삼광의료재단
서울특별시 서초구 바우뫼로41길 58 (양재동, 선화빌딩)
검사기관 11365200
Tel. 1661-5117
www.smlab.co.kr



**Patient Name:** 김인덕
**Gender:** F
**Sample ID:** N25-320

**Primary Tumor Site:** Lung
**Collection Date:** 2025.11.12.

## Sample Cancer Type: Lung Cancer



### Report Highlights

15 Relevant Biomarkers
8 Therapies Available
54 Clinical Trials

## Relevant Lung Cancer Findings

| Gene | Finding | Gene | Finding |
|---|---|---|---|
| ALK | None detected | NTRK1 | None detected |
| BRAF | None detected | NTRK2 | None detected |
| EGFR | ***EGFR exon 20 insertion, EGFR amplification*** | NTRK3 | None detected |
| ERBB2 | None detected | RET | None detected |
| KRAS | None detected | ROS1 | None detected |
| MET | None detected | | |

| Genomic Alteration | Finding |
|---|---|
| Tumor Mutational Burden | ***0.95 Mut/Mb measured*** |

## Relevant Biomarkers

| Tier | Genomic Alteration | Relevant Therapies (In this cancer type) | Relevant Therapies (In other cancer type) | Clinical Trials |
|---|---|---|---|---|
| IA | *EGFR exon 20 insertion*<br>epidermal growth factor receptor<br>Allele Frequency: 55.97%<br>Locus: chr7:55249013<br>Transcript: NM_005228.5 | **amivantamab + chemotherapy** [1, 2 / I]<br>**amivantamab** [1, 2 / II+]<br>**sunvozertinib** [1 / II+]<br>**datopotamab deruxtecan-dlnk** [1]<br>mobocertinib [II+] | None* | 43 |
| IIC | *BRCA2 deletion*<br>BRCA2, DNA repair associated<br>Locus: chr13:32890491 | None* | niraparib [II+]<br>olaparib [II+]<br>rucaparib [II+] | 2 |
| IIC | *EGFR amplification*<br>epidermal growth factor receptor<br>Locus: chr7:55211010 | None* | None* | 7 |

*** Public data sources included in relevant therapies: FDA**[1], NCCN, **EMA**[2], ESMO
*** Public data sources included in prognostic and diagnostic significance:** NCCN, ESMO
**Line of therapy:** I: First-line therapy, II+: Other line of therapy
**Tier Reference:** Li et al. *Standards and Guidelines for the Interpretation and Reporting of Sequence Variants in Cancer: A Joint Consensus Recommendation of the Association for Molecular Pathology, American Society of Clinical Oncology, and College of American Pathologists.* J Mol Diagn. 2017 Jan;19(1):4-23.

## Relevant Biomarkers (continued)

| Tier | Genomic Alteration | Relevant Therapies (In this cancer type) | Relevant Therapies (In other cancer type) | Clinical Trials |
|---|---|---|---|---|
| IIC | *ATM deletion*<br>ATM serine/threonine kinase<br>Locus: chr11:108098341 | None* | None* | 4 |
| IIC | *AKT1 p.(L52R) c.155T>G*<br>AKT serine/threonine kinase 1<br>Allele Frequency: 3.75%<br>Locus: chr14:105246445<br>Transcript: NM_001014431.2 | None* | None* | 3 |
| IIC | *BRCA1 deletion*<br>BRCA1, DNA repair associated<br>Locus: chr17:41197602 | None* | None* | 2 |
| IIC | *BARD1 deletion*<br>BRCA1 associated RING domain 1<br>Locus: chr2:215593375 | None* | None* | 1 |
| IIC | *BRIP1 deletion*<br>BRCA1 interacting protein C-terminal helicase 1<br>Locus: chr17:59760627 | None* | None* | 1 |
| IIC | *CDK12 deletion*<br>cyclin dependent kinase 12<br>Locus: chr17:37618286 | None* | None* | 1 |
| IIC | *CHEK1 deletion*<br>checkpoint kinase 1<br>Locus: chr11:125496639 | None* | None* | 1 |
| IIC | *CHEK2 deletion*<br>checkpoint kinase 2<br>Locus: chr22:29083868 | None* | None* | 1 |
| IIC | *FANCL deletion*<br>Fanconi anemia complementation group L<br>Locus: chr2:58386886 | None* | None* | 1 |
| IIC | *PALB2 deletion*<br>partner and localizer of BRCA2<br>Locus: chr16:23614759 | None* | None* | 1 |
| IIC | *RAD51C deletion*<br>RAD51 paralog C<br>Locus: chr17:56769933 | None* | None* | 1 |
| IIC | *RAD51D deletion*<br>RAD51 paralog D<br>Locus: chr17:33427950 | None* | None* | 1 |

*** Public data sources included in relevant therapies: FDA**[1], NCCN, **EMA**[2], ESMO
*** Public data sources included in prognostic and diagnostic significance:** NCCN, ESMO
**Line of therapy:** I: First-line therapy, II+: Other line of therapy
**Tier Reference:** Li et al. *Standards and Guidelines for the Interpretation and Reporting of Sequence Variants in Cancer: A Joint Consensus Recommendation of the Association for Molecular Pathology, American Society of Clinical Oncology, and College of American Pathologists.* J Mol Diagn. 2017 Jan;19(1):4-23.

## Relevant Biomarkers (continued)

**Alerts informed by public data sources:** Contraindicated, Resistance, Breakthrough, Fast Track

*EGFR exon 20 insertion*

- **gefitinib** [2]
- afatinib, dacomitinib, erlotinib, gefitinib
- **zipalertinib** [1]

**Public data sources included in alerts: FDA**[1], NCCN, **EMA**[2], ESMO

**Prevalent cancer biomarkers without relevant evidence based on included data sources**

*GNAS amplification, Microsatellite stable, RAD51B deletion, RAD52 deletion, RNASEH2A deletion, TP53 p.(R337L) c.1010G>T, CASP8 p.(F26Pfs*9) c.74_75dup, HLA-B deletion, CSMD3 deletion, TPP2 deletion, NQO1 p.(P187S) c.559C>T, ZNF429 amplification, Tumor Mutational Burden*

## Variant Details

### DNA Sequence Variants

| Gene | Amino Acid Change | Coding | Variant ID | Locus | Allele Frequency | Transcript | Variant Effect |
|---|---|---|---|---|---|---|---|
| EGFR | p.(S768_D770dup) | c.2311_2312insGCGTGGATA | . | chr7:55249013 | 55.97% | NM_005228.5 | nonframeshift Insertion |
| AKT1 | p.(L52R) | c.155T>G | COSM93893 | chr14:105246445 | 3.75% | NM_001014431.2 | missense |
| TP53 | p.(R337L) | c.1010G>T | . | chr17:7574017 | 31.93% | NM_000546.6 | missense |
| CASP8 | p.(F26Pfs*9) | c.74_75dup | . | chr2:202123024 | 42.39% | NM_001080125.2 | frameshift Insertion |
| NQO1 | p.(P187S) | c.559C>T | . | chr16:69745145 | 99.20% | NM_000903.3 | missense |

### Copy Number Variations

| Gene | Locus | Copy Number | CNV Ratio |
|---|---|---|---|
| BRCA2 | chr13:32890491 | 1 | 0.81 |
| EGFR | chr7:55211010 | 5.22 | 1.74 |
| ATM | chr11:108098341 | 1 | 0.81 |
| BRCA1 | chr17:41197602 | 1 | 0.95 |
| BARD1 | chr2:215593375 | 1 | 0.91 |
| BRIP1 | chr17:59760627 | 1 | 0.92 |
| CDK12 | chr17:37618286 | 1 | 0.91 |
| CHEK1 | chr11:125496639 | 1 | 0.83 |
| CHEK2 | chr22:29083868 | 1 | 0.89 |
| FANCL | chr2:58386886 | 1 | 0.89 |
| PALB2 | chr16:23614759 | 1 | 0.94 |
| RAD51C | chr17:56769933 | 1 | 0.99 |
| RAD51D | chr17:33427950 | 1 | 0.98 |
| GNAS | chr20:57415551 | 15.37 | 4.07 |
| RAD51B | chr14:68290164 | 1 | 0.85 |

# Variant Details (continued)

## Copy Number Variations (continued)

| Gene | Locus | Copy Number | CNV Ratio |
|---|---|---|---|
| RAD52 | chr12:1022494 | 0.61 | 0.68 |
| RNASEH2A | chr19:12917452 | 0.43 | 0.64 |
| HLA-B | chr6:31322252 | 0.22 | 0.59 |
| CSMD3 | chr8:113237020 | 0.2 | 0.59 |
| TPP2 | chr13:103249399 | 0.57 | 0.67 |
| ZNF429 | chr19:21688488 | 9.83 | 2.8 |
| FGFR3 | chr4:1801456 | 0.37 | 0.63 |
| FAM135B | chr8:139144776 | 0.65 | 0.69 |
| ETV6 | chr12:11803059 | 6.11 | 1.95 |
| KEAP1 | chr19:10597314 | 4.74 | 1.63 |

# Biomarker Descriptions

**EGFR amplification, EGFR exon 20 insertion**

*epidermal growth factor receptor*

Background: The EGFR gene encodes the epidermal growth factor receptor (EGFR), a member of the ERBB/human epidermal growth factor receptor (HER) tyrosine kinase family[1]. In addition to EGFR/ERBB1/HER1, other members of the ERBB/HER family include ERBB2/HER2, ERBB3/HER3, and ERBB4/HER4[108]. EGFR ligand-induced dimerization results in kinase activation and leads to stimulation of oncogenic signaling pathways, including the PI3K/AKT/MTOR and RAS/RAF/MEK/ERK pathways[109]. Activation of these pathways promotes cell proliferation, differentiation, and survival[110,111].

Alterations and prevalence: Recurrent somatic mutations in the tyrosine kinase domain (TKD) of EGFR are observed in approximately 10-20% of lung adenocarcinoma, and at higher frequencies in never-smoker, female, and Asian populations[5,6,112,113]. The most common mutations occur near the ATP-binding pocket of the TKD and include short in-frame deletions in exon 19 (EGFR exon 19 deletion) and the L858R amino acid substitution in exon 21[114]. These mutations constitutively activate EGFR resulting in downstream signaling, and represent 80% of the EGFR mutations observed in lung cancer[114]. A second group of less prevalent activating mutations includes E709K, G719X, S768I, L861Q, and short in-frame insertion mutations in exon 20[115,116,117,118]. EGFR activating mutations in lung cancer tend to be mutually exclusive to KRAS activating mutations[119]. In contrast, a different set of recurrent activating EGFR mutations in the extracellular domain includes R108K, A289V and G598V and are primarily observed in glioblastoma[114,120]. Amplification of EGFR is observed in several cancer types including 44% of glioblastoma multiforme, 12% of esophageal adenocarcinoma, 10% of head and neck squamous cell carcinoma, 8% of brain lower grade glioma, 6% of lung squamous cell carcinoma, 5% of bladder urothelial carcinoma cancer, lung adenocarcinoma, and stomach adenocarcinoma, 3% of cholangiocarcinoma, and 2% of cervical squamous cell carcinoma, sarcoma, and breast invasive carcinoma[5,6,113,120,121]. Deletion of exons 2-7, encoding the extracellular domain of EGFR (EGFRvIII), results in overexpression of a ligand-independent constitutively active protein and is observed in approximately 30% of glioblastoma[122,123,124]. Alterations in EGFR are rare in pediatric cancers[5,6]. Somatic mutations are observed in 2% of bone cancer and glioma, 1% of leukemia (4 in 354 cases), and less than 1% of B-lymphoblastic leukemia/lymphoma (2 in 252 cases), peripheral nervous system cancers (1 in 1158 cases), and embryonal tumors (3 in 332 cases)[5,6]. Amplification of EGFR is observed in 2% of bone cancer and less than 1% of Wilms tumor (1 in 136 cases), B-lymphoblastic leukemia/lymphoma (2 in 731 cases), and leukemia (1 in 250 cases)[5,6].

Potential relevance: Approved first-generation EGFR tyrosine kinase inhibitors (TKIs) include erlotinib[125] (2004) and gefitinib[126] (2015), which block the activation of downstream signaling by reversible interaction with the ATP-binding site. Although initially approved for advanced lung cancer, the discovery that drug sensitivity was associated with exon 19 and exon 21 activating mutations allowed first-generation TKIs to become subsequently approved for front-line therapy in lung cancer tumors containing exon 19 or exon 21 activating mutations[127]. Second-generation TKIs afatinib[128] (2013) and dacomitinib[129] (2018) bind EGFR and other ERBB/HER gene family members irreversibly and were subsequently approved. First- and second-generation TKIs afatinib, dacomitinib, erlotinib, and gefitinib are recommended for the treatment NSCLC harboring EGFR exon 19 insertions, exon 19 deletions, point mutations L861Q, L858R, S768I, and codon 719 mutations, whereas most EGFR exon 20 insertions, except p.A763_Y764insFQEA, confer resistance

## Biomarker Descriptions (continued)

to the same therapies[130,131,132,133]. In 2025, the FDA approved the irreversible EGFR inhibitor, sunvozertinib[134], for the treatment of locally advanced or metastatic non-small cell lung cancer in adult patients with EGFR exon 20 insertion mutations whose disease has progressed on or after platinum-based chemotherapy. In 2022, the FDA granted breakthrough therapy designation to the irreversible EGFR inhibitor, CLN-081 (TPC-064)[135] for locally advanced or metastatic non-small cell lung cancer harboring EGFR exon 20 insertion mutations. In lung cancer containing EGFR exon 19 or 21 activating mutations, treatment with TKIs is eventually associated with the emergence of drug resistance[136]. The primary resistance mutation that emerges following treatment with first-generation TKI is T790M, accounting for 50-60% of resistant cases[114]. Third generation TKIs were developed to maintain sensitivity in the presence of T790M[136]. Osimertinib[137] (2015) is an irreversible inhibitor indicated for metastatic EGFR T790M positive lung cancer and for the first-line treatment of metastatic NSCLC containing EGFR exon 19 deletions or exon 21 L858R mutations. Like first-generation TKIs, treatment with osimertinib is associated with acquired resistance, specifically the C797S mutation, which occurs in 22-44% of cases[136]. The T790M and C797S mutations may be each selected following sequential treatment with a first-generation TKI followed by a third-generation TKI or vice versa[138]. T790M and C797S can occur in either cis or trans allelic orientation[138]. If C797S is observed following progression after treatment with a third-generation TKI in the first-line setting, sensitivity may be retained to first-generation TKIs[138]. If C797S co-occurs in trans with T790M following sequential treatment with first- and third-generation TKIs, patients may exhibit sensitivity to combination first- and third-generation TKIs, but resistance to third-generation TKIs alone[138,139]. However, C797S occurring in cis conformation with T790M, confers resistance to first- and third-generation TKIs[138]. Fourth-generation TKIs are in development to overcome acquired resistance mutations after osimertinib treatment, including BDTX-1535[140] (2024), a CNS-penetrating small molecule inhibitor, that received fast track designation from the FDA for the treatment of patients with EGFR C797S-positive NSCLC who have disease progression on or after a third-generation EGFR TKI. EGFR-targeting antibodies including cetuximab (2004), panitumumab (2006), and necitumumab (2016) are under investigation in combination with EGFR-targeting TKIs for efficacy against EGFR mutations[141]. The bispecific antibody, amivantamab[142] (2021), targeting EGFR and MET was approved for NSCLC tumors harboring EGFR exon 20 insertion mutations. A small molecule kinase inhibitor, lazertinib[143] (2024), was approved in combination with amivantamab as a first-line treatment for adult patients with locally advanced or metastatic NSCLC with EGFR exon 19 deletions or exon 21 L858R mutations. HLX-42[144], an anti-EFGR-antibody-drug conjugate (ADC) consisting of an anti-EGFR monoclonal antibody conjugated with a novel high potency DNA topoisomerase I (topo I) inhibitor, also received fast track designation (2024) for the treatment of patients with advanced or metastatic EGFR-mutated non-small cell lung cancer whose disease has progressed on a third-generation EGFR tyrosine kinase inhibitor. CPO301[145] (2023) received a fast track designation from the FDA for the treatment of EGFR mutations in patients with metastatic NSCLC who are relapsed/refractory or ineligible for EGFR targeting therapy such as 3rd-generation EGFR inhibitors, including osimertinib. The Oncoprex immunogene therapy quaratusugene ozeplasmid[146] (2020), in combination with osimertinib, received fast track designation from the FDA for NSCLC tumors harboring EGFR mutations that progressed on osimertinib alone. Amplification and mutations of EGFR commonly occur in H3-wild type IDH-wild type diffuse pediatric high-grade glioma[147,148,149].

**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[18,19]. Specifically, BRCA1/2 are required for repair of chromosomal double strand breaks (DSBs) which are highly unstable and compromise genome integrity[18,19]. 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[20,21,22]. 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%[20,23].

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[24,25,26,27,28,29,30,31]. 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[5,6].

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)[32]. Inhibitors targeting PARP induce synthetic lethality in recombination deficient BRCA1/2 mutant cells[33,34]. Consequently, several PARP inhibitors have been FDA approved for BRCA1/2-mutated cancers. Olaparib[15] (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[15] is approved

## Biomarker Descriptions (continued)

(2020) for metastatic castration-resistant prostate cancer (mCRPC) with deleterious or suspected deleterious, germline or somatic mutations in HRR genes that includes BRCA2. Rucaparib[35] is also approved (2020) for deleterious gBRCAm or sBRCAm mCRPC and ovarian cancer. Talazoparib[36] (2018) is indicated for the treatment of gBRCAm HER2-negative locally advanced or metastatic breast cancer. Additionally, talazoparib[36] in combination with enzalutamide is approved (2023) for metastatic castration-resistant prostate cancer (mCRPC) with mutations in HRR genes that includes BRCA2. Niraparib[37] (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[38] 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[39]. One of the most common mechanisms of resistance includes secondary intragenic mutations that restore BRCA1/2 functionality[40]. 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[17], 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.

**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)[48]. 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[49]. ATM is recruited to the DNA damage site by the MRE11/RAD50/NBN (MRN) complex that senses DSB[49,50]. Upon activation, ATM phosphorylates several downstream proteins such as the NBN, MDC1, BRCA1, CHK2 and TP53BP1 proteins[51]. 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[11,52]. 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[53].

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[5,6].

Potential relevance: The PARP inhibitor, olaparib[15] 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[36] 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[52,54,55]. 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[56]. In 2022, the FDA granted fast track designation to the small molecule inhibitor, pidnarulex[17], for BRCA1/2, PALB2, or other homologous recombination deficiency (HRD) mutations in breast and ovarian cancers.

**AKT1 p.(L52R) c.155T>G**

*AKT serine/threonine kinase 1*

Background: The AKT1 gene encodes Protein Kinase B, a serine/threonine kinase, that belongs to a family of closely related protein kinases that also includes AKT2 and AKT3. Growth factor signaling leads to the activation of phosphatidylinositol 3-kinase (PI3K), recruitment of AKT to the plasma membrane, and subsequent activation of downstream effectors including MTOR. The PI3K/AKT/MTOR pathway is central to the regulation of cancer cell proliferation, survival, and metabolism[206,207].

Alterations and prevalence: AKT1 encodes a proto-oncogene that is the target of recurrent somatic mutations in cancer[208]. The most common recurrent mutation is E17K, which is located in the N-terminal pleckstrin homology (PH) domain. E17K is a gain-of-function activating mutation that constitutively targets AKT1 to the plasma membrane and leads to downstream signaling[209,210]. Other recurrent activating mutations include L52H, Q79K, and D323Y/G/N, which disrupt negative regulatory interactions between the PH domain and the kinase domain[211]. AKT1 mutations in cancer are common in breast and endometrial cancers, where they occur at a prevalence of 2-5%[5]. AKT1 mutations are observed at a prevalence of 1-2% in bladder, colorectal, melanoma, and thyroid cancers[5,6]. AKT1 is overexpressed via gene amplification in ovarian cancer, lung squamous cell cancer, and sarcoma at a prevalence of 2-5%[5,6].

Potential relevance: Currently no therapies are approved for AKT1 aberrations. However, in the phase II NCI-MATCH trial, the pan-AKT inhibitor capivasertib (AZD5363) demonstrated a partial response in 23% (8/35) of AKT1 E17K mutated solid tumor patients[212]. Results from a phase I clinical trial of capivasertib demonstrated partial responses in 9/52 heavily pre-treated patients with AKT1

## Biomarker Descriptions (continued)

E17K mutated solid tumors, with a median progression-free survival (PFS) of 5.5 months in ER positive breast cancer, 6.6 months in gynecologic cancers, and 4.2 months in other solid tumors[213]. In the same phase I study, an ovarian cancer patient with an AKT1 Q79K mutation demonstrated stable disease lasting 14 months[213].

**BRCA1 deletion**

*BRCA1, DNA repair associated*

Background: The breast cancer early onset gene 1 (BRCA1) 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[18,19]. Specifically, BRCA1/2 are required for the repair of chromosomal double strand breaks (DSBs) which are highly unstable and compromise genome integrity[18,19]. 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[20,21,22]. 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%[20,23].

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[24,25,26,27,28,29,30,31]. Somatic alterations in BRCA1 are observed in 5-10% of uterine corpus endometrial carcinoma, cutaneous melanoma, bladder urothelial carcinoma, diffuse large B-cell lymphoma, and cervical squamous cell carcinoma, 3-4% of lung squamous cell carcinoma, lung adenocarcinoma, stomach adenocarcinoma, ovarian serous cystadenocarcinoma, colorectal adenocarcinoma, and breast invasive carcinoma, and 2% of head and neck squamous cell carcinoma and glioblastoma multiforme[5,6].

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)[32]. Inhibitors targeting PARP induce synthetic lethality in recombination deficient BRCA1/2 mutant cells[33,34]. Consequently, several PARP inhibitors have been FDA approved for BRCA1/2-mutated cancers. Olaparib[15] (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[15] is approved (2020) for metastatic castration-resistant prostate cancer (mCRPC) with deleterious or suspected deleterious, germline or somatic mutations in HRR genes that includes BRCA1. Rucaparib[35] is also approved (2020) for deleterious gBRCAm or sBRCAm mCRPC and ovarian cancer. Talazoparib[36] (2018) is indicated for the treatment of gBRCAm HER2-negative locally advanced or metastatic breast cancer. Additionally, talazoparib[36] in combination with enzalutamide is approved (2023) for metastatic castration-resistant prostate cancer (mCRPC) with mutations in HRR genes that includes BRCA1. Niraparib[37] (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[38] 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[39]. One of the most common mechanisms of resistance includes secondary intragenic mutations that restore BRCA1/2 functionality[40]. 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[17], 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.

**BARD1 deletion**

*BRCA1 associated RING domain 1*

Background: The BARD1 gene encodes the BRCA1 associated RING domain 1 protein which binds to BRCA1 and contributes to the in vitro E3 ligase activity that is required for the tumor suppressor function of the BRCA1 gene[1,78]. The cysteine-rich N-terminal RING finger domains of BARD1 and BRCA1 heterodimerize to regulate a diverse range of cellular pathways, such as ubiquitination, transcriptional regulation, and homologous recombination repair (HRR) of double-stranded DNA damage[1,78,79,80]. Mutual stability between BARD1 and BRCA1 is essential in maintaining HRR functionality. Genetic alterations in either BARD1 or BRCA1 can disrupt the BARD1/BRCA1 interaction[1,79,81,82]. BARD1 is a tumor suppressor and loss of function (LOF) mutations are implicated in the BRCAness phenotype, which is characterized by a defect in HRR mimicking BRCA1 or BRCA2 loss[82,83]. Copy number deletion, nonsense or frameshift mutations attributed to BARD1 LOF and are associated with familial breast cancer susceptibility[81]. Independent of BRCA1, BARD1 acts as a mediator of apoptosis by binding to p53[84]. Specifically, the BARD1 Q564H germline mutation is associated with a decrease in pro-apoptotic activity and implicated in cases of breast and endometrial cancer[84,85].

## Biomarker Descriptions (continued)

Alterations and prevalence: Somatic mutations in BARD1 are found in 5% of uterine cancer, 3% of stomach cancer as well as melanoma, and 2% of bladder cancer as well as lung adenocarcinoma[5,6]. BARD1 copy number loss is observed in 2% of mesothelioma, head and neck cancer, and esophageal cancer[5,6].

Potential relevance: The PARP inhibitor, olaparib[15] is approved (2020) for metastatic castration-resistant prostate cancer (mCRPC) with deleterious or suspected deleterious, germline or somatic mutations in HRR genes that includes BARD1. In 2022, the FDA granted fast track designation to the small molecule inhibitor, pidnarulex[17], for BRCA1/2, PALB2, or other homologous recombination deficiency (HRD) mutations in breast and ovarian cancers.

**BRIP1 deletion**

*BRCA1 interacting protein C-terminal helicase 1*

Background: The BRIP1 gene encodes the BRCA1 interacting protein C-terminal helicase 1 and is a member of the RecQ DEAH helicase family that plays a role in homologous recombination repair (HRR) of double-stranded breaks (DSBs) in DNA[73]. BRIP1 interacts directly with BRCA1 through the BRCT domain and controls BRCA1-dependent DNA repair and the DNA damage-induced G2-M checkpoint control[74]. BRIP1 is a tumor suppressor gene. Loss of function mutations in BRIP1 are implicated in the BRCAness phenotype, characterized by a defect in HRR, mimicking BRCA1 or BRCA2 loss[11,52]. Germline aberrations in BRIP1 are associated with inherited disorders such as Fanconi anemia (FA)[75]. Specifically, BRIP1 was shown to be biallelically inactivated in FA patients and is also considered a high-risk gene for familial late-onset ovarian cancer[75,76]. BRIP1 germline mutations confer ~ 10% cumulative risk of ovarian cancer and are associated with an increased risk of colorectal cancer[73,77].

Alterations and prevalence: Somatic mutations in BRIP1 are observed in up to 8% of uterine corpus endometrial carcinoma, 5% of skin cutaneous melanoma, and 4% of bladder urothelial carcinoma[5,6].

Potential relevance: The PARP inhibitor, olaparib[15] is approved (2020) for metastatic castration-resistant prostate cancer (mCRPC) with deleterious or suspected deleterious, germline or somatic mutations in HRR genes that includes BRIP1. Consistent with other genes associated with the BRCAness phenotype, BRIP1 mutations may aid in selecting patients likely to respond to PARP inhibitors or platinum therapy[52,55]. In 2022, the FDA granted fast track designation to the small molecule inhibitor, pidnarulex[17], for BRCA1/2, PALB2, or other homologous recombination deficiency (HRD) mutations in breast and ovarian cancers.

**CDK12 deletion**

*cyclin dependent kinase 12*

Background: CDK12 encodes the cyclin-dependent kinase 12 protein and is required for the maintenance of genomic stability[180,181,182]. CDK12 phosphorylates RNA polymerase II and is a regulator of transcription elongation and expression of DNA repair genes[11,180,181,182,183]. Alterations in CDK12 impair the transcription of homologous recombination repair (HRR) genes such as BRCA1, ATR, FANCI, and FANCD2, contributing to a BRCAness phenotype[11,182]. CDK12 is a tumor suppressor gene and loss of function mutations are observed in various solid tumors[183]. However, observations of CDK12 amplification and overexpression in breast cancer indicate that it could also function as an oncogene[183].

Alterations and prevalence: Somatic alterations of CDK12 include mutations and amplification. Missense and truncating mutations in CDK12 are observed in 8% of undifferentiated stomach adenocarcinoma, 7% of bladder urothelial, and 6% endometrial carcinoma[1,5]. CDK12 is amplified in 9% of esophagogastric adenocarcinoma and invasive breast carcinoma, 8% of undifferentiated stomach adenocarcinoma, and 3% of bladder urothelial and endometrial carcinoma[1,5].

Potential relevance: The PARP inhibitor, olaparib[15] is approved (2020) for metastatic castration-resistant prostate cancer (mCRPC) with deleterious or suspected deleterious, germline or somatic mutations in HRR genes that includes CDK12. Additionally, talazoparib[36] in combination with enzalutamide is approved (2023) for mCRPC with mutations in HRR genes that includes CDK12. Consistent with other genes associated with homologous recombination repair, CDK12 loss may aid in selecting patients likely to respond to PARP inhibitors[11,183]. In 2022, the FDA granted fast track designation to the small molecule inhibitor, pidnarulex[17], for BRCA1/2, PALB2, or other homologous recombination deficiency (HRD) mutations in breast and ovarian cancers.

**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[1]. Checkpoint kinases play an important role in S phase and G2/M transition and DNA damage induced cell cycle arrest[176]. 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)[157,177]. Upon DNA damage, CHEK1 is phosphorylated and activated by

## Biomarker Descriptions (continued)

DNA damage repair proteins ATM and ATR[177]. Activated CHEK1 subsequently phosphorylates and negatively regulates downstream proteins such as CDC25A thereby slowing or stalling DNA replication[177,178].

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[5,179]. 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[5,179].

Potential relevance: The PARP inhibitor, olaparib[15] 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[17], 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[154]. 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)[155,156,157]. Germline mutations in the CHEK2 gene are associated with Li-Fraumeni syndrome and inherited risk of breast cancer[158,159,160].

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[5,6]. CHEK2 gene deletions are observed in adrenocortical carcinoma, thymoma, and prostate cancer[5,6].

Potential relevance: The PARP inhibitor, olaparib[15] 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[36] 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[17], for BRCA1/2, PALB2, or other homologous recombination deficiency (HRD) mutations in breast and ovarian cancers.

**FANCL deletion**

*Fanconi anemia complementation group L*

Background: The FANCL gene encodes the FA complementation group L protein, a member of Fanconi Anemia (FA) family, which also includes FANCA, FANCB, FANCC, FANCD1 (BRCA2), FANCD2, FANCE, FANCF, FANCG, FANCI, FANCJ (BRIP1), FANCM and FANCN (PALB2)[1]. FA genes are tumor suppressors that are responsible for the maintenance of replication fork stability, DNA damage repair through the removal of interstrand cross-links (ICL), and subsequent initiation of the homologous recombination repair (HRR) pathway[7,8]. In response to DNA damage, FANCA, FANCB, FANCC, FANCE, FANCF, FANCG, FANCL, and FANCM assemble to form the FA core complex which is responsible for the monoubiquitination of the FANCI-FANCD2 (ID2) complex[7]. Monoubiquitination of the ID2 complex promotes co-localization with BRCA1/2, which is critical in BRCA mediated DNA repair[9,10]. Loss of function mutations in the FA family and HRR pathway can result in the BRCAness phenotype, characterized by a defect in the HRR pathway, mimicking BRCA1 or BRCA2 loss[11,12]. 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[13,14].

Alterations and prevalence: Somatic mutations in FANCL are observed in 2% of diffuse large B-cell lymphoma (DLBCL), uterine corpus endometrial carcinoma, colorectal adenocarcinoma, and cervical squamous cell carcinoma, and 1% of skin cutaneous melanoma, uveal melanoma, lung squamous cell carcinoma, bladder urothelial carcinoma and stomach adenocarcinoma[5,6].

Potential relevance: The PARP inhibitor, olaparib[15] is approved (2020) for metastatic castration-resistant prostate cancer (mCRPC) with deleterious or suspected deleterious germline or somatic mutations in HRR genes, including FANCL. Inhibitors targeting PARP induce synthetic lethality in HRR deficient cells[16]. In 2022, the FDA granted fast track designation to the small molecule inhibitor, pidnarulex[17], 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[67]. Also known as FANCN, PALB2 belongs to the Fanconi Anemia (FA)

## Biomarker Descriptions (continued)

complementation group of proteins that also include FANCA, FANCB, FANCC, FANCD1 (BRCA2), FANCD2, FANCE, FANCF, FANCG, FANCI, FANCJ (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)[7]. 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[11,12]. 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[13,14]. Specifically, biallelic germline mutations resulting in PALB2 loss of function confer a predisposition to pediatric malignancies[68,69]. Additionally, monoallelic germline mutations in PALB2 have been associated with an increased risk of developing breast cancer[68,70].

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[5].

Potential relevance: The PARP inhibitor, olaparib[15] 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[36] 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[56,71]. 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[40,71]. In 2022, the FDA granted fast track designation to the small molecule inhibitor, pidnarulex[17], 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[72].

**RAD51C deletion**

*RAD51 paralog C*

Background: The RAD51C gene encodes the RAD51 paralog C protein, a member of the RAD51 recombinase family that also includes RAD51, RAD51B (RAD51L1), RAD51D (RAD51L3), XRCC2, and XRCC3 paralogs[57]. The RAD51 family proteins are involved in homologous recombination repair (HRR) and DNA repair of double strand breaks (DSB)[58]. RAD51C associates with other RAD51 paralogs to form two distinct complexes, namely RAD51B-RAD51C-RAD51D-XRCC2 (BCDX2) and RAD51C-XRCC3 (CX3)[59]. The BCDX2 complex binds single- and double-stranded DNA to hydrolyze ATP, whereas the CX3 complex is involved in homologous pairing[60]. RAD51C is also involved in checkpoint activation by CHEK2 and in maintaining centrosome integrity[61,62]. RAD51C is a tumor suppressor gene and loss of function mutations in RAD51C are implicated in the BRCAness phenotype, characterized by a defect in HRR mimicking BRCA1 or BRCA2 loss[11,52].

Alterations and prevalence: Somatic mutations in RAD51C are observed in 1-3% of adrenocortical carcinoma, melanoma, squamous lung, bladder, and uterine cancers[5].

Potential relevance: The PARP inhibitor, olaparib[15] is approved (2020) for metastatic castration-resistant prostate cancer (mCRPC) with deleterious or suspected deleterious, germline or somatic mutations in HRR genes that includes RAD51C. Additionally, talazoparib[36] in combination with enzalutamide is approved (2023) for mCRPC with mutations in HRR genes that includes RAD51C. In one study, RAD51C underexpression was observed in olaparib-sensitive gastric cancer cell lines, and olaparib treatment sensitized cells to irradiation[63]. In 2022, the FDA granted fast track designation to the small molecule inhibitor, pidnarulex[17], for BRCA1/2, PALB2, or other homologous recombination deficiency (HRD) mutations in breast and ovarian cancers.

**RAD51D deletion**

*RAD51 paralog D*

Background: The RAD51D gene encodes the RAD51 paralog D protein, a member of the RAD51 recombinase family that also includes RAD51, RAD51B (RAD51L1), RAD51C (RAD51L2), XRCC2, and XRCC3 paralogs. The RAD51 family proteins are involved in homologous recombination repair (HRR) and DNA repair of double-strand breaks (DSB)[58]. RAD51D associates with other RAD51 paralogs to form RAD51B-RAD51C-RAD51D-XRCC2 (BCDX2) complex[59]. The BCDX2 complex binds single- and double-stranded DNA to hydrolyze ATP[60]. RAD51D is a tumor suppressor gene. Loss of function mutations in RAD51D are implicated in the BRCAness phenotype, which is characterized by a defect in HRR, mimicking BRCA1 or BRCA2 loss[11,52]. Germline point mutations in RAD51D are implicated in non-BRCA2 associated breast, ovarian, and colorectal cancer[64].

Alterations and prevalence: Somatic mutations in RAD51D are rare but have been reported in 1-2% of uterine cancer[5].

Potential relevance: The PARP inhibitor, olaparib[15] is approved (2020) for metastatic castration-resistant prostate cancer (mCRPC) with deleterious or suspected deleterious, germline or somatic mutations in HRR genes that includes RAD51D. Additionally, consistent with other genes associated with the BRCAness phenotype, RAD51D mutations may aid in selecting patients likely to respond to PARP

## Biomarker Descriptions (continued)

inhibitors[52]. In 2022, the FDA granted fast track designation to the small molecule inhibitor, pidnarulex[17], for BRCA1/2, PALB2, or other homologous recombination deficiency (HRD) mutations in breast and ovarian cancers.

**GNAS amplification**

*GNAS complex locus*

Background: GNAS encodes the stimulatory alpha subunit of the guanine nucleotide-binding protein (G-protein). G-protein alpha subunits bind guanine nucleotide, hydrolyze GTP, and interact with specific receptor and effector molecules. GNAS links receptor-ligand interactions with the activation of adenylyl cyclase and a variety of cellular responses.

Alterations and prevalence: Recurrent somatic mutations at amino acid positions R201 and Q227 lead to constitutive activation of GNAS and are observed in pancreatic cancer (3%) as well as lung adenocarcinoma, colorectal, and gastric cancers (approximately 1%)[5,6,150,151]. In colorectal cancer, GNAS mutations were enriched in right-sided tumors[152]. In lung adenocarcinoma, GNAS mutations were enriched in female patients with invasive mucinous adenocarcinoma[151]. Specifically, GNAS mutations in these patients were exclusively observed at R201C/H, along with concurrent mutations in KRAS or BRAF.[151].

Potential relevance: Currently, no therapies are approved for GNAS aberrations. A case study of a patient with appendiceal adenocarcinoma harboring a GNAS R201H mutation reported a progression-free survival (PFS) of 4 months when treated with the MEK inhibitor trametinib[153].

**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[86]. Microsatellite instability (MSI) is defined as a change in the length of a microsatellite in a tumor as compared to normal tissue[87,88]. 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[89]. 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[90]. 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)[90]. Tumors classified as MSI-L are often phenotypically indistinguishable from MSS tumors and tend to be grouped with MSS[91,92,93,94,95]. MSI-H is a hallmark of Lynch syndrome (LS), also known as hereditary non-polyposis colorectal cancer, which is caused by germline mutations in the MMR genes[88]. LS is associated with an increased risk of developing colorectal cancer, as well as other cancers, including endometrial and stomach cancer[87,88,92,96].

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[87,88,97,98]. 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[97,98].

Potential relevance: Anti-PD-1 immune checkpoint inhibitors including pembrolizumab[99] (2014) and nivolumab[100] (2015) are approved for patients with MSI-H or dMMR colorectal cancer who have progressed following chemotherapy. Pembrolizumab[99] 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[99]. Dostarlimab[101] (2021) is also approved for dMMR recurrent or advanced endometrial carcinoma or solid tumors that have progressed on prior treatment and is recommended as a subsequent therapy option in dMMR/MSI-H advanced or metastatic colon or rectal cancer[93,102]. The cytotoxic T-lymphocyte antigen 4 (CTLA-4) blocking antibody, ipilimumab[103] (2011), is approved alone or in combination with nivolumab in MSI-H or dMMR colorectal cancer that has progressed following treatment with chemotherapy. MSI-H may confer a favorable prognosis in colorectal cancer although outcomes vary depending on stage and tumor location[93,104,105]. 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[105]. 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[106,107]. However, checkpoint blockade with the addition of chemotherapy or targeted therapies have demonstrated response in MSS or pMMR cancers[106,107].

**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)[58]. RAD51B associates with other RAD51

## Biomarker Descriptions (continued)

paralogs to form RAD51B-RAD51C-RAD51D-XRCC2 (BCDX2) complex[59]. The BCDX2 complex binds single- and double-stranded DNA to hydrolyze ATP[60]. 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[11,52]. 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[65]. Genetic variation within the RAD51B locus on 14q24.1 is significantly associated with familial breast cancer risk[66].

Alterations and prevalence: Somatic mutations in RAD51B are observed in up to 3% of uterine cancer[5,6]. Loss of function mutations in RAD51B are rare, but variation within the RAD51B locus is significantly associated with familial breast cancer risk[66].

Potential relevance: The PARP inhibitor, olaparib[15] 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[17], for BRCA1/2, PALB2, or other homologous recombination deficiency (HRD) mutations in breast and ovarian cancers.

**RAD52 deletion**

*RAD52 homolog, DNA repair protein*

Background: The RAD52 gene encodes the RAD52 homolog, DNA repair protein[1]. RAD52 binds to single- and double-stranded DNA and enables strand exchange for double-strand break (DSB) repair by binding to RAD51[161]. RAD52 also promotes DSB repair through homologous recombination repair (HRR) by recruiting BRCA1 to sites of DSBs, which leads to the removal of TP53BP1 and prevents DSB repair by non-homologous end joining (NHEJ)[162].

Alterations and prevalence: Somatic mutations in RAD52 are observed in 2% of uterine corpus endometrial carcinoma, uterine carcinosarcoma, and skin cutaneous melanoma[5,6].

Potential relevance: Currently, no therapies are approved for RAD52 aberrations.

**RNASEH2A deletion**

*ribonuclease H2 subunit A*

Background: The RNASEH2A gene encodes the ribonuclease H2 subunit A protein[1]. RNASEH2A functions as the catalytic subunit of the RNase H2 holoenzyme along with the auxiliary RNASEH2B and RNASEH2C subunits[163,164]. RNase H2 removes ribonucleotides that have been misincorporated in DNA, and also degrades DNA:RNA hybrids formed during transcription[163]. Specifically, RNase H2 interacts with BRCA1 for DNA:RNA hybrid resolution at double-strand breaks (DSBs) through homologous recombination repair (HRR)[163]. Although deregulation of RNASEH2A expression has been observed in multiple cancer types, its role in oncogenesis is unclear[165].

Alterations and prevalence: Somatic mutations in RNASEH2A are observed in 2% of uterine corpus endometrial carcinoma, skin cutaneous melanoma, and kidney chromophobe[5,6].

Potential relevance: Currently, no therapies are approved for RNASEH2A aberrations.

**TP53 p.(R337L) c.1010G>T**

*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[1]. In unstressed cells, TP53 is kept inactive by targeted degradation via MDM2, a substrate recognition factor for ubiquitin-dependent proteolysis[184]. Alterations in TP53 are required for oncogenesis as they result in loss of protein function and gain of transforming potential[185]. Germline mutations in TP53 are the underlying cause of Li-Fraumeni syndrome, a complex hereditary cancer predisposition disorder associated with early-onset cancers[186,187].

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%)[5,6,121,188,189,190]. 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[5,6]. Invariably, recurrent missense mutations in TP53 inactivate its ability to bind DNA and activate transcription of target genes[191,192,193,194]. Alterations in TP53 are also observed in pediatric cancers[5,6]. 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,

## Biomarker Descriptions (continued)

2% of T-lymphoblastic leukemia/lymphoma, and less than 1% of peripheral nervous system cancers (5 in 1158 cases )[5,6]. Biallelic loss of TP53 is observed in 10% of bone cancer, 2% of Wilms tumor, and less than 1% of B-lymphoblastic leukemia/lymphoma (2 in 731 cases) and leukemia (1 in 250 cases)[5,6].

Potential relevance: The small molecule p53 reactivator, PC14586[195] (2020), received a fast track designation by the FDA for advanced tumors harboring a TP53 Y220C mutation. In addition to investigational therapies aimed at restoring wild-type TP53 activity, compounds that induce synthetic lethality are also under clinical evaluation[196,197]. TP53 mutation are a diagnostic marker of SHH-activated, TP53-mutant medulloblastoma[198]. 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)[199,200,201,202,203]. In mantle cell lymphoma, TP53 mutations are associated with poor prognosis when treated with conventional therapy including hematopoietic cell transplant[204]. 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[205].

**CASP8 p.(F26Pfs*9) c.74_75dup**

*caspase 8*

Background: CASP8 encodes caspase 8, a member of the cysteine-aspartic acid protease (caspase) family consisting of inflammatory caspases and apoptotic caspases. Apoptotic caspases consist of initiator and effector caspases[1,166,167]. CASP8 functions as an initiator caspase and following external stimulation of death receptors, undergoes processing and activation leading to CASP8 mediated cleavage of downstream targets[168]. CASP8 propagates the extrinsic apoptotic pathway by direct cleavage of effector caspases such as CASP3 and activates the intrinsic apoptotic pathway by cleaving BID, a pro-apoptotic proximal substrate of CASP8, resulting in an amplification of the death-inducing signal[168,169]. Certain cancer types have decreased expression or inactivation of CASP8, which results in poor prognosis and metastasis[170,171].

Alterations and prevalence: Somatic mutations in CASP8 are observed in 11% head and neck squamous cell carcinoma, 10% uterine corpus endometrial carcinoma, 5% stomach adenocarcinoma, 4% cervical squamous cell carcinoma, colorectal adenocarcinoma, and bladder urothelial carcinoma, 3% skin cutaneous melanoma, and 2% diffuse large B-cell lymphoma, lung squamous cell carcinoma, uterine carcinosarcoma, and breast invasive carcinoma[5,6]. Biallelic loss of CASP8 is observed in 2% bladder urothelial carcinoma[5,6].

Potential relevance: Currently, no therapies are approved for CASP8 aberrations.

**HLA-B deletion**

*major histocompatibility complex, class I, B*

Background: The HLA-B gene encodes the major histocompatibility complex, class I, B[1]. MHC (major histocompatibility complex) class I molecules are located on the cell surface of nucleated cells and present antigens from within the cell for recognition by cytotoxic T cells[42]. MHC class I molecules are heterodimers composed of two polypeptide chains, α and B2M[43]. The classical MHC class I genes include HLA-A, HLA-B, and HLA-C and encode the α polypeptide chains, which present short polypeptide chains, of 7 to 11 amino acids, to the immune system to distinguish self from non-self[44,45,46]. Downregulation of MHC class I promotes tumor evasion of the immune system, suggesting a tumor suppressor role for HLA-B[47].

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

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

**CSMD3 deletion**

*CUB and Sushi multiple domains 3*

Background: CSMD3 encodes the CUB and Sushi multiple domains 3 protein, a member of the CSMD family, which includes CSMD1 and CSMD2[1,2]. Proteins containing CUB and Sushi domains are known to mediate protein-protein interactions between the transmembrane and extracellular proteins[2,3]. CSMD family proteins have 14 CUB and 26–28 Sushi domains, which are reported to regulate dendrite growth, neuronal migration, and synapse formation[2,3]. In cancer, mutation of CMSD3 has been associated with greater tumor mutational burden (TMB)[2,4].

Alterations and prevalence: Somatic mutations of CSMD3 are observed in 43% of lung squamous cell carcinoma, 40% of lung adenocarcinoma, 37% of skin cutaneous melanoma, 25% of stomach adenocarcinoma, 24% of uterine corpus endometrial carcinoma,

## Biomarker Descriptions (continued)

19% of esophageal adenocarcinoma and head and neck squamous cell carcinoma, 17% of colorectal adenocarcinoma, 14% of bladder urothelial carcinoma, 10% of diffuse large B-cell lymphoma, 8% of liver hepatocellular carcinoma and cervical squamous cell carcinoma, 7% of ovarian serous cystadenocarcinoma, 5% of uterine carcinosarcoma, and 4% of adrenocortical carcinoma, kidney renal clear cell carcinoma, breast invasive carcinoma, prostate adenocarcinoma and, uveal melanoma[5,6]. Amplification of CSMD3 is observed in 20% of ovarian serous cystadenocarcinoma, 12% of breast invasive carcinoma, 11% of uterine carcinosarcoma, 10% of liver hepatocellular carcinoma, and esophageal adenocarcinoma, 8% of prostate adenocarcinoma, 7% of pancreatic adenocarcinoma, 6% of uveal melanoma and head and neck squamous cell carcinoma, and 5% of bladder urothelial carcinoma and stomach adenocarcinoma[5,6]. Biallelic loss of CSMD3 is observed in 2% of mesothelioma and prostate adenocarcinoma[5,6].

Potential relevance: Currently, no therapies are approved for CSMD3 aberrations.

**TPP2 deletion**

*tripeptidyl peptidase 2*

Background: The TPP2 gene encodes the tripeptidyl peptidase 2[1]. TPP2 is a serine peptidase that becomes activated upon homopolymer complex formation[41]. Upon activation, TPP2 cleaves amino terminal tripeptides from substrates[41]. TPP2 is involved in antigen processing, cell growth, DNA damage repair, and carcinogenesis, potentially through its control of ERK1/2 phosphorylation[41].

Alterations and prevalence: Somatic mutations in TPP2 are observed in 8% of uterine corpus endometrial carcinoma, 6% of skin cutaneous melanoma, 4% of bladder urothelial carcinoma, colorectal adenocarcinoma, stomach adenocarcinoma, 3% of cervical squamous cell carcinoma, and 2% of diffuse large B-cell lymphoma (DLBCL), kidney renal papillary cell carcinoma, lung adenocarcinoma, and lung squamous cell carcinoma[5,6]. Biallelic deletions in TPP2 are observed in 2% of DLBCL[5,6].

Potential relevance: Currently, no therapies are approved for TPP2 aberrations.

**ZNF429 amplification**

*zinc finger protein 429*

Background: ZNF429 encodes zinc finger protein 429[1,172]. Zinc finger proteins function as transcriptional regulators through their ability to bind to DNA by means of their zinc finger domains and have been observed to influence response to targeted therapy, including imatinib[173]. Like other zinc finger proteins, ZNF429 is predicted to be involved in the regulation of transcription, although, its exact biological role is yet to be reported[1,172,173,174].

Alterations and prevalence: Somatic mutations in ZNF429 are observed in 7% of uterine corpus endometrial carcinoma, 5% of skin cutaneous melanoma, 3% of colorectal adenocarcinoma, and 2% of stomach adenocarcinoma, esophageal adenocarcinoma, lung squamous cell carcinoma, and bladder urothelial carcinoma[5,6]. In a study evaluating 21 patients with thymic epithelial tumors, ZNF429 demonstrated the highest mutation frequency (36%)[175]. Amplification of ZNF429 is observed in 4% of ovarian serous cystadenocarcinoma, and 2% of esophageal adenocarcinoma, uterine corpus endometrial carcinoma, and uterine carcinosarcoma[5,6].

Potential relevance: Currently, no therapies are approved for ZNF429 aberrations.

# Alerts Informed By Public Data Sources

## Current FDA Information

Contraindicated Not recommended Resistance Breakthrough Fast Track

FDA information is current as of 2025-09-17. For the most up-to-date information, search www.fda.gov.

### EGFR exon 20 insertion

#### zipalertinib

**Cancer type:** Non-Small Cell Lung Cancer **Variant class:** EGFR exon 20 insertion

**Supporting Statement:**
The FDA has granted Breakthrough Therapy designation to an irreversible EGFR inhibitor, zipalertinib (CLN-081), for EGFR exon 20 insertion mutations in locally advanced or metastatic non-small cell lung cancer who have previously received platinum-based systemic chemotherapy.

**Reference:**

https://investors.cullinanoncology.com/news-releases/news-release-details/fda-grants-breakthrough-therapy-designation-cullinan-oncologys

## Current NCCN Information

Contraindicated Not recommended Resistance Breakthrough Fast Track

NCCN information is current as of 2025-09-02. To view the most recent and complete version of the guideline, go online to NCCN.org.
For NCCN International Adaptations & Translations, search www.nccn.org/global/what-we-do/international-adaptations.

Some variant specific evidence in this report may be associated with a broader set of alterations from the NCCN Guidelines. Specific variants listed in this report were sourced from approved therapies or scientific literature. These therapeutic options are appropriate for certain population segments with cancer. Refer to the NCCN Guidelines® for full recommendation.



### EGFR exon 20 insertion

#### afatinib

**Cancer type:** Non-Small Cell Lung Cancer **Variant class:** EGFR exon 20 insertion

**Summary:**
NCCN Guidelines® include the following supporting statement(s):

- "EGFR exon 20 insertions are generally associated with a lack of response to first, second, and third generation tyrosine kinase inhibitors with select exceptions."

**Reference:** NCCN Guidelines® - NCCN-Non-Small Cell Lung Cancer [Version 8.2025]

## EGFR exon 20 insertion (continued)

### dacomitinib

**Cancer type:** Non-Small Cell Lung Cancer **Variant class:** EGFR exon 20 insertion

**Summary:**
NCCN Guidelines® include the following supporting statement(s):
- "EGFR exon 20 insertions are generally associated with a lack of response to first, second, and third generation tyrosine kinase inhibitors with select exceptions."

**Reference:** NCCN Guidelines® - NCCN-Non-Small Cell Lung Cancer [Version 8.2025]

### erlotinib

**Cancer type:** Non-Small Cell Lung Cancer **Variant class:** EGFR exon 20 insertion

**Summary:**
NCCN Guidelines® include the following supporting statement(s):
- "EGFR exon 20 insertions are generally associated with a lack of response to first, second, and third generation tyrosine kinase inhibitors with select exceptions."

**Reference:** NCCN Guidelines® - NCCN-Non-Small Cell Lung Cancer [Version 8.2025]

### gefitinib

**Cancer type:** Non-Small Cell Lung Cancer **Variant class:** EGFR exon 20 insertion

**Summary:**
NCCN Guidelines® include the following supporting statement(s):
- "EGFR exon 20 insertions are generally associated with a lack of response to first, second, and third generation tyrosine kinase inhibitors with select exceptions."

**Reference:** NCCN Guidelines® - NCCN-Non-Small Cell Lung Cancer [Version 8.2025]

## Current EMA Information

Contraindicated Not recommended Resistance Breakthrough Fast Track

EMA information is current as of 2025-09-17. For the most up-to-date information, search www.ema.europa.eu.

## EGFR exon 20 insertion

### gefitinib

**Cancer type:** Non-Small Cell Lung Cancer **Label as of:** 2023-07-17 **Variant class:** EGFR exon 20 insertion

**Reference:**

https://www.ema.europa.eu/en/documents/product-information/iressa-epar-product-information_en.pdf

# Genes Assayed

## Genes Assayed for the Detection of DNA Sequence Variants

ABL1, ABL2, ACVR1, AKT1, AKT2, AKT3, ALK, AR, ARAF, ATP1A1, AURKA, AURKB, AURKC, AXL, BCL2, BCL2L12, BCL6, BCR, BMP5, BRAF, BTK, CACNA1D, CARD11, CBL, CCND1, CCND2, CCND3, CCNE1, CD79B, CDK4, CDK6, CHD4, CSF1R, CTNNB1, CUL1, CYSLTR2, DDR2, DGCR8, DROSHA, E2F1, EGFR, EIF1AX, EPAS1, ERBB2, ERBB3, ERBB4, ESR1, EZH2, FAM135B, FGF7, FGFR1, FGFR2, FGFR3, FGFR4, FLT3, FLT4, FOXA1, FOXL2, FOXO1, GATA2, GLI1, GNA11, GNAQ, GNAS, HIF1A, HRAS, IDH1, IDH2, IKBKB, IL6ST, IL7R, IRF4, IRS4, KCNJ5, KDR, KIT, KLF4, KLF5, KNSTRN, KRAS, MAGOH, MAP2K1, MAP2K2, MAPK1, MAX, MDM4, MECOM, MED12, MEF2B, MET, MITF, MPL, MTOR, MYC, MYCN, MYD88, MYOD1, NFE2L2, NRAS, NSD2, NT5C2, NTRK1, NTRK2, NTRK3, NUP93, PAX5, PCBP1, PDGFRA, PDGFRB, PIK3C2B, PIK3CA, PIK3CB, PIK3CD, PIK3CG, PIK3R2, PIM1, PLCG1, PPP2R1A, PPP6C, PRKACA, PTPN11, PTPRD, PXDNL, RAC1, RAF1, RARA, RET, RGS7, RHEB, RHOA, RICTOR, RIT1, ROS1, RPL10, SETBP1, SF3B1, SIX1, SIX2, SLCO1B3, SMC1A, SMO, SNCAIP, SOS1, SOX2, SPOP, SRC, SRSF2, STAT3, STAT5B, STAT6, TAF1, TERT, TGFBR1, TOP1, TOP2A, TPMT, TRRAP, TSHR, U2AF1, USP8, WAS, XPO1, ZNF217, ZNF429

## Genes Assayed for the Detection of Copy Number Variations

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

## Genes Assayed for the Detection of Fusions

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

## Genes Assayed with Full Exon Coverage

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

## Relevant Therapy Summary

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

### EGFR exon 20 insertion

| Relevant Therapy | FDA | NCCN | EMA | ESMO | Clinical Trials* |
|---|---|---|---|---|---|
| amivantamab | ● | ● | ● | ● | ✖ |
| amivantamab + carboplatin + pemetrexed | ● | ● | ● | ✖ | ✖ |
| sunvozertinib | ● | ● | ✖ | ✖ | ● (II) |
| datopotamab deruxtecan-dlnk | ● | ✖ | ✖ | ✖ | ✖ |
| mobocertinib | ✖ | ✖ | ✖ | ● | ● (II) |
| bevacizumab, osimertinib | ✖ | ✖ | ✖ | ✖ | ● (III) |
| furmonertinib | ✖ | ✖ | ✖ | ✖ | ● (III) |
| osimertinib, JMT-101 | ✖ | ✖ | ✖ | ✖ | ● (III) |
| PLB-1004, chemotherapy, sintilimab | ✖ | ✖ | ✖ | ✖ | ● (III) |
| almonertinib | ✖ | ✖ | ✖ | ✖ | ● (II) |
| almonertinib, adebrelimab, chemotherapy | ✖ | ✖ | ✖ | ✖ | ● (II) |
| amivantamab, chemotherapy | ✖ | ✖ | ✖ | ✖ | ● (II) |
| BEBT-109 | ✖ | ✖ | ✖ | ✖ | ● (II) |
| befotertinib | ✖ | ✖ | ✖ | ✖ | ● (II) |
| cetuximab, chemotherapy | ✖ | ✖ | ✖ | ✖ | ● (II) |
| ensartinib | ✖ | ✖ | ✖ | ✖ | ● (II) |
| osimertinib | ✖ | ✖ | ✖ | ✖ | ● (II) |
| pembrolizumab, bevacizumab, chemotherapy | ✖ | ✖ | ✖ | ✖ | ● (II) |
| sintilimab | ✖ | ✖ | ✖ | ✖ | ● (II) |
| sunvozertinib, bevacizumab | ✖ | ✖ | ✖ | ✖ | ● (II) |
| sunvozertinib, catequentinib | ✖ | ✖ | ✖ | ✖ | ● (II) |
| zipalertinib | ✖ | ✖ | ✖ | ✖ | ● (II) |
| AP-L1898 | ✖ | ✖ | ✖ | ✖ | ● (I/II) |
| BH-30643 | ✖ | ✖ | ✖ | ✖ | ● (I/II) |
| FWD-1509 | ✖ | ✖ | ✖ | ✖ | ● (I/II) |
| GB263T | ✖ | ✖ | ✖ | ✖ | ● (I/II) |
| HS-10376 | ✖ | ✖ | ✖ | ✖ | ● (I/II) |
| JIN-A-04 | ✖ | ✖ | ✖ | ✖ | ● (I/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

### EGFR exon 20 insertion (continued)

| Relevant Therapy | FDA | NCCN | EMA | ESMO | Clinical Trials* |
|---|---|---|---|---|---|
| MCLA-129 | ✖ | ✖ | ✖ | ✖ | ● (I/II) |
| ORIC-114 | ✖ | ✖ | ✖ | ✖ | ● (I/II) |
| RC-108, furmonertinib, toripalimab | ✖ | ✖ | ✖ | ✖ | ● (I/II) |
| STX-721 | ✖ | ✖ | ✖ | ✖ | ● (I/II) |
| YK-029A | ✖ | ✖ | ✖ | ✖ | ● (I/II) |
| BG-60366 | ✖ | ✖ | ✖ | ✖ | ● (I) |
| KQB-198, osimertinib | ✖ | ✖ | ✖ | ✖ | ● (I) |
| NIP-142 (China Resources Pharmaceutical) | ✖ | ✖ | ✖ | ✖ | ● (I) |
| ORIC-114, amivantamab | ✖ | ✖ | ✖ | ✖ | ● (I) |
| palcitoclax, osimertinib | ✖ | ✖ | ✖ | ✖ | ● (I) |
| PLB-1004 | ✖ | ✖ | ✖ | ✖ | ● (I) |
| YH-013 | ✖ | ✖ | ✖ | ✖ | ● (I) |

### BRCA2 deletion

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

### EGFR amplification

| Relevant Therapy | FDA | NCCN | EMA | ESMO | Clinical Trials* |
|---|---|---|---|---|---|
| nimotuzumab | ✖ | ✖ | ✖ | ✖ | ● (III) |
| ensartinib, sintilimab | ✖ | ✖ | ✖ | ✖ | ● (II) |
| DF-9001 | ✖ | ✖ | ✖ | ✖ | ● (I/II) |
| GB263T | ✖ | ✖ | ✖ | ✖ | ● (I/II) |
| MCLA-129 | ✖ | ✖ | ✖ | ✖ | ● (I/II) |
| SAR-446368, pembrolizumab | ✖ | ✖ | ✖ | ✖ | ● (I) |
| TAVO-412 | ✖ | ✖ | ✖ | ✖ | ● (I) |

* 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

### ATM deletion

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

### AKT1 p.(L52R) c.155T>G

| Relevant Therapy | FDA | NCCN | EMA | ESMO | Clinical Trials* |
|---|---|---|---|---|---|
| ipatasertib + chemotherapy | ✖ | ✖ | ✖ | ✖ | ● (II) |
| HTL-0039732, atezolizumab | ✖ | ✖ | ✖ | ✖ | ● (I/II) |
| IPN-60090, capivasertib | ✖ | ✖ | ✖ | ✖ | ● (I) |

### BRCA1 deletion

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

### BARD1 deletion

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

### BRIP1 deletion

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

### CDK12 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

### CHEK1 deletion

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

### CHEK2 deletion

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

### FANCL deletion

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

### PALB2 deletion

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

### RAD51C deletion

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

### RAD51D 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.

## HRR Details

| Gene/Genomic Alteration | Finding |
|---|---|
| LOH percentage | ***59.57%*** |
| BRCA1 | ***CNV, CN:1.0*** |
| BRCA1 | ***LOH, 17q21.31(41197602-41276231)x1*** |
| BRCA2 | ***CNV, CN:1.0*** |
| BRCA2 | ***LOH, 13q13.1(32890491-32972932)x1*** |
| ATM | ***CNV, CN:1.0*** |

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.

## HRR Details (continued)

| Gene/Genomic Alteration | Finding |
|---|---|
| ATM | ***LOH, 11q22.3(108098341-108236285)x1*** |
| BARD1 | ***CNV, CN:1.0*** |
| BARD1 | ***LOH, 2q35(215593375-215674382)x1*** |
| BRIP1 | ***CNV, CN:1.0*** |
| BRIP1 | ***LOH, 17q23.2(59760627-59938976)x1*** |
| CDK12 | ***CNV, CN:1.0*** |
| CDK12 | ***LOH, 17q12(37618286-37687611)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*** |
| FANCL | ***CNV, CN:1.0*** |
| FANCL | ***LOH, 2p16.1(58386886-58468467)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*** |
| RAD51C | ***CNV, CN:1.0*** |
| RAD51C | ***LOH, 17q22(56769933-56811619)x1*** |
| RAD51D | ***CNV, CN:1.0*** |
| RAD51D | ***LOH, 17q12(33427950-33446720)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 Oncomine Reporter software was used in generation of this report. Software was developed and designed internally by Thermo Fisher Scientific. The analysis was based on Oncomine Reporter (6.1.1 data version 2025.10(006)). The data presented here are from a curated knowledge base of publicly available information, but may not be exhaustive. FDA information was sourced from www.fda.gov and is current as of 2025-09-17. NCCN information was sourced from www.nccn.org and is current as of 2025-09-02. EMA information was sourced from www.ema.europa.eu and is current as of 2025-09-17. ESMO information was sourced from www.esmo.org and is current as of 2025-09-02. Clinical Trials information is current as of 2025-09-02. For the most up-to-date information regarding a particular trial, search www.clinicaltrials.gov by NCT ID or search local clinical trials authority website by local identifier listed in 'Other identifiers.' Variants are reported according to HGVS nomenclature and classified following AMP/ASCO/CAP guidelines (Li et al. 2017). Based on the data sources selected, variants, therapies, and trials listed in this report are listed in order of potential clinical significance but not for predicted efficacy of the therapies.

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