibitors including tofacitinib (2012) and baricitinib (2018) are approved for the treatment of rheumatoid arthritis. JAK2 mutations and fusions are associated with poor risk in acute lymphoblastic leukemia<sup>23</sup>. Clinical cases associated with high tumor mutational burden (TMB) but failure to respond to anti-PD1 therapy were associated with loss of function mutations in JAK1/2<sup>24</sup>. Some case studies report efficacy with ruxolitinib in myeloid and lymphoid leukemias, although duration of complete response was limited<sup>14,15,16,17</sup>.

### GNA13 amplification

#### *G protein subunit alpha 13*

**Background:** The GNA13 gene encodes the G protein subunit  $\alpha$  13. GNA13 functions as the  $\alpha$  subunit of heterotrimeric G proteins, which are responsible for binding guanine nucleotide, hydrolyzing GTP, and interacting with specific receptor and effector molecules<sup>94</sup>. Specifically, GNA13 mediated signaling is observed to impact several cellular processes including the regulation of cell growth, transformation, cell adhesion, and migration<sup>95</sup>. GNA13 deregulation, including overexpression, has been observed to result in increased levels of chemokines which can promote cell proliferation<sup>94</sup>. In contrast, mutations in GNA13 leading to inactivation result in B-cell release from germinal centers of lymphoid tissues to peripheral blood and may promote lymphomagenesis in germinal center diffuse large B-cell and Burkitt's lymphomas<sup>96</sup>.

**Alterations and prevalence:** Somatic mutations in GNA13 are observed in 5% of DLBCL, 4% of uterine and 3% of bladder cancer<sup>18,19</sup>. Homozygous deletions are observed in 6% of DLBCL<sup>18,19</sup>. GNA13 is the most frequently mutated gene in germinal center derived B-cell lymphomas, including 25% of Burkitt lymphoma<sup>96</sup>. The majority of such mutations are predicted to result in loss of protein function<sup>96</sup>.

**Potential relevance:** Currently, no therapies are approved for GNA13 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, CTNNA1, 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, MYO10, 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, PXDN, 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, TGFB1, 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, PXDN, 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, SLC01B3, SLX4, SMAD2, SMAD4, SMARCA4, SMARCB1, SMC1A, SMO, SOX9, SPEN, SPOP, SRC, STAG2, STAT3, STAT6, STK11, SUFU, TAP1, TAP2, TBX3, TCF7L2, TERT, TET2, TGFB2, TNFAIP3, TNFRSF14, TOP1, TP53, TP63, TPMT, TPP2, TSC1, TSC2, U2AF1, USP8, USP9X, VHL, WT1, XPO1, XRCC2, XRCC3, YAP1, YES1, ZFH3, 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, TGFB2, TMEM132D, TNFAIP3, TNFRSF14, TP53, TP63, TPP2, TSC1, TSC2, UGT1A1, USP9X, VHL, WT1, XRCC2, XRCC3, ZBTB20, ZFH3, ZMYM3, ZRSR2

## Relevant Therapy Summary

☒ In this cancer type    
 ☐ In other cancer type    
 ☒ In this cancer type and other cancer types    
 ✕ No evidence

### PIK3CA p.(H1047R) c.3140A>G

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
alpelisib + fulvestrant	●	●	●	●	✕
capiwasertib + fulvestrant	●	●	●	✕	✕
inavolisib + palbociclib + fulvestrant	●	●	✕	✕	✕
alpelisib, hormone therapy	✕	✕	✕	✕	● (II)
alpelisib, hormone therapy, dapagliflozin	✕	✕	✕	✕	● (II)
HTL-0039732, atezolizumab	✕	✕	✕	✕	● (I/II)
ipatasertib, atezolizumab	✕	✕	✕	✕	● (I/II)
STX-478, hormone therapy	✕	✕	✕	✕	● (I/II)
JS-105	✕	✕	✕	✕	● (I)
OKI-219, hormone therapy	✕	✕	✕	✕	● (I)
RLY-2608	✕	✕	✕	✕	● (I)
SNV-4818, hormone therapy	✕	✕	✕	✕	● (I)

### MTAP deletion

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
AMG 193	✕	✕	✕	✕	● (I/II)
MRTX-1719	✕	✕	✕	✕	● (I/II)
TNG-456, abemaciclib	✕	✕	✕	✕	● (I/II)
TNG-462	✕	✕	✕	✕	● (I/II)
GTA-182	✕	✕	✕	✕	● (I)
ISM-3412	✕	✕	✕	✕	● (I)
S-095035	✕	✕	✕	✕	● (I)
SYH-2039	✕	✕	✕	✕	● (I)

### FGFR1 amplification

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
hormone therapy, catequentinib	✕	✕	✕	✕	● (II)
pemigatinib	✕	✕	✕	✕	● (II)
regorafenib	✕	✕	✕	✕	● (II)

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

## Relevant Therapy Summary (continued)

☒ In this cancer type    
 ☐ In other cancer type    
 ☒ In this cancer type and other cancer types    
 ✕ No evidence

### FGFR1 amplification (continued)

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
sunitinib	✕	✕	✕	✕	● (II)
BBI-355, futibatinib	✕	✕	✕	✕	● (I/II)
ABSK-121	✕	✕	✕	✕	● (I)

### CDKN2A deletion

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
palbociclib	✕	✕	✕	✕	● (II)
palbociclib, abemaciclib	✕	✕	✕	✕	● (II)
AMG 193	✕	✕	✕	✕	● (I/II)

### KIT amplification

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
nilotinib, pazopanib	✕	✕	✕	✕	● (II)
regorafenib	✕	✕	✕	✕	● (II)
sunitinib, regorafenib	✕	✕	✕	✕	● (II)

### ARID1A p.(Q944\*) c.2830C>T

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
talazoparib	✕	✕	✕	✕	● (II)

### CDKN2B deletion

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

### PDGFRA amplification

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
nilotinib, pazopanib	✕	✕	✕	✕	● (II)

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



Relevant Therapy Summary (continued)

In this cancer type

In other cancer type

In this cancer type and other cancer types

No evidence

TP53 p.(R273H) c.818G>A

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
TP53-EphA-2-CAR-DC, anti-PD-1	×	×	×	×	<div></div> (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	25.07%
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 OncoPrint Reporter software was used in generation of this report. Software was developed and designed internally by Thermo Fisher Scientific. The analysis was based on OncoPrint Reporter (6.1.1 data version 2025.05(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](http://www.fda.gov) and is current as of 2025-04-16. NCCN information was sourced from [www.nccn.org](http://www.nccn.org) and is current as of 2025-04-01. EMA information was sourced from [www.ema.europa.eu](http://www.ema.europa.eu) and is current as of 2025-04-16. ESMO information was sourced from [www.esmo.org](http://www.esmo.org) and is current as of 2025-04-01. Clinical Trials information is current as of 2025-04-01. For the most up-to-date information regarding a particular trial, search [www.clinicaltrials.gov](http://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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