

Patient Name: 왕학래  
Gender: M  
Sample ID: N25-147

Primary Tumor Site: Lung  
Collection Date: 2025.07.23

Sample Cancer Type: Non-Small Cell Lung Cancer

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Relevant Non-Small Cell Lung Cancer Findings

Gene	Finding	Gene	Finding
ALK	None detected	MET	None detected
BRAF	None detected	NRG1	None detected
EGFR	None detected	NTRK1	None detected
ERBB2	None detected	NTRK2	None detected
FGFR1	None detected	NTRK3	None detected
FGFR2	None detected	RET	None detected
FGFR3	None detected	ROS1	None detected
KRAS	None detected		

Genomic Alteration	Finding
Tumor Mutational Burden	3.79 Mut/Mb measured

Relevant Biomarkers

Tier	Genomic Alteration	Relevant Therapies (In this cancer type)	Relevant Therapies (In other cancer type)	Clinical Trials
IIC	BRCA2 deletion BRCA2, DNA repair associated Locus: chr13:32890491	None*	niraparib II+ olaparib II+ rucaparib II+	2
IIC	ATM deletion ATM serine/threonine kinase Locus: chr11:108098341	None*	None*	4
IIC	CDKN2A deletion cyclin dependent kinase inhibitor 2A Locus: chr9:21968178	None*	None*	3

\* Public data sources included in relevant therapies: FDA1, NCCN, EMA2, 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	<i>BAP1 deletion</i> BRCA1 associated protein 1 Locus: chr3:52436290	None*	None*	1
IIC	<i>CDKN2B deletion</i> cyclin dependent kinase inhibitor 2B Locus: chr9:22005728	None*	None*	1
IIC	<i>CHEK1 deletion</i> checkpoint kinase 1 Locus: chr11:125496639	None*	None*	1
IIC	<i>CHEK2 deletion</i> checkpoint kinase 2 Locus: chr22:29083868	None*	None*	1
IIC	<i>PALB2 deletion</i> partner and localizer of BRCA2 Locus: chr16:23614759	None*	None*	1

\* Public data sources included in relevant therapies: FDA1, NCCN, EMA2, 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**  
*ABRAXAS1 deletion, MAP2K7 deletion, Microsatellite stable, RAD51B deletion, XRCC3 deletion, DOCK3 deletion, FAT1 deletion, PRDM1 deletion, HDAC2 deletion, NQO1 p.(P187S) c.559C>T, PTPRT deletion, Tumor Mutational Burden*

Variant Details

DNA Sequence Variants							
Gene	Amino Acid Change	Coding	Variant ID	Locus	Allele Frequency	Transcript	Variant Effect
NQO1	p.(P187S)	c.559C>T	.	chr16:69745145	41.47%	NM_000903.3	missense
JAK1	p.(Y1048C)	c.3143A>G	.	chr1:65301896	26.35%	NM_002227.4	missense
FUBP1	p.(?)	c.1705+3A>G	.	chr1:78422254	26.78%	NM_003902.5	unknown
ABRAXAS1	p.(?)	c.477-3C>G	.	chr4:84390307	33.04%	NM_139076.3	unknown
MSH3	p.(A61_P63dup)	c.189_190insGCAGCG CCC	.	chr5:79950735	50.04%	NM_002439.5	nonframeshift Insertion
CYP2C9	p.(M406R)	c.1217T>G	.	chr10:96745857	17.60%	NM_000771.4	missense
PARP4	p.(?)	c.3285_3285+5delinsA GT	.	chr13:25021149	100.00%	NM_006437.4	unknown
CYLD	p.(?)	c.1675+1_1675+2insT ATTGGA	.	chr16:50815323	10.71%	NM_001042355.2	unknown
PAGE3	p.(R77Q)	c.230G>A	.	chrX:55287056	99.87%	NM_001017931.2	missense

Variant Details (continued)

Copy Number Variations			
Gene	Locus	Copy Number	CNV Ratio
BRCA2	chr13:32890491	1	0.72
ATM	chr11:108098341	1	0.84
CDKN2A	chr9:21968178	0	0.36
BAP1	chr3:52436290	0.87	0.7
CDKN2B	chr9:22005728	0	0.43
CHEK1	chr11:125496639	1	0.87
CHEK2	chr22:29083868	1	0.77
PALB2	chr16:23614759	1	0.98
ABRAXAS1	chr4:84383635	0.85	0.7
MAP2K7	chr19:7968792	0.77	0.67
RAD51B	chr14:68290164	1	0.75
XRCC3	chr14:104165043	0.79	0.68
DOCK3	chr3:51101879	0.72	0.66
FAT1	chr4:187509708	0.66	0.65
PRDM1	chr6:106534408	0.85	0.69
HDAC2	chr6:114262171	0.66	0.65
PTPRT	chr20:40710527	0.7	0.65
CD276	chr15:73991923	0.79	0.68

Biomarker Descriptions

BRCA2 deletion

BRCA2, DNA repair associated

**Background:** The breast cancer early onset gene 2 (BRCA2) encodes one of two BRCA proteins (BRCA1 and BRCA2) initially discovered as major hereditary breast cancer genes. Although structurally unrelated, both BRCA1 and BRCA2 exhibit tumor suppressor function and are integrally involved in the homologous recombination repair (HRR) pathway, a pathway critical in the repair of damaged DNA<sup>16,17</sup>. Specifically, BRCA1/2 are required for repair of chromosomal double strand breaks (DSBs) which are highly unstable and compromise genome integrity<sup>16,17</sup>. Inherited pathogenic mutations in BRCA1/2 are known to confer increased risk in women for breast and ovarian cancer and in men for breast and prostate cancer<sup>18,19,20</sup>. For individuals diagnosed with inherited pathogenic or likely pathogenic BRCA1/2 variants, the cumulative risk of breast cancer by 80 years of age was 69-72% and the cumulative risk of ovarian cancer by 70 years was 20-48%<sup>18,21</sup>.

**Alterations and prevalence:** Inherited BRCA1/2 mutations occur in 1:400 to 1:500 individuals and are observed in 10-15% of ovarian cancer, 5-10% of breast cancer, and 1-4% of prostate cancer<sup>22,23,24,25,26,27,28,29</sup>. Somatic alterations in BRCA2 are observed in 5-15% of uterine corpus endometrial carcinoma, cutaneous melanoma, bladder urothelial carcinoma, stomach adenocarcinoma, colorectal adenocarcinoma, lung squamous cell carcinoma, lung adenocarcinoma, and uterine carcinosarcoma, 3-4% of cervical squamous cell carcinoma, head and neck squamous cell carcinoma, esophageal adenocarcinoma, ovarian serous cystadenocarcinoma, cholangiocarcinoma, breast invasive carcinoma, renal papillary cell carcinoma, and 2% of renal clear cell carcinoma, hepatocellular carcinoma, thymoma, prostate adenocarcinoma, sarcoma, and glioblastoma multiforme<sup>6,7</sup>.

**Potential relevance:** Individuals possessing BRCA1/2 pathogenic germline or somatic mutations are shown to exhibit sensitivity to platinum based chemotherapy as well as treatment with poly (ADP-ribose) polymerase inhibitors (PARPi)<sup>30</sup>. Inhibitors targeting

## Biomarker Descriptions (continued)

PARP induce synthetic lethality in recombination deficient BRCA1/2 mutant cells<sup>31,32</sup>. Consequently, several PARP inhibitors have been FDA approved for BRCA1/2-mutated cancers. Olaparib<sup>33</sup> (2014) was the first PARPi to be approved by the FDA for BRCA1/2 aberrations. Originally approved for the treatment of germline variants, olaparib is now indicated (2018) for the maintenance treatment of both germline BRCA1/2-mutated (gBRCAm) and somatic BRCA1/2-mutated (sBRCAm) epithelial ovarian, fallopian tube, or primary peritoneal cancers that are responsive to platinum-based chemotherapy. Olaparib is also indicated for the treatment of patients with gBRCAm HER2-negative metastatic breast cancer and metastatic pancreatic adenocarcinoma. Additionally, olaparib<sup>33</sup> is approved (2020) for metastatic castration-resistant prostate cancer (mCRPC) with deleterious or suspected deleterious, germline or somatic mutations in HRR genes that includes BRCA2. Rucaparib<sup>34</sup> is also approved (2020) for deleterious gBRCAm or sBRCAm mCRPC and ovarian cancer. Talazoparib<sup>35</sup> (2018) is indicated for the treatment of gBRCAm HER2-negative locally advanced or metastatic breast cancer. Additionally, talazoparib<sup>35</sup> in combination with enzalutamide is approved (2023) for metastatic castration-resistant prostate cancer (mCRPC) with mutations in HRR genes that includes BRCA2. Niraparib<sup>36</sup> (2017) is another PARPi approved for the treatment of epithelial ovarian, fallopian tube, or primary peritoneal cancers with a deleterious or suspected deleterious BRCA mutation. Niraparib in combination with abiraterone acetate<sup>37</sup> received FDA approval (2023) for the treatment of deleterious or suspected deleterious BRCA-mutated (BRCAm) mCRPC. Despite tolerability and efficacy, acquired resistance to PARP inhibition has been clinically reported<sup>38</sup>. One of the most common mechanisms of resistance includes secondary intragenic mutations that restore BRCA1/2 functionality<sup>39</sup>. In addition to PARP inhibitors, other drugs which promote synthetic lethality have been investigated for BRCA mutations. In 2022, the FDA granted fast track designation to the small molecule inhibitor, pidnarulex<sup>40</sup>, for BRCA1/2, PALB2, or other homologous recombination deficiency (HRD) mutations in breast and ovarian cancers. Like PARPi, pidnarulex promotes synthetic lethality but through an alternative mechanism which involves stabilization of G-quadruplexes at the replication fork leading to DNA breaks and genomic instability. In 2024, the FDA granted fast track designation to TNG-348<sup>41</sup>, a USP1 inhibitor, for the treatment of BRCA1/2 mutated breast and ovarian cancer.

### ATM deletion

#### *ATM serine/threonine kinase*

**Background:** The ATM gene encodes a serine/threonine kinase that belongs to the phosphatidylinositol-3-kinase related kinases (PIKKs) family of genes that also includes ATR and PRKDC (also known as DNA-PKc)<sup>78</sup>. ATM and ATR act as master regulators of DNA damage response. Specifically, ATM is involved in double-stranded break (DSB) repair while ATR is involved in single-stranded DNA (ssDNA) repair<sup>79</sup>. ATM is recruited to the DNA damage site by the MRE11/RAD50/NBN (MRN) complex that senses DSB<sup>79,80</sup>. Upon activation, ATM phosphorylates several downstream proteins such as the NBN, MDC1, BRCA1, CHK2 and TP53BP1 proteins<sup>81</sup>. ATM is a tumor suppressor gene and loss of function mutations in ATM are implicated in the BRCAness phenotype, which is characterized by a defect in homologous recombination repair (HRR), mimicking BRCA1 or BRCA2 loss<sup>82,83</sup>. Germline mutations in ATM often result in Ataxia-telangiectasia, a hereditary disease also referred to as DNA damage response syndrome that is characterized by chromosomal instability<sup>84</sup>.

**Alterations and prevalence:** Recurrent somatic mutations in ATM are observed in 17% of endometrial carcinoma, 15% of undifferentiated stomach adenocarcinoma, 13% of bladder urothelial carcinoma, 12% of colorectal adenocarcinoma, 9% of melanoma as well as esophagogastric adenocarcinoma and 8% of non-small cell lung cancer<sup>6,7</sup>.

**Potential relevance:** The PARP inhibitor, olaparib<sup>33</sup> is approved (2020) for metastatic castration-resistant prostate cancer (mCRPC) with deleterious or suspected deleterious, germline or somatic mutations in HRR genes that includes ATM. Additionally, talazoparib<sup>35</sup> in combination with enzalutamide is approved (2023) for metastatic castration-resistant prostate cancer (mCRPC) with mutations in HRR genes that includes ATM. Consistent with other genes associated with the BRCAness phenotype, ATM mutations may aid in selecting patients likely to respond to PARP inhibitors<sup>82,85,86</sup>. Specifically, in a phase II trial of metastatic, castration-resistant prostate cancer, four of six patients with germline or somatic ATM mutations demonstrated clinical responses to olaparib<sup>87</sup>. In 2022, the FDA granted fast track designation to the small molecule inhibitor, pidnarulex<sup>40</sup>, for BRCA1/2, PALB2, or other homologous recombination deficiency (HRD) mutations in breast and ovarian cancers.

### 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>49</sup>. The INK4 family regulates cell cycle progression by inhibiting CDK4 or CDK6, thereby preventing the phosphorylation of Rb<sup>50,51,52</sup>. CDKN2A encodes two alternative transcript variants, namely p16 and p14ARF, both of which exhibit differential tumor suppressor functions<sup>53</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>1,53,54</sup>. CDKN2A aberrations commonly co-occur with CDKN2B<sup>49</sup>. Loss of CDKN2A/p16 results in downstream inactivation of the Rb and p53 pathways,

## Biomarker Descriptions (continued)

leading to uncontrolled cell proliferation<sup>55</sup>. Germline mutations of CDKN2A are known to confer a predisposition to melanoma and pancreatic cancer<sup>56,57</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>58</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>6,7</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>6,7</sup>. Alterations in CDKN2A are also observed in pediatric cancers<sup>7</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>7</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>7</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>59,60,61</sup>. Additionally, deletion of CDKN2B is a molecular marker used in staging Grade 4 pediatric IDH-mutant astrocytoma<sup>62</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>63,64,65</sup>. Alternatively, CDKN2A expression and Rb inactivation demonstrate resistance to palbociclib in cases of glioblastoma multiforme<sup>66</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>67,68,69,70</sup>.

### BAP1 deletion

#### *BRCA1 associated protein 1*

**Background:** The BAP1 gene encodes the BRCA1 associated protein 1 that belongs to the ubiquitin C-terminal hydrolase subfamily of deubiquitinating enzymes<sup>1</sup>. BAP1 is a tumor suppressor deubiquitinase that is involved in chromatin modification, transcription, and cell cycle regulation<sup>88</sup>. BAP1 deubiquitylation targets include HCF-1, which modulates chromatin structure<sup>88</sup>. Germline mutations in BAP1 are associated with BAP1-tumor predisposition syndrome (BAP1-TPDS), a heritable condition which confers an elevated risk of developing uveal melanoma, malignant mesothelioma, and renal cell carcinoma<sup>89,90,91,92,93,94</sup>.

**Alterations and prevalence:** Recurrent somatic mutations in BAP1 are observed in 21% of mesothelioma, 19% of cholangiocarcinoma, 16% of uveal melanoma, and 7% of kidney renal clear cell carcinoma<sup>6,7</sup>. BAP1 biallelic deletions are observed in 11% of mesothelioma<sup>6,7</sup>.

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

### 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>1,49</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>49</sup>. The INK4 family regulates cell cycle progression by inhibiting CDK4 or CDK6, thereby preventing the phosphorylation of Rb<sup>50,51,52</sup>. CDKN2B is a tumor suppressor and aberrations in this gene commonly co-occur with CDKN2A<sup>49</sup>. Germline mutations in CDKN2B are linked to pancreatic cancer predisposition and familial renal cell carcinoma<sup>1,71,72</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>6,7</sup>. Somatic mutations in CDKN2B are observed in 2% of uterine carcinosarcoma<sup>6,7</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%

## Biomarker Descriptions (continued)

of pediatric bone cancers, 6% of embryonal tumors, and 2% of peripheral nervous system cancers<sup>6,7</sup>. Somatic mutations in CDKN2B are observed in less than 1% of bone cancer (1 in 327 cases)<sup>6,7</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>62</sup>.

### CHEK1 deletion

*checkpoint kinase 1*

Background: The CHEK1 gene encodes the checkpoint kinase 1 protein and belongs to a family of serine/threonine checkpoint kinases, that also includes CHEK2<sup>1</sup>. Checkpoint kinases play an important role in S phase and G2/M transition and DNA damage induced cell cycle arrest<sup>73</sup>. CHEK1 is a tumor suppressor and it interacts with proteins involved in transcription regulation, cell-cycle arrest, and DNA repair including homologous recombination repair (HRR)<sup>74,75</sup>. Upon DNA damage, CHEK1 is phosphorylated and activated by DNA damage repair proteins ATM and ATR<sup>74</sup>. Activated CHEK1 subsequently phosphorylates and negatively regulates downstream proteins such as CDC25A thereby slowing or stalling DNA replication<sup>74,76</sup>.

Alterations and prevalence: Recurrent somatic alterations of CHEK1 include mutations and copy number loss. Somatic mutations of CHEK1 are observed in 3% of endometrial carcinoma, 2% of non-small cell lung cancer and 1% of cervical squamous carcinoma cases<sup>6,77</sup>. CHEK1 copy number loss occurs in 10% of seminoma, 8% of non-seminomatous germ cell tumor, 5% of ocular melanoma, and 3% of melanoma cases<sup>6,77</sup>.

Potential relevance: The PARP inhibitor, olaparib<sup>33</sup> is approved (2020) for metastatic castration-resistant prostate cancer (mCRPC) with deleterious or suspected deleterious, germline or somatic mutations in HRR genes that includes CHEK1. In 2022, the FDA granted fast track designation to the small molecule inhibitor, pidnarulex<sup>40</sup>, for BRCA1/2, PALB2, or other homologous recombination deficiency (HRD) mutations in breast and ovarian cancers.

### CHEK2 deletion

*checkpoint kinase 2*

Background: The CHEK2 gene encodes the checkpoint kinase-2 serine/threonine kinase, which is a cell-cycle checkpoint regulator. In response to DNA damage, CHEK2 is phosphorylated by ATM and subsequently phosphorylates and negatively regulates CDC25C to prevent entry into mitosis<sup>143</sup>. CHEK2 also stabilizes p53, leading to cell-cycle arrest in G1 phase, and is capable of phosphorylating BRCA1 and promoting DNA repair including homologous recombination repair (HRR)<sup>75,144,145</sup>. Germline mutations in the CHEK2 gene are associated with Li-Fraumeni syndrome and inherited risk of breast cancer<sup>146,147,148</sup>.

Alterations and prevalence: Consistent with its role as a tumor suppressor, CHEK2 is enriched for deleterious truncating mutations. Somatic mutations in CHEK2 are common (2-6%) in uterine carcinoma, bladder carcinoma, and lung adenocarcinoma<sup>6,7</sup>. CHEK2 gene deletions are observed in adrenocortical carcinoma, thymoma, and prostate cancer<sup>6,7</sup>.

Potential relevance: The PARP inhibitor, olaparib<sup>33</sup> is approved (2020) for metastatic castration-resistant prostate cancer (mCRPC) with deleterious or suspected deleterious, germline or somatic mutations in HRR genes that includes CHEK2. Additionally, talazoparib<sup>35</sup> in combination with enzalutamide is approved (2023) for mCRPC with mutations in HRR genes that includes CHEK2. In 2022, the FDA granted fast track designation to the small molecule inhibitor, pidnarulex<sup>40</sup>, for BRCA1/2, PALB2, or other homologous recombination deficiency (HRD) mutations in breast and ovarian cancers.

### PALB2 deletion

*partner and localizer of BRCA2*

Background: The PALB2 gene encodes the partner and localizer of BRCA2 protein that binds to and promotes intranuclear localization of the breast cancer 2 early onset (BRCA2) protein<sup>102</sup>. Also known as FANCN, PALB2 belongs to the Fanconi Anemia (FA) complementation group of proteins that also include FANCA, FANCB, FANCC, FANCD1 (BRCA2), FANCD2, FANCE, FANCF, FANCG, FANCI, FANCL, FANCM, and FANCD1 (BRIP1), FANCL, and FANCM. FA genes are tumor suppressors that play a role in interstrand cross-link (ICL) DNA repair through homologous recombination repair (HRR) of double-strand breaks (DSB) and nucleotide excision repair (NER)<sup>103</sup>. Loss of function mutations of genes in the FA family and HRR pathway, including PALB2, can result in the BRCAness phenotype, characterized by a defect in the HRR pathway, mimicking BRCA1 or BRCA2 loss<sup>83,104</sup>. Germline mutations in FA genes lead to Fanconi Anemia, a condition characterized by chromosomal instability and congenital abnormalities including bone marrow failure and cancer predisposition<sup>105,106</sup>. Specifically, biallelic germline mutations resulting in PALB2 loss of function confer a predisposition to pediatric malignancies<sup>107,108</sup>. Additionally, monoallelic germline mutations in PALB2 have been associated with an increased risk of developing breast cancer<sup>107,109</sup>.



## Biomarker Descriptions (continued)

**Alterations and prevalence:** Somatic alterations in PALB2 include missense or truncating mutations and are observed in 2-6% of melanoma, uterine, bladder, breast, lung, stomach and colorectal cancers<sup>6</sup>.

**Potential relevance:** The PARP inhibitor, olaparib<sup>33</sup> is approved (2020) for metastatic castration-resistant prostate cancer (mCRPC) with deleterious or suspected deleterious, germline or somatic mutations in HRR genes that includes PALB2. Additionally, talazoparib<sup>35</sup> in combination with enzalutamide is approved (2023) for mCRPC with mutations in HRR genes that includes PALB2. In a phase II trial of patients with metastatic, castration-resistant prostate cancer, one patient exhibiting a somatic PALB2 frameshift mutation exhibited durable response to olaparib for 39 weeks<sup>87,110</sup>. However, olaparib resistance was observed following 9-months of treatment due to the emergence of a secondary deletion which restored the PALB2 reading frame, a resistance mechanism similar to that observed in PARPi treated BRCA mutated patients<sup>39,110</sup>. In 2022, the FDA granted fast track designation to the small molecule inhibitor, pidnarulex<sup>40</sup>, for BRCA1/2, PALB2, or other homologous recombination deficiency (HRD) mutations in breast and ovarian cancers. Rucaparib is recommended as a maintenance therapy for germline or somatic PALB2 mutations in metastatic pancreatic cancer<sup>111</sup>.

### ABRAXAS1 deletion

*family with sequence similarity 175 member A*

**Background:** The ABRAXAS1 gene encodes the abraxas 1, BRCA1-A complex subunit<sup>1</sup>. ABRAXAS1, also known as FAM175A, is capable of binding both BRCA1 and RAP80 which promotes the BRCA1-A complex formation along with BABAM2 and BRCC36<sup>8,100</sup>. Following formation, the BRCA1-A complex is capable of recognizing polyubiquitylated histones, including H2AX, through recognition by RAP80, resulting in complex localization to sites of DNA damage such as double-strand breaks<sup>8</sup>. BRCA1 localization to DNA double-strand breaks through BRCA1-A is essential for DNA-damage signaling and repair<sup>8</sup>. Together with the rest of the BRCA1-A complex, ABRAXAS1 is suggested to function as a tumor suppressor where germline mutations in such genes have been associated with an increased risk of breast cancer<sup>8,101</sup>.

**Alterations and prevalence:** Somatic mutations in ABRAXAS1 are observed in 3% of uterine corpus endometrial carcinoma, 2% of colorectal adenocarcinoma, and 1% of stomach adenocarcinoma and lung squamous cell carcinoma<sup>6,7</sup>.

**Potential relevance:** Currently, no therapies are approved for ABRAXAS1 aberrations.

### MAP2K7 deletion

*mitogen-activated protein kinase kinase 7*

**Background:** The MAP2K7 gene encodes the mitogen-activated protein kinase kinase 7, also known as MEK7<sup>1</sup>. MAP2K7 is involved in the JNK signaling pathway along with MAP3K4, MAP3K12, MAP2K4, MAPK8, MAPK9, and MAPK10<sup>12,13,14</sup>. Activation of MAPK proteins occurs through a kinase signaling cascade<sup>12,13,15</sup>. Specifically, MAP3Ks are responsible for phosphorylation of MAP2K family members<sup>12,13,15</sup>. Once activated, MAP2Ks are responsible for the phosphorylation of various MAPK proteins whose signaling is involved in several cellular processes including cell proliferation, differentiation, and inflammation<sup>12,13,15</sup>.

**Alterations and prevalence:** Somatic mutations in MAP2K7 are observed in 7% of stomach adenocarcinoma, 4% of colorectal adenocarcinoma, and 2% of skin cutaneous melanoma and uterine corpus endometrial carcinoma<sup>6,7</sup>. Biallelic deletions are observed in 4% of uterine carcinosarcoma, 2% of esophageal adenocarcinoma, and 1% of uveal melanoma<sup>6,7</sup>.

**Potential relevance:** Currently, no therapies are approved for MAP2K7 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>117</sup>. Microsatellite instability (MSI) is defined as a change in the length of a microsatellite in a tumor as compared to normal tissue<sup>118,119</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>120</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>121</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>121</sup>. Tumors classified as MSI-L are often phenotypically indistinguishable from MSS tumors and tend to be grouped with MSS<sup>122,123,124,125,126</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>119</sup>. LS is associated with an increased risk of developing colorectal cancer, as well as other cancers, including endometrial and stomach cancer<sup>118,119,123,127</sup>.

## Biomarker Descriptions (continued)

**Alterations and prevalence:** The MSI-H phenotype is observed in 30% of uterine corpus endothelial carcinoma, 20% of stomach adenocarcinoma, 15-20% of colon adenocarcinoma, and 5-10% of rectal adenocarcinoma<sup>118,119,128,129</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>128,129</sup>.

**Potential relevance:** Anti-PD-1 immune checkpoint inhibitors including pembrolizumab<sup>130</sup> (2014) and nivolumab<sup>131</sup> (2015) are approved for patients with MSI-H or dMMR colorectal cancer who have progressed following chemotherapy. Pembrolizumab<sup>130</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>130</sup>. Dostarlimab<sup>132</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>124,133</sup>. The cytotoxic T-lymphocyte antigen 4 (CTLA-4) blocking antibody, ipilimumab<sup>134</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>124,135,136</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>136</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>137,138</sup>. However, checkpoint blockade with the addition of chemotherapy or targeted therapies have demonstrated response in MSS or pMMR cancers<sup>137,138</sup>.

### RAD51B deletion

#### *RAD51 paralog B*

**Background:** The RAD51B gene encodes the RAD51 paralog B protein, a member of the RAD51 recombinase family that also includes RAD51, RAD51C (RAD51L2), RAD51D (RAD51L3), XRCC2, and XRCC3 paralogs. The RAD51 family of proteins are involved in homologous recombination repair (HRR) and DNA repair of double-strand breaks (DSB)<sup>95</sup>. RAD51B associates with other RAD51 paralogs to form RAD51B-RAD51C-RAD51D-XRCC2 (BCDX2) complex<sup>96</sup>. The BCDX2 complex binds single- and double-stranded DNA to hydrolyze ATP<sup>97</sup>. RAD51B is a tumor suppressor gene. Loss of function mutations in RAD51B are implicated in the BRCAness phenotype, which is characterized by a defect in HRR mimicking BRCA1 or BRCA2 loss<sup>82,83</sup>. Biallelic expression of RAD51B is required for chromosomal integrity and haploinsufficiency leads to aberrant HRR resulting in centrosome fragmentation, aneuploidy, and mild hypersensitivity to DNA-damaging agents<sup>98</sup>. Genetic variation within the RAD51B locus on 14q24.1 is significantly associated with familial breast cancer risk<sup>99</sup>.

**Alterations and prevalence:** Somatic mutations in RAD51B are observed in up to 3% of uterine cancer<sup>6,7</sup>. Loss of function mutations in RAD51B are rare, but variation within the RAD51B locus is significantly associated with familial breast cancer risk<sup>99</sup>.

**Potential relevance:** The PARP inhibitor, olaparib<sup>33</sup> is approved (2020) for metastatic castration-resistant prostate cancer (mCRPC) with deleterious or suspected deleterious, germline or somatic mutations in HRR genes that includes RAD51B. In 2022, the FDA granted fast track designation to the small molecule inhibitor, pidnarulex<sup>40</sup>, for BRCA1/2, PALB2, or other homologous recombination deficiency (HRD) mutations in breast and ovarian cancers.

### XRCC3 deletion

#### *X-ray repair cross complementing 3*

**Background:** The XRCC3 gene encodes the X-ray cross complementing 3 protein, a member of the RAD51 recombinase family that also includes RAD51, RAD51C, RAD51D, and XRCC2 paralogs<sup>1,8</sup>. XRCC3 complexes with RAD51C to form the CX3 complex, which functions in strand exchange and Holliday junction resolution during homologous recombination repair (HRR)<sup>8,9</sup>. XRCC3 may complex with BRCA2, FANCD2, and FANCG to maintain chromosome stability<sup>10</sup>.

**Alterations and prevalence:** Somatic mutations in XRCC3 are observed in 1% of uveal melanoma, colorectal adenocarcinoma, and cervical squamous cell carcinoma<sup>6,7</sup>. Biallelic deletions in XRCC3 are observed in 3% of cholangiocarcinoma and 2% of diffuse large B-cell lymphoma (DLBCL) and bladder urothelial carcinoma<sup>6,7</sup>.

**Potential relevance:** Currently, no therapies are approved for XRCC3 aberrations. Pre-clinical evidence suggests that XRCC3 mutations may demonstrate sensitivity to cisplatin<sup>10</sup>.



## Biomarker Descriptions (continued)

### DOCK3 deletion

*dedicator of cytokinesis 3*

**Background:** The DOCK3 gene encodes dedicator of cytokinesis 3, a member of the DOCK (dedicator of cytokinesis) family of guanine nucleotide exchange factors (GEFs)<sup>1</sup>. As a GEF, DOCK3 functions by catalyzing the exchange of GDP for GTP, and activates the G protein, Rac1, thereby facilitating RAC1 mediated signaling<sup>112</sup>. Consequently, DOCK3 has been observed to facilitate the regulation of several cellular processes including axonal outgrowth, cytoskeletal organization, and cell adhesion<sup>1,113,114</sup>. Unlike other GEFs found to be altered in cancer, DOCK3 has been shown to exhibit tumor suppressor like properties through inhibition of  $\beta$ -catenin/WNT signaling<sup>115,116</sup>. Additionally knockdown of DOCK3 has been observed to inhibit tumor cell adhesion, migration, and invasion in non-small cell lung cancer cell lines, further supporting a tumor suppressive role for DOCK3<sup>114</sup>.

**Alterations and prevalence:** Somatic mutations in DOCK3 are observed in 21% of skin cutaneous melanoma, 16% of uterine corpus endometrial carcinoma, 12% of stomach adenocarcinoma, 9% of colorectal adenocarcinoma, 6% of esophageal adenocarcinoma, 4% of sarcoma, and lung adenocarcinoma, 3% of bladder urothelial carcinoma, lung squamous cell carcinoma, cervical squamous cell carcinoma, and 2% of diffuse large B-cell lymphoma, pancreatic adenocarcinoma, head and neck squamous cell carcinoma, kidney renal papillary cell carcinoma, ovarian serous cystadenocarcinoma, liver hepatocellular carcinoma, and kidney chromophobe<sup>6,7</sup>. Biallelic loss of DOCK3 is observed in 4% of diffuse large B-cell lymphoma, 3% of esophageal adenocarcinoma and kidney renal clear cell carcinoma, and 2% of sarcoma<sup>6,7</sup>.

**Potential relevance:** Currently, no therapies are approved for DOCK3 aberrations.

### FAT1 deletion

*FAT atypical cadherin 1*

**Background:** FAT1 encodes the FAT atypical cadherin 1 protein, a member of the cadherin superfamily characterized by the presence of cadherin-type repeats<sup>1,11</sup>. FAT cadherins, which also include FAT2, FAT3, and FAT4, are transmembrane proteins containing a cytoplasmic domain and a number of extracellular laminin G-like motifs and EGF-like motifs, which contributes to their individual functions<sup>11</sup>. The cytoplasmic tail of FAT1 is known to interact with a number of protein targets involved in cell adhesion, proliferation, migration, and invasion<sup>11</sup>. FAT1 has been observed to influence the regulation of several oncogenic pathways, including the WNT/ $\beta$ -catenin, Hippo, and MAPK/ERK signaling pathways, as well as epithelial to mesenchymal transition<sup>11</sup>. Alterations of FAT1 lead to down-regulation or loss of function, supporting a tumor suppressor role for FAT1<sup>11</sup>.

**Alterations and prevalence:** Somatic mutations in FAT1 are predominantly truncating although, the R1627Q mutation has been identified as a recurrent hotspot<sup>6,7</sup>. Mutations in FAT1 are observed in 22% of head and neck squamous cell carcinoma, 20% of uterine corpus endometrial carcinoma, 14% of lung squamous cell carcinoma and skin cutaneous melanoma, and 12% diffuse large b-cell lymphoma and bladder urothelial carcinoma<sup>6,7</sup>. Biallelic loss of FAT1 is observed in 7% of head and neck squamous cell carcinoma, 6% of lung squamous cell carcinoma, 5% of esophageal adenocarcinoma, and 4% of diffuse large b-cell lymphoma, stomach adenocarcinoma and uterine carcinosarcoma<sup>6,7</sup>.

**Potential relevance:** Currently, no therapies are approved for FAT1 aberrations.

### PRDM1 deletion

*PR/SET domain 1*

**Background:** The PRDM1 gene encodes the PR/SET domain 1 protein, also known as BLIMP1<sup>1</sup>. PRDM1 is a transcriptional repressor that regulates B- and T-cell differentiation<sup>139,140,141</sup>. PRDM1 drives the differentiation of mature B-cells to antibody-secreting cells (ASCs) and is commonly expressed in ASCs<sup>142</sup>. PRDM1, along with other transcription factors, also regulates the expression of IL-2, IL-21, and IL-10 in effector T-cells, resulting in T-cell mediated immunosuppression through IL repression<sup>141</sup>. Dysregulation of B-cell terminal differentiation, as a result of PRDM1 mutations, has been observed to contribute to lymphoma development, supporting a tumor suppressor role for PRDM1<sup>142</sup>.

**Alterations and prevalence:** Somatic mutations in PRDM1 are observed in 7% of skin cutaneous melanoma, 6% of uterine corpus endometrial carcinoma, 5% diffuse large B-cell lymphoma (DLBCL), and 3% of cholangiocarcinoma<sup>6,7</sup>. Additionally, PRDM1 mutations have been reported in 25% of activated B-cell phenotype diffuse large B-cell lymphoma (ABC-DLBCL)<sup>142</sup>. PRDM1 biallelic deletions are observed in 10% of DLBCL, 9% of prostate adenocarcinoma, and 6% of uveal melanoma<sup>6,7</sup>.

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

## Biomarker Descriptions (continued)

### HDAC2 deletion

#### *histone deacetylase 2*

**Background:** The HDAC2 gene encodes the histone deacetylase 2 protein<sup>1</sup>. HDAC2 is part of the histone deacetylase (HDAC) family consisting of 18 different isoforms categorized into four classes (I-IV)<sup>42</sup>. Specifically, HDAC2 is a member of class I, along with HDAC1, HDAC3, and HDAC8<sup>42</sup>. HDACs, including HDAC2, function by removing acetyl groups on histone lysines resulting in chromatin condensation, transcriptional repression, and regulation of cell proliferation and differentiation<sup>42,43</sup>. HDAC2 negatively regulates antigen presentation by inhibiting CIITA, which regulates MHC class II genes<sup>42</sup>. Further, HDAC2 and HDAC1 are essential for B-cell proliferation during development and antigen stimulation in mature B-cells<sup>42</sup>. HDAC deregulation, including overexpression, is observed in a variety of tumor types, which is proposed to affect the expression of genes involved in cellular regulation and promote tumor development<sup>42,44</sup>.

**Alterations and prevalence:** Somatic mutations in HDAC2 are observed in 4% of uterine corpus endometrial carcinoma, 2% of diffuse large B-cell lymphoma (DLBCL) and colorectal adenocarcinoma<sup>6,7</sup>. Biallelic deletions in HDAC2 are observed in 8% of prostate adenocarcinoma and DLBCL, and 6% of uveal melanoma<sup>6,7</sup>.

**Potential relevance:** Currently, no therapies are approved for HDAC2 aberrations. Although not approved for specific HDAC2 alterations, the pan-HDAC inhibitor vorinostat (2006) is approved for the treatment of progressive, persistent, or recurrent cutaneous T-cell lymphoma (CTCL) following treatment with two systemic therapies<sup>45</sup>. The pan-HDAC inhibitor, romidepsin (2009), is approved for the treatment of CTCL and peripheral T-cell lymphoma (PTCL) having received at least one prior systemic therapy<sup>46</sup>. The pan-HDAC inhibitor, belinostat (2014), is approved for the treatment of relapsed or refractory PTCL<sup>47</sup>. The pan-HDAC inhibitor, panobinostat (2015), is approved for the treatment of multiple myeloma in combination of bortezomib and dexamethasone having received at least 2 prior regimens<sup>48</sup>.

### PTPRT deletion

#### *protein tyrosine phosphatase, receptor type T*

**Background:** PTPRT encodes protein tyrosine phosphatase receptor type T, part of the protein tyrosine phosphatase (PTP) family which consists of 125 members<sup>1,2,3</sup>. PTPs are responsible for protein dephosphorylation of tyrosine residues and are involved in several cellular processes including proliferation, differentiation, adhesion, and survival<sup>4,5</sup>. Aberrant tyrosine phosphorylation resulting from PTP dysfunction has been linked to cancer progression<sup>4,5</sup>.

**Alterations and prevalence:** Somatic mutations in PTPRT are observed in 29% of skin cutaneous melanoma, 12% of stomach adenocarcinoma and uterine corpus endometrial carcinoma, 10% of colorectal adenocarcinoma and lung adenocarcinoma, 7% of esophageal adenocarcinoma and lung squamous cell carcinoma, 5% of uterine carcinosarcoma and bladder urothelial carcinoma, 4% of head and neck squamous cell carcinoma and cervical squamous cell carcinoma, 3% of glioblastoma multiforme and liver hepatocellular carcinoma, and 2% of diffuse large B-cell lymphoma, pancreatic adenocarcinoma, adrenocortical carcinoma, kidney renal clear cell carcinoma, and ovarian serous cystadenocarcinoma<sup>6,7</sup>. Biallelic loss of PTPRT is observed in about 1% of mesothelioma, prostate adenocarcinoma, and acute myeloid leukemia<sup>6,7</sup>.

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

## Genes Assayed

### Genes Assayed for the Detection of DNA Sequence Variants

ABL1, ABL2, ACVR1, AKT1, AKT2, AKT3, ALK, AR, ARAF, ATP1A1, AURKA, AURKB, AURKC, AXL, BCL2, BCL2L12, BCL6, BCR, BMP5, BRAF, BTK, CACNA1D, CARD11, CBL, CCND1, CCND2, CCND3, CCNE1, CD79B, CDK4, CDK6, CHD4, CSF1R, CTNNB1, CUL1, CYSLTR2, DDR2, DGCR8, DROSHA, E2F1, EGFR, EIF1AX, EPAS1, ERBB2, ERBB3, ERBB4, ESR1, EZH2, FAM135B, FGF7, FGFR1, FGFR2, FGFR3, FGFR4, FLT3, FLT4, FOXA1, FOXL2, FOXO1, GATA2, GLI1, GNA11, GNAQ, GNAS, HIF1A, HRAS, IDH1, IDH2, IKBKB, IL6ST, IL7R, IRF4, IRS4, KCNJ5, KDR, KIT, KLF4, KLF5, KNSTRN, KRAS, MAGOH, MAP2K1, MAP2K2, MAPK1, MAX, MDM4, MECOM, MED12, MEF2B, MET, MITF, MPL, MTOR, MYC, MYCN, MYD88, MYO1, NFE2L2, NRAS, NSD2, NT5C2, NTRK1, NTRK2, NTRK3, NUP93, PAX5, PCBP1, PDGFRA, PDGFRB, PIK3C2B, PIK3CA, PIK3CB, PIK3CD, PIK3CG, PIK3R2, PIM1, PLCG1, PPP2R1A, PPP6C, PRKACA, PTPN11, PTPRD, PXDNL, RAC1, RAF1, RARA, RET, RGS7, RHEB, RHOA, RICTOR, RIT1, ROS1, RPL10, SETBP1, SF3B1, SIX1, SIX2, 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    
 ① In this cancer type and other cancer types    
 × No evidence

### BRCA2 deletion

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
olaparib	×	○	×	×	● (II)
niraparib	×	○	×	×	×
rucaparib	×	○	×	×	×
pamiparib, tislelizumab	×	×	×	×	● (II)

### ATM deletion

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
olaparib	×	×	×	×	● (II)
pamiparib, tislelizumab	×	×	×	×	● (II)
senaparib, IMP-9064	×	×	×	×	● (I/II)

### CDKN2A deletion

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

### BAP1 deletion

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

### CDKN2B deletion

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

### CHEK1 deletion

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

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

Relevant Therapy Summary (continued)

In this cancer type

In other cancer type

In this cancer type and other cancer types

No evidence

CHEK2 deletion

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
pamiparib, tislelizumab	×	×	×	×	<div></div> (II)

PALB2 deletion

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
pamiparib, tislelizumab	×	×	×	×	<div></div> (II)

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

HRR Details

Gene/Genomic Alteration	Finding
LOH percentage	60.68%
BRCA2	CNV, CN:1.0
BRCA2	LOH, 13q13.1(32890491-32972932)x1
ATM	CNV, CN:1.0
ATM	LOH, 11q22.3(108098341-108236285)x1
CHEK1	CNV, CN:1.0
CHEK1	LOH, 11q24.2(125496639-125525271)x1
CHEK2	CNV, CN:1.0
CHEK2	LOH, 22q12.1(29083868-29130729)x1
PALB2	CNV, CN:1.0
PALB2	LOH, 16p12.2(23614759-23652528)x1
RAD51B	CNV, CN:1.0
RAD51B	LOH, 14q24.1(68290164-69061406)x1

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 2025.06(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](http://www.fda.gov) and is current as of 2025-05-14. NCCN information was sourced from [www.nccn.org](http://www.nccn.org) and is current as of 2025-05-01. EMA information was sourced from [www.ema.europa.eu](http://www.ema.europa.eu) and is current as of 2025-05-14. ESMO information was sourced from [www.esmo.org](http://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](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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