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Patient Name: 구영희
Gender: F
Sample ID: N25-115

Primary Tumor Site: breast
Collection Date: 2025.06.05

Sample Cancer Type: Breast Cancer

Table of Contents	Page

Report Highlights
13 Relevant Biomarkers
55 Therapies Available
254 Clinical Trials

Relevant Breast Cancer Findings

Gene	Finding
BRCA1	None detected
ERBB2	***ERBB2 amplification, ERBB2 p.(L755S) c.2264T>C***

Genomic Alteration	Finding
Tumor Mutational Burden	***4.74 Mut/Mb measured***

Relevant Biomarkers

Tier	Genomic Alteration	Relevant Therapies (In this cancer type)	Relevant Therapies (In other cancer type)	Clinical Trials
IA	*ERBB2 amplification* erb-b2 receptor tyrosine kinase 2 Locus: chr17:37863255	**lapatinib + hormone therapy** [1, 2 / I, II+] **pertuzumab + trastuzumab + chemotherapy** [1, 2 / I, II+] **trastuzumab deruxtecan** [1, 2 / I, II+] **trastuzumab† + hormone therapy** [2 / I, II+] **ado-trastuzumab emtansine** [1, 2 / II+] **lapatinib + chemotherapy** [1, 2 / II+] **lapatinib + trastuzumab** [2 / II+] **margetuximab + chemotherapy** [1 / II+] **neratinib** [1, 2 / II+] **neratinib + chemotherapy** [1 / II+] **trastuzumab + tucatinib + chemotherapy** [1, 2 / II+] **trastuzumab†** [1, 2 / II+] **trastuzumab† + chemotherapy** [1, 2 / II+] **pertuzumab/trastuzumab/ hyaluronidase-zzxf + chemotherapy** [1, 2]	**trastuzumab + tucatinib** [1 / I, II+] **trastuzumab deruxtecan** [1, 2 / I, II+] **trastuzumab† + chemotherapy** [1, 2 / I, II+] **pembrolizumab + trastuzumab + chemotherapy** [1, 2 / I] **zanidatamab** [1 / II+] **trastuzumab†** [1] lapatinib + trastuzumab [I, II+] pertuzumab + trastuzumab [I, II+] ado-trastuzumab emtansine	236

*** Public data sources included in relevant therapies: FDA**[1], NCCN, **EMA**[2], ESMO
*** Public data sources included in prognostic and diagnostic significance:** NCCN, ESMO
† Includes biosimilars/generics
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
		trastuzumab and hyaluronidase-oysk [1] **trastuzumab and hyaluronidase-oysk + chemotherapy** [1] pertuzumab + trastuzumab [I, II+] pertuzumab + trastuzumab + hormone therapy [I, II+] lapatinib + trastuzumab + hormone therapy [I] abemaciclib + trastuzumab + hormone therapy [II+] ado-trastuzumab emtansine + hormone therapy [II+] hormone therapy [II+] margetuximab [II+] pertuzumab + trastuzumab + hormone therapy + chemotherapy [II+] trastuzumab + hormone therapy + chemotherapy [II+]		
IIC	*ERBB2 p.(L755S) c.2264T>C* erb-b2 receptor tyrosine kinase 2 Allele Frequency: 89.93% Locus: chr17:37880220 Transcript: NM_004448.4	None*	**trastuzumab deruxtecan** [1, 2 / II+]	13
IIC	*BRCA2 deletion* BRCA2, DNA repair associated Locus: chr13:32890491	None*	niraparib [II+] olaparib [II+] rucaparib [II+]	3
IIC	*MTAP deletion* methylthioadenosine phosphorylase Locus: chr9:21802646	None*	None*	9
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
IIC	*ARID1A deletion* AT-rich interaction domain 1A Locus: chr1:27022875	None*	None*	2
IIC	*BAP1 deletion* BRCA1 associated protein 1 Locus: chr3:52436290	None*	None*	1
IIC	*CDKN2B deletion* cyclin dependent kinase inhibitor 2B Locus: chr9:22005728	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
† Includes biosimilars/generics
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	*CHEK1 deletion* checkpoint kinase 1 Locus: chr11:125496639	None*	None*	1
IIC	*FANCA deletion, FANCA p.(E1240Dfs*36) c.3719_3723delAAAAC* Fanconi anemia complementation group A Allele Frequency: 86.49% Locus: chr16:89804984, chr16:89809249 (2 variants)	None*	None*	1
IIC	*FBXW7 deletion* F-box and WD repeat domain containing 7 Locus: chr4:153243999	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
† Includes biosimilars/generics
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.

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

ERBB2 amplification	**anvatabart opadotin** [1], **CT-0508** [1], **CT-0525** [1]

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

Prevalent cancer biomarkers without relevant evidence based on included data sources

ABRAXAS1 deletion, AKT3 p.(L77H) c.230T>A, CDKN2C deletion, ESR1::CCDC170 fusion, FANCD2 deletion, KMT2A deletion, MLH1 deletion, MLH3 deletion, MRE11 deletion, MUTYH deletion, Microsatellite stable, PARP3 deletion, RAD51B deletion, RAD54L deletion, RPA1 deletion, SDHB deletion, SETD2 deletion, TP53 deletion, TNFRSF14 deletion, ERRFI1 deletion, ENO1 deletion, PGD deletion, SPEN deletion, EPHA2 deletion, JAK1 deletion, FUBP1 deletion, DPYD deletion, VHL deletion, TGFBR2 deletion, DOCK3 deletion, PBRM1 deletion, TET2 deletion, INPP4B deletion, FAT1 deletion, ERAP2 deletion, HLA-B deletion, JAK2 deletion, PTCH1 deletion, MAPK8 deletion, MEN1 deletion, SDHD deletion, ACVR1B deletion, DICER1 deletion, CYLD deletion, CBFB deletion, CTCF deletion, CDH1 deletion, NQO1 p.(P187S) c.559C>T, ZFHX3 deletion, GPS2 deletion, NCOR1 deletion, RUNX1 deletion, Tumor Mutational Burden

Variant Details

DNA Sequence Variants

Gene	Amino Acid Change	Coding	Variant ID	Locus	Allele Frequency	Transcript	Variant Effect
ERBB2	p.(L755S)	c.2264T>C	COSM14060	chr17:37880220	89.93%	NM_004448.4	missense
FANCA	p.(E1240Dfs*36)	c.3719_3723delAAAAC	.	chr16:89809249	86.49%	NM_000135.4	frameshift Deletion
AKT3	p.(L77H)	c.230T>A	.	chr1:243828128	29.38%	NM_005465.7	missense
NQO1	p.(P187S)	c.559C>T	.	chr16:69745145	17.33%	NM_000903.3	missense
ATR	p.(F1658L)	c.4972T>C	.	chr3:142226832	50.30%	NM_001184.4	missense
HLA-B	p.(I90K)	c.269_270delTCinsAG	.	chr6:31324538	68.75%	NM_005514.8	missense
KMT2A	p.(P3197S)	c.9589C>T	.	chr11:118376196	18.14%	NM_001197104.2	missense

Variant Details (continued)

DNA Sequence Variants (continued)

Gene	Amino Acid Change	Coding	Variant ID	Locus	Allele Frequency	Transcript	Variant Effect
PPM1D	p.(S376A)	c.1126T>G	.	chr17:58734068	38.00%	NM_003620.4	missense

Gene Fusions

Genes	Variant ID	Locus
ESR1::CCDC170	ESR1-CCDC170.E2C7.1	chr6:152023140 - chr6:151907024
ESR1::CCDC170	ESR1-CCDC170.E2C8.1	chr6:152023140 - chr6:151914242

Copy Number Variations

Gene	Locus	Copy Number	CNV Ratio
ERBB2	chr17:37863255	4.53	1.99
BRCA2	chr13:32890491	1	0.79
MTAP	chr9:21802646	0.96	0.6
ATM	chr11:108098341	1	0.63
CDKN2A	chr9:21968178	0.69	0.49
ARID1A	chr1:27022875	1.06	0.63
BAP1	chr3:52436290	0.99	0.6
CDKN2B	chr9:22005728	0.82	0.54
CHEK1	chr11:125496639	1	0.61
FANCA	chr16:89804984	1.06	0.64
FBXW7	chr4:153243999	1.01	0.62
ABRAXAS1	chr4:84383635	1.01	0.62
CDKN2C	chr1:51434849	1.04	0.62
FANCD2	chr3:10070306	1.05	0.63
KMT2A	chr11:118307146	1.04	0.62
MLH1	chr3:37034957	1.03	0.62
MLH3	chr14:75483761	1.08	0.64
MRE11	chr11:94153270	0.95	0.59
MUTYH	chr1:45794962	1.06	0.63
PARP3	chr3:51976651	1.01	0.62
RAD51B	chr14:68290164	1	0.66
RAD54L	chr1:46714017	1	0.62
RPA1	chr17:1733385	1.05	0.63
SDHB	chr1:17345303	0.99	0.6
SETD2	chr3:47058542	1.01	0.62

Variant Details (continued)

Copy Number Variations (continued)

Gene	Locus	Copy Number	CNV Ratio
TP53	chr17:7572848	0.06	0.25
TNFRSF14	chr1:2488070	1.14	0.66
ERRFI1	chr1:8073246	1.09	0.64
ENO1	chr1:8921399	1.05	0.63
PGD	chr1:10459132	0.96	0.59
SPEN	chr1:16174516	1.08	0.64
EPHA2	chr1:16451707	1.06	0.63
JAK1	chr1:65300225	1.03	0.62
FUBP1	chr1:78414385	1	0.61
DPYD	chr1:97544504	1.06	0.64
VHL	chr3:10183418	1.22	0.69
TGFBR2	chr3:30648337	1.05	0.63
DOCK3	chr3:51101879	0.87	0.56
PBRM1	chr3:52582040	1.1	0.65
TET2	chr4:106155068	1.03	0.62
INPP4B	chr4:142949914	1.03	0.62
FAT1	chr4:187509708	1.06	0.64
ERAP2	chr5:96219500	0.71	0.49
HLA-B	chr6:31322252	0.96	0.6
JAK2	chr9:5021954	1.08	0.64
PTCH1	chr9:98209140	1.14	0.67
MAPK8	chr10:49609682	1	0.61
MEN1	chr11:64571785	0.96	0.6
SDHD	chr11:111957573	0.87	0.56
ACVR1B	chr12:52345528	1.04	0.62
DICER1	chr14:95556791	1.1	0.65
CYLD	chr16:50783549	1.05	0.63
CBFB	chr16:67063242	0.91	0.57
CTCF	chr16:67644720	1.03	0.62
CDH1	chr16:68771249	1.09	0.64
ZFHX3	chr16:72820995	0.91	0.57
GPS2	chr17:7216071	1.09	0.64
NCOR1	chr17:15935586	1.06	0.64
RUNX1	chr21:36164357	1.1	0.65

Variant Details (continued)

Copy Number Variations (continued)

Gene	Locus	Copy Number	CNV Ratio
MYCL	chr1:40362966	0.88	0.56
MPL	chr1:43803495	1.06	0.63
MAGOH	chr1:53692690	1.08	0.64
RAF1	chr3:12625930	0.97	0.6
MYD88	chr3:38180156	1.06	0.64
MITF	chr3:69788729	1.1	0.65
FGFR3	chr4:1801456	1.01	0.62
PDGFRA	chr4:55131078	1.05	0.63
KIT	chr4:55589693	1.1	0.65
KDR	chr4:55955541	0.9	0.57
CD274	chr9:5456050	1.05	0.63
PDCD1LG2	chr9:5522530	1.08	0.64
NTRK2	chr9:87549097	1.06	0.64
HRAS	chr11:532637	1.04	0.62
EMSY	chr11:76157926	0.91	0.58
YAP1	chr11:101981594	0.96	0.59
CBL	chr11:119103202	1.03	0.62
MAX	chr14:65472833	1.04	0.63
YES1	chr18:724481	1.01	0.61
U2AF1L5	chr21:44513260	1.17	0.68

Biomarker Descriptions

ERBB2 amplification, ERBB2 p.(L755S) c.2264T>C

erb-b2 receptor tyrosine kinase 2

Background: The ERBB2 gene encodes the erb-b2 receptor tyrosine kinase 2, a member of the human epidermal growth factor receptor (HER) family. Along with ERBB2/HER2, EGFR/ERBB1/HER1, ERBB3/HER3, and ERBB4/HER4 make up the HER protein family[447]. All ERBB/HER proteins encode transmembrane receptor tyrosine kinases. However, ERBB2/HER2 is an orphan receptor with no known ligand. ERBB2 preferentially binds other ligand bound ERBB/HER family members to form hetero-dimers resulting in the activation of ERBB2 tyrosine kinase activity and subsequent activation of the PI3K/AKT/MTOR and RAS/RAF/MAPK/ERK signaling pathways which promote cell proliferation, differentiation, and survival[448]. Recurrent focal amplification of the ERBB2 gene leads to increased expression in several cancer types. ERBB2 overexpression in immortalized cell lines is oncogenic and leads to ERBB2 homo-dimerization and activation without ligand binding[449,450,451].

Alterations and prevalence: ERBB2 gene amplification occurs in 10-20% of breast, esophageal, and gastric cancers, 5-10% of bladder, cervical, pancreas, and uterine cancers, and 1-5% of colorectal, lung, and ovarian cancers[4,5,177,178,452,453,454,455]. Recurrent somatic activating mutations in ERBB2/HER2 occur at low frequencies (<1%) in diverse cancer types[5,456,457]. In breast, bladder, and colorectal cancers, the most common recurrent ERBB2 activating mutations include kinase domain mutations L755S and V777L and the extracellular domain mutation S310F. In lung cancer, the most common recurrent ERBB2 activating mutations include in-frame exon 20 insertions, particularly Y772_A775dup.

Biomarker Descriptions (continued)

Potential relevance: The discovery of ERBB2/HER2 as an important driver of breast cancer in 1987 led to the development of trastuzumab, a humanized monoclonal antibody with specificity to the extracellular domain of HER2[458,459]. Trastuzumab[460] was FDA approved for the treatment of HER2 positive breast cancer in 1998, and subsequently in HER2 positive metastatic gastric and gastroesophageal junction adenocarcinoma in 2010. Additional monoclonal antibody therapies have been approved by the FDA for HER2-positive breast cancer including pertuzumab[461] (2012), a humanized monoclonal antibody that inhibits HER2 dimerization, and ado-trastuzumab emtansine[462] (2013), a conjugate of trastuzumab and a potent antimicrotubule agent. The combination of pertuzumab, trastuzumab, and a taxane is the preferred front-line regimen for HER2-positive metastatic breast cancer[274]. In addition to monoclonal antibodies, the small molecule inhibitor lapatinib[463], with specificity for both EGFR and ERBB2, was FDA approved (2007) for the treatment of patients with advanced HER2-positive breast cancer who have received prior therapy including trastuzumab. In 2017, the FDA approved the use of neratinib[464], an irreversible kinase inhibitor of EGFR, ERBB2/HER2, and ERBB4, for the extended adjuvant treatment of adult patients with early stage HER2-positive breast cancer. In 2020, the FDA approved neratinib[464] in combination with capecitabine for HER2-positive advanced or metastatic patients after two or more prior HER2-directed therapies. Also in 2020, the TKI irbinitinib[465] was FDA approved for HER2 overexpressing or amplified breast cancer in combination with trastuzumab and capecitabine. In 2021, the PD-1 blocking antibody, pembrolizumab, in combination with trastuzumab, fluoropyrimidine- and platinum-based chemotherapy, was approved for HER2 amplified gastric or gastroesophageal (GEJ) adenocarcinoma in the first line[151]. In 2024, a bispecific HER2 antibody, zanidatamab[466], was approved for the treatment of adults with previously treated, unresectable or metastatic ERBB2 overexpressing biliary tract cancer. The vaccine, nelipepimut-S[467], was granted fast track designation by the FDA (2016) in patients with low to intermediate HER2 expressing (IHC score 1+ or 2+) breast cancer. In 2018 fast track designation was granted to the monoclonal antibody margetuximab[468] in patients with ERBB2 positive breast cancer previously treated with an anti-HER2 therapy. In 2019, fast track designation was granted to the HER2-targeting antibody drug conjugate, amcenestrant[469], for HER2-positive advanced or metastatic breast cancer after one or more prior anti-HER2 based regimens. Additionally, in 2019, zanidatamab[470], received fast track designation in combination with standard chemotherapy for patients with HER2-overexpressing gastroesophageal adenocarcinoma (GEA). In 2020, BDTX-189[471] received fast track designation for adult patients with solid tumors harboring an allosteric human ERBB2 mutation or exon 20 insertion, and the humanized anti-HER2 antibody drug conjugate disitamab vedotin received breakthrough designation for adult patients with HER2-positive urothelial cancer after previous platinum-chemotherapy treatment[472]. In 2021, the antibody-drug conjugate ARX788[473] received fast track designation as a monotherapy for advanced or metastatic HER2-positive breast cancer that have progressed on one or more anti-HER2 regimens. Additionally, fast track designation was granted to HER2-targeted chimeric antigen receptor macrophage (CAR-M) (2019), CT-0508[474], and to ex vivo gene-modified autologous chimeric antigen receptor-monocyte (CAR-Monocyte) cellular therapy (2024), CT-0525[475], for HER2-overexpressing solid tumors. In 2024, a small molecule inhibitor, BAY-2927088[476], received breakthrough designation for the treatment of NSCLC patients with ERBB2 activating mutations. Certain activating mutations have been observed to impart sensitivity to neratinib, afatinib, lapatinib, and trastuzumab, or dacomitinib in early and ongoing clinical studies[477,478,479,480,481]. ERBB2 kinase domain mutations R896G and V659E both showed response to afatinib in two NSCLC case studies[482,483]. Additionally, acquired HER2 mutations in estrogen receptor-positive (ER+) breast cancer have been shown to confer resistance to hormone therapy[484]. However, this was shown to be overcome by neratinib in combination with therapies targeting ER[484]. Additionally, in 2024, FDA granted fast track designation to zongertinib[485], an irreversible ERBB2 tyrosine kinase inhibitor, for HER2-mutant NSCLC tumors that have progressed on or after platinum-based therapy.

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. Specifically, BRCA1/2 are required for repair of chromosomal double strand breaks (DSBs) which are highly unstable and compromise genome integrity[388,389]. Inherited pathogenic mutations in BRCA1/2 are known to confer increased risk in women for breast and ovarian cancer[390] and in men for breast and prostate cancer[391,392]. For individuals diagnosed with inherited pathogenic or likely pathogenic BRCA1/2 variants, estimated lifetime risks range from 41% to 90% for developing breast cancer and 8 to 62% for developing ovarian cancer[393].테스트 입니다.

Alterations and prevalence: Inherited BRCA1/2 mutations occur in 1:400 to 1:500 individuals and are observed in 10-15% of ovarian cancer and 5-10% of breast cancer[394,395,396,397,398,399,400]. Somatic alterations in BRCA2 are observed in 5-15% of melanomas, uterine, cervical, gastric, colorectal, esophageal, and lung cancers[4,5].

Potential clinical 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)[401]. Inhibitors targeting PARP induce synthetic lethality in recombination deficient BRCA1/2 mutant cells[402,403]. Consequently, several PARP inhibitors have been FDA approved for BRCA1/2-mutated cancers. Olaparib[] (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

Biomarker Descriptions (continued)

with gBRCAm HER2-negative metastatic breast cancer who have been treated with chemotherapy in the neoadjuvant, adjuvant, or metastatic setting. Rucaparib[] (2016) was the first PARPi approved for the treatment of patients with either gBRCAm or sBRCAm epithelial ovarian, fallopian tube, or primary peritoneal cancers treated with two or more chemotherapies. Talazoparib[] (2018) is indicated for the treatment of gBRCAm HER2-negative locally advanced or metastatic breast cancer. Due to efficacy in both gBRCAm and non-gBRCAm patients, Niraparib (2017) is another PARPi approved for maintenance of epithelial ovarian, fallopian tube, or primary peritoneal cancers, regardless of BRCA status[404]. Despite tolerability and efficacy, acquired resistance to PARP inhibition has been clinically reported[405]. One of the most common mechanisms of resistance includes secondary intragenic mutations that restore BRCA1/2 functionality[406].

MTAP deletion

methylthioadenosine phosphorylase

Background: The MTAP gene encodes methylthioadenosine phosphorylase[1]. Methylthioadenosine phosphorylase, a key enzyme in polyamine biosynthesis and methionine salvage pathways, catalyzes the reversible phosphorylation of S-methyl-5'-thioadenosine (MTA) to adenine and 5-methylthioribose-1-phosphate[311,312]. Loss of MTAP function is commonly observed in cancer due to deletion or promotor methylation which results in the loss of MTA phosphorylation and sensitivity of MTAP-deficient cells to purine synthesis inhibitors and to methionine deprivation[312].

Alterations and prevalence: MTAP is flanked by CDKN2A tumor suppressor on chromosome 9p21 and is frequently found to be co-deleted with CDKN2A in numerous solid and hematological cancers[312,313]. Consequently, biallelic loss of MTAP has been observed in 42% of glioblastoma multiforme, 32% of mesothelioma, 26% of bladder urothelial carcinoma, 22% of pancreatic adenocarcinoma, 21% of esophageal adenocarcinoma, 20% of lung squamous cell carcinoma and skin cutaneous melanoma, 15% of diffuse large B-cell lymphoma and head and neck squamous cell carcinoma, 12% of lung adenocarcinoma, 11% of cholangiocarcinoma, 9% of sarcoma, stomach adenocarcinoma and brain lower grade glioma, and 3% of ovarian serous cystadenocarcinoma, breast invasive carcinoma, adrenocortical carcinoma, thymoma and liver hepatocellular carcinoma[4,5]. Somatic mutations in MTAP have been found in 3% of uterine corpus endometrial carcinoma[4,5].

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

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)[128]. 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[129]. ATM is recruited to the DNA damage site by the MRE11/RAD50/NBN (MRN) complex that senses DSB[129,130]. Upon activation, ATM phosphorylates several downstream proteins such as the NBN, MDC1, BRCA1, CHK2 and TP53BP1 proteins[131]. 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[45,46]. 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[132].

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[4,5].

Potential relevance: The PARP inhibitor, olaparib[90] 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[55] 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[45,133,134]. 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[135]. In 2022, the FDA granted fast track designation to the small molecule inhibitor, pidnarulex[136], 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[1]. CDKN2A, also known as p16/INK4A, belongs to a family of INK4 cyclin-dependent kinase inhibitors, which also includes CDKN2B (p15/

Biomarker Descriptions (continued)

INK4B), CDKN2C (p18/INK4C), and CDKN2D (p19/INK4D)[209]. The INK4 family regulates cell cycle progression by inhibiting CDK4 or CDK6, thereby preventing the phosphorylation of Rb[210,211,212]. CDKN2A encodes two alternative transcript variants, namely p16 and p14ARF, both of which exhibit differential tumor suppressor functions[213]. 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[1,213,214]. CDKN2A aberrations commonly co-occur with CDKN2B[209]. Loss of CDKN2A/p16 results in downstream inactivation of the Rb and p53 pathways, leading to uncontrolled cell proliferation[215]. Germline mutations of CDKN2A are known to confer a predisposition to melanoma and pancreatic cancer[216,217].

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[218]. 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[4,5]. 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[4,5]. Alterations in CDKN2A are also observed in pediatric cancers[5]. 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[5]. Somatic mutations in CDKN2A are observed in less that 1.5% of bone cancer (5 in 327 cases), B-lymphoblastic leukemia/lymphoma (3 in 252 cases), and leukemia (1 in 354 cases)[5].

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[219,220,221]. Additionally, deletion of CDKN2B is a molecular marker used in staging Grade 4 pediatric IDH-mutant astrocytoma[222]. 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[223,224,225]. Alternatively, CDKN2A expression and Rb inactivation demonstrate resistance to palbociclib in cases of glioblastoma multiforme[226]. 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[227,228,229,230].

ARID1A deletion

AT-rich interaction domain 1A

Background: The ARID1A gene encodes the AT-rich interaction domain 1A tumor suppressor protein[1]. ARID1A, also known as BAF250A, belongs to the ARID1 subfamily that also includes AR1D1B[1,100]. ARID1A and ARID1B are mutually exclusive subunits of the BAF variant of the SWI/SNF chromatin-remodeling complex[95,100]. The BAF complex is a multisubunit protein that consists of SMARCB1/IN1, SMARCC1/BAF155, SMARCC2/BAF170, SMARCA4/BRG1 or SMARCA2/BRM, and ARID1A or ARID1B[95]. The BAF complex remodels chromatin at promoter and enhancer elements to alter and regulate gene expression[95,101]. ARID1A binds to transcription factors and coactivator/corepressor complexes to alter transcription[100]. Recurrent inactivating mutations in BAF complex subunits, including ARID1A, lead to transcriptional dysfunction thereby, altering its tumor suppressor function[100].

Alterations and prevalence: Mutations in SWI/SNF complex subunits are the most commonly mutated chromatin modulators in cancer and have been observed in 20% of all tumors[101]. The majority of ARID1A inactivating mutations are nonsense or frameshift mutations[100]. Somatic mutations in ARID1A have been identified in 50% of ovarian clear cell carcinoma, 30% of endometrioid carcinoma, and 24-43% of uterine corpus endometrial carcinoma, bladder urothelial carcinoma, and stomach adenocarcinoma[4,5,95]. In microsatellite stable (MSS) colorectal cancer, mutations in ARID1A have been observed to correlate with increased tumor mutational burden (TMB) and expression of genes involved in the immune response[102].

Potential relevance: Currently, no therapies are approved for ARID1A aberrations. However, the FDA has granted fast track designation (2022) to HSF1 pathway inhibitor, NXP-800[103], for the treatment of platinum resistant ARID1A-mutated ovarian carcinoma. Tulmimetostat[104], dual inhibitor of EZH2 and EZH1, was also granted a fast track designation (2023) for the treatment of patients with advanced, recurrent or metastatic endometrial cancer harboring ARID1A mutations and who have progressed on at least one prior line of treatment.

Biomarker Descriptions (continued)

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[1]. BAP1 is a tumor suppressor deubiquitinase that is involved in chromatin modification, transcription, and cell cycle regulation[249]. BAP1 deubiquitylation targets include HCF-1, which modulates chromatin structure[249]. 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[250,251,252,253,254,255].

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[4,5]. BAP1 biallelic deletions are observed in 11% of mesothelioma[4,5].

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[1,209]. 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)[209]. The INK4 family regulates cell cycle progression by inhibiting CDK4 or CDK6, thereby preventing the phosphorylation of Rb[210,211,212]. CDKN2B is a tumor suppressor and aberrations in this gene commonly co-occur with CDKN2A[209]. Germline mutations in CDKN2B are linked to pancreatic cancer predisposition and familial renal cell carcinoma[1,238,239].

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[4,5]. Somatic mutations in CDKN2B are observed in 2% of uterine carcinosarcoma[4,5]. CDKN2B copy number loss is also observed in pediatric cancers, including 64% of childhood T-lymphoblastic leukemia/lymphoma, 37% of pediatric B-lymphoblastic leukemia/lymphoma, 25% of pediatric gliomas, 14% of pediatric bone cancers, 6% of embryonal tumors, and 2% of peripheral nervous system cancers[4,5]. Somatic mutations in CDKN2B are observed in less than 1% of bone cancer (1 in 327 cases)[4,5].

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[222].

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[244]. 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)[245,246]. Upon DNA damage, CHEK1 is phosphorylated and activated by DNA damage repair proteins ATM and ATR[245]. Activated CHEK1 subsequently phosphorylates and negatively regulates downstream proteins such as CDC25A thereby slowing or stalling DNA replication[245,247].

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[4,248]. 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[4,248].

Potential relevance: The PARP inhibitor, olaparib[90] 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[136], for BRCA1/2, PALB2, or other homologous recombination deficiency (HRD) mutations in breast and ovarian cancers.

Biomarker Descriptions (continued)

FANCA deletion, FANCA p.(E1240Dfs*36) c.3719_3723delAAAAC

Fanconi anemia complementation group A

Background: The FANCA gene encodes the FA complementation group A protein, a member of the Fanconi Anemia (FA) family, which also includes FANCB, FANCC, FANCD1 (BRCA2), FANCD2, FANCE, FANCF, FANCG, FANCI, FANCJ (BRIP1), FANCL, 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[61,62]. 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[61]. Monoubiquitination of the ID2 complex promotes co-localization with BRCA1/2, which is critical in BRCA mediated DNA repair[63,64]. Loss of function mutations in the FA family and HRR pathway, including FANCA, can result in the BRCAness phenotype, characterized by a defect in the HRR pathway, mimicking BRCA1 or BRCA2 loss[46,65]. 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[66,67]. Of those diagnosed with FA, mutations in FANCA are the most common and confer predisposition to myelodysplastic syndrome, acute myeloid leukemia, and solid tumors[62,67,80,81,82].

Alterations and prevalence: Somatic mutations in FANCA are observed in 4-8% of uterine, colorectal, and bladder cancers and about 6% of melanoma[4]. Biallelic loss is also reported in 2-5% of uveal melanoma, invasive breast carcinoma, ovarian cancer, and prostate cancer[4].

Potential relevance: The PARP inhibitor, talazoparib[55] in combination with enzalutamide is approved (2023) for metastatic castration-resistant prostate cancer (mCRPC) with mutations in HRR genes that includes FANCA. Consistent with other genes that contribute to the BRCAness phenotype, mutations in FANCA are shown to confer enhanced sensitivity in vitro to DNA damaging agents, including cisplatin, as well as PARP inhibitors such as olaparib[68,83]. FANCA copy number loss along with reduced expression has also been associated with genetic instability in sporadic acute myeloid leukemia (AML)[82].

FBXW7 deletion

F-box and WD repeat domain containing 7

Background: The FBXW7 gene encodes a member of the F-box protein family that functions as the substrate recognition component of the SCF complex, which is responsible for protein ubiquitination and subsequent degradation by the proteasome[169]. FBXW7 is a tumor suppressor gene that plays a crucial role in the degradation and turnover of various proto-oncogenes. Aberrations such as mutations or deletions that alter the tumor suppression function can lead to the deregulation of downstream genes, including MYC, MTOR, and NOTCH1, thereby promoting cell proliferation and survival[169,170,171,172,173,174,175].

Alterations and prevalence: Mutations in FBXW7 occur at high frequencies in various malignancies, including 40% of uterine carcinoma and 10-15% of stomach, bladder, cervical, and colorectal cancers[4,5,176,177,178].

Potential relevance: The FDA has granted fast track designation (2024) to the small molecule PKMYT1 inhibitor, lunresertib[179], in combination with camonsertib for the treatment of adult patients with FBXW7 mutated endometrial cancer and platinum resistant ovarian cancer. Missense mutations in FBXW7 are associated with poor prognosis and worse overall survival (OS) in comparison to FBXW7 wild-type metastatic colorectal cancer[176]. In a clinical case report, a patient with FBXW7 R465H-mutated, EGFR/ALK-wildtype lung adenocarcinoma demonstrated tumor shrinkage after treatment with the mTOR inhibitor temsirolimus. In a phase I clinical trial of sirolimus, one hepatocellular fibrolamellar carcinoma patient with the FBXW7 E192A mutation demonstrated stable disease for over 6 months[175].

ABRAXAS1 deletion

family with sequence similarity 175 member A

Background: The ABRAXAS1 gene encodes the abraxas 1, BRCA1-A complex subunit[1]. 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[161,162]. 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[161]. BRCA1 localization to DNA double-strand breaks through BRCA1-A is essential for DNA-damage signaling and repair[161]. 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[161,163].

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[4,5].

Biomarker Descriptions (continued)

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

AKT3 p.(L77H) c.230T>A

AKT serine/threonine kinase 3

Background: The AKT3 gene encodes a serine/threonine kinase that belongs to a family of closely related protein kinases that also includes AKT1 and AKT2. 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[288,289]. Amongst the three AKT isoforms (AKT1, AKT2, and AKT3), AKT3 is implicated in cytokinesis and activation of the DNA repair pathway[290,291].

Alterations and prevalence: AKT3 is altered by recurrent activating mutations at amino acid positions homologous to those observed in AKT1 which are found in 1-6% of melanoma, colorectal, bladder, lung, uterine, esophageal, and head and neck cancers[292]. In AKT3, recurrent activating mutations occur at E17K, L51R, Q78K, and D320H[292]. AKT3 is subject to gene amplification in breast and ovarian cancers, typically as part of broader chromosome 1q alterations. AKT3 fusions have been identified in breast and other solid cancers[4,269].

Potential relevance: Currently, no therapies are approved for AKT3 aberrations. However, the pan-AKT inhibitor capivasertib (AZD5363) is active against all AKT isoforms[293], but clinical evidence in AKT3 aberrant cancers is lacking. Pre-clinical evidence suggests that AKT3 overexpression contributes to increased DNA repair and subsequent resistance to radiation and temozolomide[290].

CDKN2C deletion

cyclin dependent kinase inhibitor 2C

Background: CDKN2C encodes the cyclin-dependent kinase inhibitor 2C protein, a cell cycle regulator that controls G1/S progression[1]. CDKN2C, also known as p18/INK4C, belongs to a family of INK4 cyclin-dependent kinase inhibitors, which includes CDKN2A (p16/INK4A), CDKN2B (p15/INK4B), and CDKN2D (p19/INK4D). The INK4 family regulates cell cycle progression by inhibiting CDK4 or CDK6, thereby preventing the phosphorylation of Rb[210,211,212]. Unlike CDKN2A and CDKN2B, inactivation of CDKN2C is not frequently observed in cancer[240].

Alterations and prevalence: Somatic mutations in CDKN2C are observed in 2% of uterine corpus endometrial carcinoma and glioblastoma. Biallelic deletion of CDKN2C is observed in 3% of glioblastoma and 2% of pheochromocytoma, paraganglioma, brain lower grade glioma, kidney chromophobe, and sarcoma[4,5]. Deletion of chromosome 1p32, where CDKN2C resides, is observed to be recurrent in multiple myeloma with variable frequency (7%-20%), depending on the study[241,242,243].

Potential relevance: Currently, no therapies are approved for CDKN2C aberrations.

ESR1::CCDC170 fusion

coiled-coil domain containing 170, estrogen receptor 1

Background: The ESR1 gene encodes estrogen receptor 1 (ERα), which is a member of the superfamily of nuclear receptors which convert extracellular signals into transcriptional responses. A related gene, ESR2, encodes the cognate ERβ protein. ERα is a ligand-activated transcription factor regulated by the hormone estrogen[261,262]. Estrogen binding to ERα results in receptor dimerization, nuclear translocation, and target gene transcription. In addition, estrogen binding to the ERα results in the activation of the RAS/RAF/MEK/ERK, PI3K/AKT/mTOR, cAMP/PKA and PLC/PKC signaling pathways and cell proliferation and survival[263].

Alterations and prevalence: Approximately 70% of breast cancers express ERα and ERβ positivity. Mutations in the ERα ligand binding domain, including S463P, Y537S, and D538G, result in endocrine-independent constitutive receptor activation, which is a common mechanism of endocrine resistance[264,265,266,267]. ESR1 gene fusions and ESR1 copy number gains have also been observed and are associated with advanced endocrine resistant disease[268,269,270,271,272].

Potential relevance: The FDA has approved elacestrant[273] (2023) for the treatment of postmenopausal women or adult men with ER-positive/ERBB2-negative, ESR1-mutated advanced or metastatic breast cancer[274]. The FDA has also granted fast track designations to the following therapies: AC699[275] (2024) and lasofoxifene[276] (2019) for ESR1-mutated, ER-positive/ERBB2-negative metastatic breast cancer, camizaestrant[277] for ESR1-mutated, HR-positive/ERBB2-negative metastatic breast cancer, and seviteronel[278] (2016) for ER-positive breast cancer. Anti-estrogen (endocrine) treatments such as tamoxifen[279] (1977), fulvestrant[280] (2002), letrozole[281] (1995), and exemestane[282] (2005) are FDA approved for ER-positive metastatic breast cancers[283,284]. Although ERα and ERβ positivity predicts response to endocrine therapies, about a quarter of patients with primary breast cancer and almost all patients with metastatic disease will develop endocrine resistance[285,286,287].

Biomarker Descriptions (continued)

FANCD2 deletion

Fanconi anemia complementation group D2

Background: The FANCD2 gene encodes the FA complementation group D2 protein, a member of the Fanconi Anemia (FA) family, which also includes FANCA, FANCB, FANCC, FANCD1 (BRCA2), FANCE, FANCF, FANCG, FANCI, FANCJ (BRIP1), FANCL, 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[61,62]. 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[61]. Monoubiquitination of the ID2 complex promotes co-localization with BRCA1/2, which is critical in BRCA mediated DNA repair[63,64]. Loss of function mutations in the FA family and HRR pathway, including FANCD2, can result in the BRCAness phenotype, characterized by a defect in the HRR pathway, mimicking BRCA1 or BRCA2 loss[46,65]. 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[66,67].

Alterations and prevalence: Somatic mutations in FANCD2 are observed in 4-8% of diffuse large B-cell lymphoma (DLBCL), melanoma, bladder, and uterine cancer[4].

Potential relevance: Currently, no therapies are approved for FANCD2 aberrations. Consistent with other genes that contribute to the BRCAness phenotype, FANCD2 deficiency or loss of function has been shown to confer enhanced sensitivity to PARP inhibitors in vitro[68,69,70].

KMT2A deletion

lysine methyltransferase 2A

Background: The KMT2A gene encodes lysine methyltransferase 2A, a transcriptional coactivator and histone H3 lysine 4 (H3K4) methyltransferase[1,105]. KMT2A, also known as mixed lineage leukemia (MLL), is part of the SET domain protein methyltransferase superfamily[105]. KMT2A influences the epigenetic regulation of several cellular functions, including neurogenesis, hematopoiesis, and osteogenesis[106]. Located at the chromosomal position 11q23, KMT2A is the target of recurrent chromosomal rearrangements observed in several leukemia subtypes, including MLL, acute myeloid leukemia (AML), and acute lymphoblastic leukemia (ALL)[107]. These translocations encode KMT2A fusion proteins that are oncogenic with simultaneous loss of KMT2A H3K4 methyltransferase activity[107]. Loss of methyltransferase activity, along with gain-of-function partner gene activation, contributes to increased HOX gene expression and promotes the transformation of hematopoietic cells into leukemic stem cells[107,108,109,110].

Alterations and prevalence: KMT2A fusions are observed in 3-10% of adult AML cases with the highest frequencies in therapy-related AML (9%) and patients younger than 60 years (5%)[4,5,107,111]. KMT2A rearrangements including t(4;11)(q21;q23)/AFF1::KMT2A, t(9;11)(p22;q23)/MLLT3::KMT2A, t(11;19)(q23;p13.3)/KMT2A::MLLT1, t(10;11)(p12;q23)/MLLT10::KMT2A, and t(6;11)(q27;q23)/AFDN::KMT2A translocations account for about 80% of all KMT2A rearranged leukemias[107]. KMT2A alterations observed in solid tumors include nonsense or frameshift mutations, which result in KMT2A truncation and loss of methyltransferase activity[4,112]. KMT2A alterations are also observed in pediatric cancers[4,5]. In infant acute leukemic cases, KMT2A rearrangement is reported in more than 70% of pediatric patients diagnosed with either AML or ALL and is observed in 5% of T-lymphoblastic leukemia/lymphoma[4,5,107,113,114].

Potential relevance: KMT2A fusions are associated with variable prognosis based on the partner genes involved in the fusion[115,116]. For example, t(6;11)(q27;q23)/AFDN::KMT2A fusions are associated with poor prognosis, whereas t(9;11)(p22;q23)/MLLT3::KMT2A fusions confer a more favorable or intermediate prognosis in AML[117,118,119]. Additionally, 11q23 rearrangements define an unfavorable karyotype in patients diagnosed with primary myelofibrosis (PMF) and may confer intermediate to high risk depending on concurrent cytogenetic abnormalities[27]. KMT2A fusion is also associated with poor risk in adult and pediatric ALL[30,120,121]. Translocations in KMT2A are recognized by the World Health Organization (WHO) as a molecular subtype of B-lymphoblastic leukemia/lymphoma with KMT2A-rearrangement[122]. In 2024, the FDA approved the oral menin inhibitor, revumenib[123], for the treatment of adult and pediatric patients 1 year and older with relapsed or refractory acute leukemia harboring a KMT2A rearrangement. In 2024, the FDA also granted fast track designation to the small molecule inhibitor, DSP-5336, for the treatment of patients with relapsed or refractory AML with KMT2A rearrangements[124].

MLH1 deletion

mutL homolog 1

Background: The MLH1 gene encodes the mutL homolog 1 protein[1]. MLH1 is a tumor suppressor gene that heterodimerizes with PMS2 to form the MutLα complex, PMS1 to form the MutLβ complex, and MLH3 to form the MutLγ complex[37]. The MutLα complex functions as an endonuclease that is specifically involved in the mismatch repair (MMR) process and mutations in MLH1 result in the inactivation of MutLα and degradation of PMS2[37,137]. Loss of MLH1 protein expression and MLH1 promoter hypermethylation correlates with mutations in these genes and are used to pre-screen colorectal cancer or endometrial hyperplasia[138,139]. MLH1,

Biomarker Descriptions (continued)

along with MSH6, MSH2, and PMS2 form the core components of the MMR pathway[37]. The MMR pathway is critical to the repair of mismatch errors which typically occur during DNA replication[37]. Deficiency in MMR (dMMR) is characterized by mutations and loss of expression in these genes[140]. dMMR is associated with microsatellite instability (MSI), which is defined as a change in the length of a microsatellite in a tumor as compared to normal tissue[141,142,143]. MSI-high (MSI-H) is a hallmark of Lynch Syndrome (LS), also known as hereditary non-polyposis colorectal cancer, which is caused by germline mutations in MMR genes[141,144]. LS is associated with an increased risk of developing colorectal cancer, as well as other cancers, including endometrial and stomach cancer[142,144,145,146]. Specifically, MLH1 mutations are associated with an increased risk of ovarian and pancreatic cancer[147,148,149,150].

Alterations and prevalence: Somatic mutations in MLH1 are observed in 6% of uterine corpus endometrial carcinoma, 4% of colorectal adenocarcinoma, and 2-3% of bladder urothelial carcinoma, stomach adenocarcinoma, and melanoma[4,5]. Alterations in MLH1 are observed in pediatric cancers[4,5]. Somatic mutations are observed in 1% of bone cancer and less than 1% of B-lymphoblastic leukemia/lymphoma (2 in 252 cases), embryonal tumor (2 in 332 cases), and leukemia (2 in 311 cases)[4,5].

Potential relevance: The PARP inhibitor, talazoparib[55] in combination with enzalutamide is approved (2023) for metastatic castration-resistant prostate cancer (mCRPC) with mutations in HRR genes that includes MLH1. Additionally, pembrolizumab (2014) is an anti-PD-1 immune checkpoint inhibitor that is approved for patients with MSI-H or dMMR solid tumors that have progressed on prior therapies[151]. Nivolumab (2015), an anti-PD-1 immune checkpoint inhibitor, is approved alone or in combination with the cytotoxic T-lymphocyte antigen 4 (CTLA-4) blocking antibody, ipilimumab (2011), for patients with dMMR colorectal cancer that have progressed on prior treatment[152,153]. MLH1 mutations are consistent with high grade in pediatric diffuse gliomas[154,155].

MLH3 deletion

mutL homolog 3

Background: The MLH3 gene encodes the mutL homolog 3 protein[1]. MLH3 heterodimerizes with MLH1 to form the MutLγ complex which functions as an endonuclease during meiosis, specifically in meiotic recombination[37]. MLH3 is considered a mismatch repair (MMR) gene due to its functional role in yeast, however, its exact MMR role in humans is less clear[37,38,39]. Low expression of MMR genes, including MLH3, have been associated with high levels of microsatellite instability (MSI-H) in colorectal cancer[40].

Alterations and prevalence: Somatic mutations in MLH3 are observed in 9% of uterine corpus endometrial carcinoma, 4% of colorectal adenocarcinoma, skin cutaneous melanoma, and stomach adenocarcinoma[4,5]. Biallelic deletions are observed in 2% of kidney chromophobe[4,5].

Potential relevance: Currently, no therapies are approved for MLH3 aberrations.

MRE11 deletion

MRE11 homolog, double strand break repair nuclease

Background: The MRE11 gene encodes the meiotic recombination 11 protein, a nuclear protein that is part of the multisubunit MRE11/RAD50/NBN (MRN) complex, which is necessary for the maintenance of genomic stability[41]. The MRN complex is involved in the repair of double-stranded breaks (DSB) through two mechanisms namely homologous recombination repair (HRR) and non-homologous end joining (NHEJ)[42,43,44]. Dimerization of MRE11 is required for DNA binding of the MRN complex, and it acts as a 3'–5' exonuclease and ssDNA endonuclease upon binding DNA[41]. MRE11 is a tumor suppressor gene and loss of function mutations are implicated in the BRCAness phenotype, characterized by a defect in the HRR pathway mimicking BRCA1 or BRCA2 loss[45,46]. Germline mutations in MRE11 have been identified as candidate susceptibility aberrations in colorectal cancer and a hallmark of ataxia-telangiectasia-like disorder (ALTD), a heritable disease resulting in progressive cerebellar degeneration and cancer predisposition[47,48,49,50].

Alterations and prevalence: Somatic mutations in MRE11 are observed in 6-7% of uterine cancer as well as 2-3% of lung adenocarcinoma and melanoma[4]. Mutations in the T11 polypyrimidine tract of MRE11 intron 5 are associated with aberrant splicing and reduced MRE11 protein expression. The presence of MRE11 splice variants is frequently observed in mismatch repair deficient (dMMR)/microsatellite instability (MSI-H) colorectal and endometrial cancers[51,52,53,54]

Potential relevance: The PARP inhibitor, talazoparib[55] in combination with enzalutamide is approved (2023) for metastatic castration-resistant prostate cancer (mCRPC) with mutations in HRR genes that includes MRE11. Loss of function in HRR genes, including MRE11, may confer sensitivity to DNA damaging agents and PARP inhibitors[45,46]. Specifically, loss of MRE11 protein expression has been observed to predict sensitivity to PARP inhibitors in colorectal, breast, and endometrial cancers in vitro[56,57,58].

Biomarker Descriptions (continued)

MUTYH deletion

mutY DNA glycosylase

Background: The MUTYH gene encodes the mutY DNA glycosylase protein[1]. DNA glycosylases are structurally specific enzymes that function in base excision repair (BER) by removing damaged or incorrect bases in DNA[71]. MUTYH functions by removing adenine residues that have been misincorporated opposite of 8-oxoG (7,8-dihydro-8-oxoguanine) and FapyG (2,6-diamino-4-hydroxy-5-formamidopyrimidine)[71]. Germline biallelic MUTYH pathogenic variants are associated with MUTYH-Associated Polyposis (MAP), a hereditary condition that confers a predisposition to colorectal cancer[72,73].

Alterations and prevalence: Somatic mutations in MUTYH are observed in 4% of skin cutaneous melanoma and uterine corpus endometrial carcinoma, 2% of lung squamous cell carcinoma, stomach adenocarcinoma, and colorectal adenocarcinoma[4,5]. Biallelic deletions in MUTYH are observed in 2% of pheochromocytoma and paraganglioma[4,5].

Potential relevance: Currently, no therapies are approved for MUTYH 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[180]. Microsatellite instability (MSI) is defined as a change in the length of a microsatellite in a tumor as compared to normal tissue[142,144]. 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[143]. 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[181]. 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)[181]. Tumors classified as MSI-L are often phenotypically indistinguishable from MSS tumors and tend to be grouped with MSS[145,182,183,184,185]. 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[144]. LS is associated with an increased risk of developing colorectal cancer, as well as other cancers, including endometrial and stomach cancer[142,144,145,146].

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[142,144,186,187]. 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[186,187].

Potential relevance: Anti-PD-1 immune checkpoint inhibitors including pembrolizumab[151] (2014) and nivolumab[152] (2015) are approved for patients with MSI-H or dMMR colorectal cancer who have progressed following chemotherapy. Pembrolizumab[151] 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[151]. Dostarlimab[188] (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[183,189]. The cytotoxic T-lymphocyte antigen 4 (CTLA-4) blocking antibody, ipilimumab[153] (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[183,190,191]. 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[191]. 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[192,193]. However, checkpoint blockade with the addition of chemotherapy or targeted therapies have demonstrated response in MSS or pMMR cancers[192,193].

PARP3 deletion

poly(ADP-ribose) polymerase family member 3

Background: The PARP3 gene encodes the poly(ADP-ribose) polymerase 3 protein[1]. PARP3 belongs to the large PARP protein family that also includes PARP1, PARP2, and PARP4[84]. PARP enzymes are responsible for the transfer of ADP-ribose, known as poly(ADP-ribosyl)ation or PARylation, to a variety of protein targets resulting in the recruitment of proteins involved in DNA repair, DNA synthesis, nucleic acid metabolism, and regulation of chromatin structure[84,85]. PARP enzymes are involved in several DNA repair pathways[84,85]. Although the functional role of PARP3 is not well understood, PARP3 may serve a role in double-strand break (DSB) repair by facilitating selection for either non-homologous end joining (NHEJ) or homologous recombination repair (HRR)[86,87]. Specifically, PARP3 is proposed to accelerate DSB repair by NHEJ by targeting APLF to chromosomal DSBs[86].

Biomarker Descriptions (continued)

Alterations and prevalence: Somatic mutations in PARP3 are observed in 4% of uterine corpus endometrial carcinoma, and 2% of skin cutaneous melanoma, lung adenocarcinoma, and stomach adenocarcinoma[4,5]. Biallelic deletions in PARP3 are observed in 4% of diffuse large B-cell lymphoma (DLBCL), 3% of kidney renal clear cell carcinoma, 2% of esophageal adenocarcinoma and sarcoma[4,5].

Potential relevance: Currently, no therapies are approved for PARP3 aberrations. However, PARP inhibition is known to induce synthetic lethality in certain cancer types that are HRR deficient (HRD) due to mutations in the HRR pathway. This is achieved from PARP inhibitors (PARPi) by promoting the accumulation of DNA damage in cells with HRD, consequently resulting in cell death[88,89]. Although not indicated for specific alterations in PARP3, several PARPis including olaparib, rucaparib, talazoparib, and niraparib have been approved in various cancer types with HRD. Olaparib[90] (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[90] 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[91] (2016) was the first PARPi approved for the treatment of patients with either gBRCAm or sBRCAm epithelial ovarian, fallopian tube, or primary peritoneal cancers and is also approved (2020) for deleterious gBRCAm or sBRCAm mCRPC. Talazoparib[55] (2018) is indicated for the treatment of gBRCAm HER2-negative locally advanced or metastatic breast cancer. Niraparib[92] (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.

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)[156]. RAD51B associates with other RAD51 paralogs to form RAD51B-RAD51C-RAD51D-XRCC2 (BCDX2) complex[157]. The BCDX2 complex binds single- and double-stranded DNA to hydrolyze ATP[158]. 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[45,46]. 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[159]. Genetic variation within the RAD51B locus on 14q24.1 is significantly associated with familial breast cancer risk[160].

Alterations and prevalence: Somatic mutations in RAD51B are observed in up to 3% of uterine cancer[4,5]. Loss of function mutations in RAD51B are rare, but variation within the RAD51B locus is significantly associated with familial breast cancer risk[160].

Potential relevance: The PARP inhibitor, olaparib[90] 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[136], for BRCA1/2, PALB2, or other homologous recombination deficiency (HRD) mutations in breast and ovarian cancers.

RAD54L deletion

RAD54 like (S. cerevisiae)

Background: The RAD54L gene encodes the RAD54-like protein and is a member of the Snf2 family of Superfamily 2 (SF2) helicase-like proteins, which also includes its homolog RAD54B[164]. The Snf2 family are a group of DNA translocases that use ATP-hydrolysis to remodel chromatin structure and therefore regulate genome integrity by controlling transcriptional regulation, chromosome stability, and DNA repair[164,165,166]. Structurally, these proteins contain a common Snf2 domain that consists of two RecA-like folds with seven conserved sequence motifs for identifying helicases[164,167]. RAD54L specifically appears to stabilize the association of RAD51 DNA strand exchange activity and binds Holliday junctions to promote branch migration during homologous recombination[168]. RAD54L is a tumor suppressor gene and loss of function mutations in RAD54L are implicated in the BRCAness phenotype, which is characterized by a defect in homologous recombination repair (HRR) mimicking BRCA1 or BRCA2 loss[45].

Alterations and prevalence: Somatic mutations in RAD54L are observed in up to 5% of uterine cancer[4,5].

Potential relevance: The PARP inhibitor, olaparib[90] is approved (2020) for metastatic castration-resistant prostate cancer (mCRPC) with deleterious or suspected deleterious, germline or somatic mutations in HRR genes that includes RAD54L. In 2022, the FDA granted fast track designation to the small molecule inhibitor, pidnarulex[136], for BRCA1/2, PALB2, or other homologous recombination deficiency (HRD) mutations in breast and ovarian cancers.

Biomarker Descriptions (continued)

RPA1 deletion

replication protein A1

Background: The RPA1 gene encodes replication protein A1[1]. Replication protein A (RPA) is a heterotrimeric complex composed of RPA1 (RPA70), RPA2 (RPA32), and RPA3 (RPA14)[349]. RPA is involved in multiple DNA repair processes including base excision repair (BER), nucleotide excision repair (NER), mismatch repair (MMR), non-homologous end joining (NHEJ) and homologous recombination repair (HRR)[349]. RPA is known to participate in DNA damage recognition by binding single stranded DNA (ssDNA) and interacting with several proteins involved in DNA repair processes including XPA, ERCC5, RAD52, RAD51, BRCA1, and BRCA2, thereby promoting DNA replication and repair[349].

Alterations and prevalence: Somatic mutations in RPA1 are observed in 3% of uterine corpus endometrial carcinoma, and 2% of colorectal adenocarcinoma, cervical squamous cell carcinoma, uterine carcinosarcoma, esophageal adenocarcinoma, and skin cutaneous melanoma[4,5]. Biallelic deletions in RPA1 are observed in 2% of adrenocortical carcinoma, liver hepatocellular carcinoma, diffuse large B-cell lymphoma (DLBCL), and lung adenocarcinoma[4,5].

Potential relevance: Currently, no therapies are approved for RPA1 aberrations.

SDHB deletion

succinate dehydrogenase complex iron sulfur subunit B

Background: The SDHB gene encodes succinate dehydrogenase complex iron sulfur subunit B, a subunit of the succinate dehydrogenase (SDH) enzyme complex[1]. The SDH enzyme complex, also known as complex II of the mitochondrial respiratory chain, is composed of four subunits encoded by SDHA, SDHB, SDHC, and SDHD[75,76]. SDH is a key mitochondrial enzyme complex that catalyzes the oxidation of succinate to fumarate in the tricarboxylic acid cycle and transfers the electrons to ubiquinone in the electron transport chain[75,76]. SDHB iron clusters facilitate the transfer of electrons from FADH2 to ubiquinone[78]. Mutations in SDH genes lead to abnormal stabilization of hypoxia-inducible factors and pseudo-hypoxia, thereby promoting cell proliferation, angiogenesis, and tumorigenesis[75,76]. Sporadic and inherited pathogenic mutations in SDHB are known to confer an increased risk for paragangliomas, pheochromocytomas, and gastrointestinal stromal tumors[1,79].

Alterations and prevalence: Somatic mutations in SDHB are observed in 1% cervical squamous cell carcinoma, uterine corpus endometrial carcinoma, skin cutaneous melanoma, colorectal adenocarcinoma, stomach adenocarcinoma, thymoma, lung squamous cell carcinoma, and kidney renal clear cell carcinoma[4,5]. Biallelic loss of SDHB is observed in 6% of cholangiocarcinoma and 2% of pheochromocytoma and paraganglioma[4,5].

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

SETD2 deletion

SET domain containing 2

Background: The SETD2 gene encodes the SET domain containing 2 histone lysine methyltransferase, a protein responsible for the trimethylation of lysine-36 on histone H3 (H3K36)[364,365]. Methylation of H3K36 is a hallmark of active transcription and can be either mono-, di-, or tri-methylated where di- and tri-methylation are thought to be responsible for transcriptional regulation[366]. Trimethylation of H3K36 by SETD2 promotes post-transcriptional gene silencing and prevents aberrant transcriptional initiation[367,368]. SETD2 trimethylation activity is also observed to be involved in DNA repair through the recruitment of DNA repair machinery[365]. Specifically, H3K36 tri-methylation by SETD2 has been shown to regulate mismatch repair (MMR) in vivo, wherein the loss of SETD2 results in MMR deficiency (dMMR) and consequent microsatellite instability (MSI)[369]. Both copy number deletion and mutations resulting in SETD2 loss of function have been observed in a variety of cancers, suggesting a tumor suppressor role for SETD2[365,370].

Alterations and prevalence: Inactivating somatic mutations in SETD2 were first described in clear cell renal cell carcinoma (ccRCC) and are observed to be predominantly missense or truncating[4,370,371]. Mutations at codon R1625 are observed to be the most recurrent with R1625C having been identified to result in loss of SETD2 H3K36 trimethylase activity[4,364]. SETD2 mutation is observed in about 14% of uterine cancer, 12% of ccRCC, 9% of mesothelioma, and 6-7% of melanoma, lung adenocarcinoma, papillary renal cell carcinoma (pRCC), colorectal and bladder cancers[364]. Biallelic loss of SETD2 is observed in about 6% of diffuse large B-cell lymphoma, and about 3% of ccRCC and mesothelioma[364].

Potential relevance: Currently, no therapies are approved for SETD2 aberrations. Mutations in SETD2 can be used to support diagnosis of hepatosplenic T-cell lymphoma (HSTCL)[310].

Biomarker Descriptions (continued)

TP53 deletion

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[410]. Alterations in TP53 are required for oncogenesis as they result in loss of protein function and gain of transforming potential[411]. Germline mutations in TP53 are the underlying cause of Li-Fraumeni syndrome, a complex hereditary cancer predisposition disorder associated with early-onset cancers[412,413].

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%)[4,5,414,415,416,417]. 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[4,5]. Invariably, recurrent missense mutations in TP53 inactivate its ability to bind DNA and activate transcription of target genes[418,419,420,421]. Alterations in TP53 are also observed in pediatric cancers[4,5]. Somatic mutations are observed in 53% of non-Hodgkin lymphoma, 24% of soft tissue sarcoma, 19% of glioma, 13% of bone cancer, 9% of B-lymphoblastic leukemia/lymphoma, 4% of embryonal tumors, 3% of Wilms tumor and leukemia, 2% of T-lymphoblastic leukemia/lymphoma, and less than 1% of peripheral nervous system cancers (5 in 1158 cases)[4,5]. 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)[4,5].

Potential relevance: The small molecule p53 reactivator, PC14586[422] (2020), received a fast track designation by the FDA for advanced tumors harboring a TP53 Y220C mutation. The FDA has granted fast track designation to the p53 reactivator, eprenetapopt[423], (2019) and breakthrough designation[424] (2020) in combination with azacitidine or azacitidine and venetoclax for acute myeloid leukemia patients (AML) and myelodysplastic syndrome (MDS) harboring a TP53 mutation, respectively. In addition to investigational therapies aimed at restoring wild-type TP53 activity, compounds that induce synthetic lethality are also under clinical evaluation[425,426]. TP53 mutation are a diagnostic marker of SHH-activated, TP53-mutant medulloblastoma[427]. 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)[27,30,115,116,206,428]. In mantle cell lymphoma, TP53 mutations are associated with poor prognosis when treated with conventional therapy including hematopoietic cell transplant[258]. 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[429].

TNFRSF14 deletion

TNF receptor superfamily member 14

Background: The TNFRSF14 gene encodes TNF receptor superfamily member 14[1]. TNFRSF14, also known as HVEM, belongs to the tumor necrosis factor superfamily of cell surface receptors (TNFRSF), which interact with the tumor necrosis factor superfamily (TNFSF) of cytokines[256]. TNFSF-TNFRSF interactions regulate several signaling pathways, including those involved in immune cell differentiation, survival, and death[256]. TNFRSF14 can be stimulated by several ligands, including the TNFSF14 ligand (also known as LIGHT), BTLA, and CD160[256,257]. Following ligand binding to TNFRSF in T-cells, TNFRSF proteins aggregate at the cell membrane and initiate co-signaling cascades which promotes activation, differentiation, and survival[256]. In lymphoma, binding of TNFRSF14 by TNFSF14 has been observed to enhance Fas-induced apoptosis, suggesting a tumor suppressor role[257].

Alterations and prevalence: Somatic mutations in TNFRSF14 are observed in 5% of diffuse large B-cell lymphoma (DLBCL), and 2% of skin cutaneous melanoma[4,5]. Biallelic loss of TNFRSF14 occurs in 8% of DLBCL and uveal melanoma, 3% of cholangiocarcinoma, and 2% of adrenocortical carcinoma and liver hepatocellular carcinoma[4,5].

Potential relevance: Currently, no therapies are approved for TNFRSF14 aberrations. Somatic mutations in TNFRSF14 are diagnostic for follicular lymphoma[258]. In addition, TNFRSF14 mutations are associated with poor prognosis in follicular lymphoma[259,260].

ERRFI1 deletion

ERBB receptor feedback inhibitor 1

Background: ERRFI1 encodes ERBB receptor feedback inhibitor 1, a scaffold adaptor protein[1,379]. As an early response gene, expression of ERRFI1 is induced by several stimuli such as stress, hormones, and growth factors such as EGF[379,380]. ERRFI1 directly binds to EGFR resulting in inhibition of EGFR catalytic activity as well as EGFR lysosomal degradation[379,381]. As a tumor suppressor, ERRFI1 induces

Biomarker Descriptions (continued)

apoptosis and inhibits proliferation and invasion[379,382,383,384,385]. ERRFI1 downregulation has been identified in several cancer types and loss of ERRFI1 promotes proliferation and migration[379,382,383,386,387].

Alterations and prevalence: Somatic mutations in ERRFI1 are observed in 4% of uterine corpus endometrial carcinoma and 2% of skin cutaneous melanoma, uterine carcinosarcoma, and colorectal adenocarcinoma[4,5]. Biallelic loss of ERRFI1 is observed in 6% of cholangiocarcinoma, 4% of adrenocortical carcinoma and diffuse large B-cell lymphoma, and 2% of liver hepatocellular carcinoma, pheochromocytoma and paraganglioma, and glioblastoma multiforme[4,5].

Potential relevance: Currently, no therapies are approved for ERRFI1 aberrations.

ENO1 deletion

enolase 1

Background: The ENO1 gene encodes enolase 1 and its alternatively spliced protein isoform, c-MYC promoter binding protein 1 (MBP1)[1,336]. ENO1 is a glycolytic enzyme that catalyzes the dehydration of 2-phosphoglyceric acid to phosphoenolpyruvic acid during glycolysis[336]. In addition to its role in glycolysis, ENO1 acts as a cell surface plasminogen receptor and is involved in cytoskeleton reorganization, stabilization of the mitochondrial membrane, and modulation of several oncogenic pathways, including PI3K/AKT, AMPK/mTOR and Wnt/β-catenin[336,337,338]. ENO1 has been found to be overexpressed in various cancers contributing to upregulation of glycolysis, cancer cell survival and proliferation, chemoresistance, extracellular matrix degradation, migration, invasion, and metastases[336,337,339]. In contrast, MBP1 is known to repress c-MYC transcription under cellular stress and low glucose conditions, leading to suppression of cellular proliferation, migration, and invasion[336,337].

Alterations and prevalence: Somatic mutations in ENO1 are observed in 3% uterine corpus endometrial carcinoma and kidney chromophobe, and 2% of diffuse large B-cell lymphoma, skin cutaneous melanoma, and cervical squamous cell carcinoma[4,5]. Amplification of ENO1 is observed in 2% of adrenocortical carcinoma, pancreatic adenocarcinoma, esophageal adenocarcinoma, ovarian serous cystadenocarcinoma, and sarcoma[4,5]. Biallelic loss of ENO1 is observed in 6% of cholangiocarcinoma, 4% of adrenocortical carcinoma, and 2% of pheochromocytoma and paraganglioma, liver hepatocellular carcinoma, and diffuse large B-cell lymphoma[4,5].

Potential relevance: Currently, no therapies are approved for ENO1 aberrations.

PGD deletion

phosphogluconate dehydrogenase

Background: The PGD gene encodes phosphogluconate dehydrogenase, an essential enzyme of the pentose phosphate pathway (PPP) that catalyzes oxidative decarboxylation of 6-phosphogluconate to ribulose-5-phosphate and reduction of NADP+ to NADPH[1,231]. PPP mediated generation of pentose phosphates and NADPH is essential for nucleic acid synthesis and fatty acid synthesis, respectively, making it a crucial metabolic pathway for cancer cell survival and proliferation[232,233]. Although biallelic deletion appears to be more common than amplification across cancer types, post-translational modifications and overexpression of PGD in cancer have also been observed to result in elevated PPP activity, which is associated with cancer cell proliferation[231,234].

Alterations and prevalence: Somatic mutations in PGD have been observed in 4% of skin cutaneous melanoma, 3% of uterine corpus endometrial carcinoma, 2% of diffuse large B-cell lymphoma, stomach adenocarcinoma, and bladder urothelial carcinoma[4,5]. Biallelic loss of PGD has been observed in 4% of adrenocortical carcinoma, 3% of cholangiocarcinoma, and 2% of pheochromocytoma and paraganglioma and diffuse large B-cell lymphoma[4,5]. Amplification of PGD has been observed in 2% of esophageal adenocarcinoma, ovarian serous cystadenocarcinoma, stomach adenocarcinoma, and sarcoma[4,5].

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

SPEN deletion

spen family transcriptional repressor

Background: SPEN encodes spen family transcriptional repressor[1]. SPEN plays a role in chromosome X inactivation and regulation of transcription[359,360,361]. As a transcriptional repressor, SPEN sequesters transcriptional activators and interacts with other repressors and chromatin remodeling complexes, such as histone deacetylases (HDACs) and the NuRD complex[359,361]. In ERα-positive breast cancers, SPEN binds ERα in a ligand-independent manner and negatively regulates the transcription of ERα targets, acting as a tumor suppressor gene to regulate cell proliferation, tumor growth, and survival[362,363].

Alterations and prevalence: Somatic mutations in SPEN are observed in 13% of skin cutaneous melanoma, 12% of uterine corpus endometrial carcinoma, 10% of stomach adenocarcinoma, 7% of diffuse large B-cell lymphoma, bladder urothelial carcinoma, and

Biomarker Descriptions (continued)

colorectal adenocarcinoma, 6% of cervical squamous cell carcinoma, 5% of head and neck squamous cell carcinoma and lung adenocarcinoma, 4% of lung squamous cell carcinoma and ovarian serous cystadenocarcinoma, 3% of kidney renal clear cell carcinoma, kidney renal papillary cell carcinoma, breast invasive carcinoma, glioblastoma multiforme, and acute myeloid leukemia, and 2% of pancreatic adenocarcinoma, adrenocortical carcinoma, liver hepatocellular carcinoma, uterine carcinosarcoma, and esophageal adenocarcinoma[4,5]. Biallelic loss of SPEN is observed in 6% of cholangiocarcinoma and 2% of pheochromocytoma and paraganglioma[4,5].

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

EPHA2 deletion

EPH receptor A2

Background: The EPHA2 gene encodes the EPH receptor A2[1]. EPHA2 is a member of the erythropoietin-producing hepatocellular carcinoma (Eph) receptors, a group of receptor tyrosine kinases divided into EPHA (EphA1-10) and EPHB (EphB1-6) classes of proteins[93,94]. Like classical tyrosine kinase receptors, Eph activation is initiated by ligand binding resulting downstream signaling involved in various cellular processes including cell growth, differentiation, and apoptosis[94]. Specifically, Eph-EphrinA ligand interaction regulates pathways critical for malignant transformation and key downstream target proteins including PI3K, SRC, Rho and Rac1 GTPases, MAPK, and integrins[93,94].

Alterations and prevalence: Somatic mutations in EPHA2 are observed in 11% of cholangiocarcinoma, 7% of uterine corpus endometrial carcinoma, stomach adenocarcinoma, and skin cutaneous melanoma, 6% of bladder urothelial carcinoma, and 5% of diffuse large B-cell lymphoma (DLBCL) and cervical squamous cell carcinoma[4,5].

Potential relevance: Currently, no therapies are approved for EPHA2 aberrations.

JAK1 deletion

Janus kinase 1

Background: The JAK1 gene encodes Janus kinase 1, a non-receptor protein tyrosine kinase (PTK)[1,11]. JAK1 is a member of the Janus kinase (JAK) family, which includes JAK1, JAK2, JAK3, and TYK2[12]. Janus kinases are characterized by the presence of a second phosphotransferase-related or pseudokinase domain immediately N-terminal to the PTK domain[12]. JAK kinases function with signal transducer and activator of transcription (STAT) proteins to facilitate intracellular signal transduction required for cytokine receptor and interferon-alpha/beta/gamma signaling[12,13,14]. Since JAK1 mediates interferon-γ regulated tumor surveillance, inactivation of JAK1 is believed to inhibit the presentation of tumor antigens and contribute to immune evasion[14,439,440].

Alterations and prevalence: Activating missense mutations in JAK1 that result in constitutive signal transduction are observed in both pediatric and adult T-cell lymphoblastic leukemia[441,442,443]. The recurrent somatic mutation V658F observed in JAK1 is homologous to the V617F mutation in JAK2 and is a known driver mutation in myeloproliferative disease[442]. Recurrent activating mutations in JAK1 are infrequently observed in solid cancers, although two variants, S703I and S729C, were reported in hepatocellular carcinomas[444,445,446]. In addition, V658F and R724H were infrequently observed in diverse cancer types[4,5]. Truncating mutations in JAK1, resulting from dispersed or recurrent frameshift mutations, are common in solid cancers and particularly enriched in uterine cancers[4,5,14]. Recurrent truncating mutations in JAK1 are also associated with high tumor mutation burden (TMB) and microsatellite instability (MSI)[439,440]. JAK1 alterations are rare in pediatric cancers[4,5]. Somatic mutations are observed in 12% of T-lymphoblastic leukemia/lymphoma, 2% of B-lymphoblastic leukemia/lymphoma (4 in 252 cases), and less than 1% of bone cancer (3 in 327 cases) and glioma (1 in 297 cases)[4,5]. JAK1 is amplified in less than 1% of leukemia (1 in 250 cases) and B-lymphoblastic leukemia/lymphoma (1 in 731 cases)[4,5].

Potential relevance: Currently, no therapies are approved for JAK1 aberrations. However, ruxolitinib[29] is a JAK1/2 inhibitor that is FDA approved (2011) for primary myelofibrosis and polycythemia vera. Other JAK inhibitors, including tofacitinib (2012) and baricitinib (2018), are approved for rheumatoid arthritis. JAK1 mutations and fusions confer poor risk in B-cell ALL[30]. Clinical cases associated with high TMB but failure to respond to anti-PD1 therapy were associated with loss of function mutations in JAK1/2[31].

FUBP1 deletion

far upstream element binding protein 1

Background: The FUBP1 gene encodes the far upstream element binding protein 1, a DNA/RNA binding protein implicated in a variety of cellular functions[1,208]. Specifically, FUBP1 is observed to bind single-stranded DNA (ssDNA) and RNA resulting in the regulation of transcription, translation, and splicing[208]. FUBP1 activates the transcription of targets including the oncogene MYC which functions in

Biomarker Descriptions (continued)

cell cycle regulation, metabolism, and apoptosis[208]. FUBP1 is also observed to repress the transcription of targets including the tumor suppressors CDKN1A, CDKN2B, and CDKN1B, which function in cell cycle regulation[208].

Alterations and prevalence: Somatic mutations in FUBP1 are observed in 9% of brain lower grade glioma, 6% of uterine corpus endometrial carcinoma, 4% of skin cutaneous melanoma, and 3% of colorectal adenocarcinoma[4,5]. Mutations typically result in inactivation of FUBP1 through alteration of splicing sites, introduction of stop codons, or out-of-frame insertions or deletions[208]. Biallelic loss of FUBP1 is observed in 3% of pheochromocytoma and paraganglioma[4,5]. Co-deletion of 1p and 19q is frequently observed in oligodendrogliomas, which results in the monoallelic loss of FUBP1 and CIC on 19q[208].

Potential relevance: Currently, no therapies are approved for FUBP1 aberrations.

DPYD deletion

dihydropyrimidine dehydrogenase

Background: The DPYD gene (also known as DPD) encodes dihydropyrimidine dehydrogenase, the initial and rate-limiting enzyme that catalyzes the reduction of uracil and thymidine in the pyrimidine catabolism pathway[1,2]. DPYD is responsible for the inactivation and liver clearance of fluoropyrimidines (fluorouracil, capecitabine, and other analogs), which are the core chemotherapies used in the treatment of solid tumors, such as colorectal, pancreatic, gastric, breast, and head and neck cancers[3]. Inherited DPYD polymorphisms, including DPYD*2A, DPYD*13, DPYD c.2846A>T, and DPYD c.1129-5923T>G, can result in DPD deficiency, which is characterized by impaired enzymatic activity and confers an increased risk of severe toxicity to fluoropyrimidine drugs due to an increase in systemic drug exposure[3].

Alterations and prevalence: Somatic mutations in DPYD have been observed in 20% of skin cutaneous melanoma, 9% of uterine corpus endometrial carcinoma, 6% of stomach adenocarcinoma, 5% of diffuse large B-cell lymphoma and colorectal adenocarcinoma, 4% of lung adenocarcinoma, 3% of bladder urothelial carcinoma, head and neck squamous cell carcinoma, and lung squamous cell carcinoma, and 2% of adrenocortical carcinoma, cervical squamous cell carcinoma, uterine carcinosarcoma, pancreatic adenocarcinoma, esophageal adenocarcinoma, liver hepatocellular carcinoma, and sarcoma[4,5]. Biallelic loss of DPYD has been observed in 4% of pheochromocytoma and paraganglioma and 2% of esophageal adenocarcinoma and lung squamous cell carcinoma[4,5].

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

VHL deletion

von Hippel-Lindau tumor suppressor

Background: The VHL gene encodes the von Hippel-Lindau tumor suppressor protein[1]. VHL possesses ubiquitin ligase activity and forms a ternary complex with transcription elongation factors C and B to make up the VCB complex, which is critical for VHL function[1,59]. VHL is involved in hypoxia-inducible-factor (HIF) regulation through ubiquitination, thereby targeting HIFs, including HIF1α, for proteasomal degradation[59]. Mutations in VHL lead to a destabilized VCB complex that is rapidly degraded by the proteasome, resulting in defective HIF regulation and tumorigenesis[59]. Germline mutations in VHL cause the Von Hippel-Lindau hereditary cancer syndrome, which confers predisposition to several cancer types including clear cell renal carcinoma, central nervous system, and retinal hemangioblastomas, pheochromocytoma, and pancreatic neuroendocrine tumors[59]. Belzutifan is considered for the treatment of progressive pancreatic neuroendocrine tumor harboring VHL germline aberrations[60].

Alterations and prevalence: Somatic mutations in VHL are predominantly truncating followed by missense mutations and are collectively observed in 41% of kidney renal clear cell carcinoma, and 2% of pheochromocytoma and paraganglioma, thymoma and kidney chromophobe[4,5]. Biallelic deletions are observed in 3% of kidney renal clear cell carcinoma and 2% of prostate adenocarcinoma[4,5].

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

TGFBR2 deletion

transforming growth factor beta receptor 2

Background: TGFBR2 encodes transforming growth factor beta receptor 2[1]. Along with TGFBR1 and TGFBR3, TGFBR2 is a member of the TGF-beta receptor family[32]. Both TGFBR1 and TGFBR2 function as serine/threonine and tyrosine kinases, whereas TGFBR3 does not possess any kinase activity[32]. TGFBR1 heterodimerizes with TGFBR2 and activates ligand binding of TGF-beta cytokines namely TGFB1, TGFB2, and TGFB3[32]. Heterodimerization with TGFBR2 enables TGFBR1 to phosphorylate downstream SMAD2/3, which leads

Biomarker Descriptions (continued)

to activation of SMAD4[33]. This process regulates various signaling pathways implicated in cancer initiation and progression, including epithelial to mesenchymal transition (EMT) and apoptosis[34,35,36].

Alterations and prevalence: Somatic mutations in TGFBR2 are observed in 5% of esophageal adenocarcinoma, and head and neck squamous cell carcinoma, 4% of pancreatic adenocarcinoma, stomach adenocarcinoma, uterine corpus endometrial carcinoma, colorectal adenocarcinoma, and cholangiocarcinoma[4,5]. Biallelic deletion of TGFRB2 is observed in 3% of kidney renal clear cell carcinoma and 2% of stomach adenocarcinoma and head and neck squamous cell carcinoma[4,5].

Potential relevance: Currently, no therapies are approved for TGFBR2 aberrations.

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)[1]. As a GEF, DOCK3 functions by catalyzing the exchange of GDP for GTP, and activates the G protein, Rac1, thereby facilitating RAC1 mediated signaling[430]. Consequently, DOCK3 has been observed to facilitate the regulation of several cellular processes including axonal outgrowth, cytoskeletal organization, and cell adhesion[1,431,432]. Unlike other GEFs found to be altered in cancer, DOCK3 has been shown to exhibit tumor suppressor like properties through inhibition of β-catenin/WNT signaling[433,434]. 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[432].

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[4,5]. 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[4,5].

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

PBRM1 deletion

polybromo 1

Background: The PBRM1 gene encodes polybromo 1 protein[1]. PBRM1, also known as BAF180, is a member of the PBAF complex, a SWI/SNF chromatin-remodeling complex[95]. The PBAF complex is a multisubunit protein complex that consists of ARID2, SMARCA4A/BRG1, BRD7, ACTL6A/BAF53A, PHF10/BAF45A, PBRM1/BAF180, SMARCC2/BAF170, SMARCC1/BAF155, SMARCB1/BAF47, SMARCD1/BAF60A, and SMARCE1/BAF57[95,96]. PBRM1 is proposed to facilitate localization of PBAF complexes to specific loci for chromatin remodeling[95,97]. PBRM1 also promotes centromere cohesion in order to maintain genomic stability and prevent aneuploidy by silencing transcription near double-stranded DNA breaks (DSBs), supporting a tumor suppressor role for PBRM1[98,99].

Alterations and prevalence: Somatic mutations in PBRM1 are observed in 38% of kidney renal clear cell carcinoma, 22% of cholangiocarcinoma, 10% of uterine corpus endometrial carcinoma, and 8% of skin cutaneous melanoma[4,5]. Biallelic deletion of PBRM1 is observed in 5% of mesothelioma, 4% of diffuse large B-cell lymphoma (DLBCL), 3% of kidney renal clear cell carcinoma, and 2% of esophageal adenocarcinoma, uterine carcinosarcoma, stomach adenocarcinoma, and sarcoma[4,5].

Potential relevance: Currently, no therapies are approved for PBRM1 aberrations.

TET2 deletion

tet methylcytosine dioxygenase 2

Background: TET2 encodes the tet methylcytosine dioxygenase 2 protein and belongs to the ten-eleven translocation (TET) family, which also includes TET1 and TET3[1,303]. The TET enzymes are involved in DNA methylation, specifically in the conversion of 5-methylcytosine to 5-hydroxymethylcytosine[304,305]. The TET proteins contain a C-terminal core catalytic domain that consists of a cysteine-rich domain and a double-stranded ß-helix domain (DSBH)[304,305]. TET1 and TET3 possess a DNA-binding N-terminal CXXC zinc finger domain, whereas TET2, lacking this domain, is regulated by the neighboring CXXC4 protein, which harbors a CXXC domain and recruits TET2 to unmethylated CpG sites[304,305]. As a tumor suppressor gene, loss of function mutations in TET2 are associated with loss of catalytic activity and transformation to hematological malignancies[303,306,307].

Biomarker Descriptions (continued)

Alterations and prevalence: Somatic TET2 mutations, including nonsense, frameshift, splice site, and missense mutations, are observed in 20-25% of myelodysplastic syndrome (MDS) associated diseases, including 40-60% chronic myelomonocytic leukemia (CMML)[206]. TET2 mutations at H1881 and R1896 are frequently observed in myeloid malignancies[306,308]. TET2 mutations are also observed in 9% of uterine corpus endometrial carcinoma and acute myeloid leukemia (AML), 8% of skin cutaneous melanoma, 7% of diffuse large B-cell lymphoma (DLBCL), 4% of colorectal adenocarcinoma, lung squamous cell carcinoma, and stomach adenocarcinoma, and 2% of sarcoma, esophageal adenocarcinoma, bladder urothelial carcinoma, cervical squamous cell carcinoma, lung adenocarcinoma, uterine carcinosarcoma, and kidney chromophobe[4,5]. Alterations in TET2 are also observed in the pediatric population[5]. Somatic mutations are observed in 3% of Hodgkin lymphoma (2 in 61 cases) and leukemia (9 in 311 cases), and less than 1 % of bone cancer (3 in 327 cases), B-lymphoblastic leukemia/lymphoma (2 in 252 cases), peripheral nervous system cancers (5 in 1158 cases), glioma (1 in 297 cases), and embryonal tumor (1 in 332 cases)[5]. Biallelic deletion of TET2 is observed in 2% of leukemia (6 in 250 cases), and less than 1% of Wilms tumor (1 in 136 cases) and B-lymphoblastic leukemia/lymphoma (4 in 731 cases)[5].

Potential relevance: The presence of TET2 mutations may be used as one of the major diagnostic criteria in pre-primary myelofibrosis (pre-PMF) and overt PMF in the absence of JAK2/CALR/MPL mutations[27]. TET2 mutations are associated with poor prognosis in PMF and an increased rate of transformation to leukemia[309]. TET2 mutations may be utilized for the diagnosis of angioimmunoblastic T-cell lymphoma (AITL) versus other peripheral T-cell lymphomas (PTCLs)[310].

INPP4B deletion

inositol polyphosphate-4-phosphatase type II B

Background: INPP4B encodes inositol polyphosphate 4-phosphatase type II, a member of the inositol polyphosphate 4-phosphatase family which also includes INPP4A[1,435]. INPP4B, along with PTEN and PIPP, is a phosphoinositide phosphatase that modulates the PI3K/AKT signaling pathway by hydrolyzing phosphatidylinositol 3,4-bisphosphate to generate phosphatidylinositol 3-phosphate, thereby suppressing the PI3K/AKT signaling cascade[436]. Although overexpression of INPP4B has been observed in several tumor types and is suggested to be associated with poor outcomes and response to therapy, alterations including mutations leading to loss of INPP4B function have been observed to result in enhanced AKT signaling, cell proliferation, and decreased survival in other tumor types, supporting a tumor suppressor role for INPP4B[437,438].

Alterations and prevalence: Somatic mutations in INPP4B are observed in 9% of uterine corpus endometrial carcinoma, 5% of diffuse large B-cell lymphoma, 4% of lung adenocarcinoma, 3% of skin cutaneous melanoma, head and neck squamous cell carcinoma, and stomach adenocarcinoma, and 2% of cervical squamous cell carcinoma, lung squamous cell carcinoma, bladder urothelial carcinoma, colorectal adenocarcinoma, and uterine carcinosarcoma[4,5]. Biallelic loss of INPP4B is observed in 2% of bladder urothelial carcinoma, uterine carcinosarcoma, and brain lower grade glioma[4,5]. Amplification of INPP4B is observed in 3% of cholangiocarcinoma and esophageal adenocarcinoma, and 2% of sarcoma, stomach adenocarcinoma, and ovarian serous cystadenocarcinoma[4,5].

Potential relevance: Currently, no therapies are approved for INPP4B 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[1,302]. 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[302]. The cytoplasmic tail of FAT1 is known to interact with a number of protein targets involved in cell adhesion, proliferation, migration, and invasion[302]. FAT1 has been observed to influence the regulation of several oncogenic pathways, including the WNT/β-catenin, Hippo, and MAPK/ERK signaling pathways, as well as epithelial to mesenchymal transition[302]. Alterations of FAT1 lead to down-regulation or loss of function, supporting a tumor suppressor role for FAT1[302].

Alterations and prevalence: Somatic mutations in FAT1 are predominantly truncating although, the R1627Q mutation has been identified as a recurrent hotspot[4,5]. 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[4,5]. 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[4,5].

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

Biomarker Descriptions (continued)

ERAP2 deletion

endoplasmic reticulum aminopeptidase 2

Background: The ERAP2 gene encodes the endoplasmic reticulum aminopeptidase 2 protein. ERAP2, and structurally related ERAP1, are zinc metallopeptidases which play a role in antigen processing within the immune response pathway[350,351]. Upon uptake by an immune cell, antigens are first processed by the proteasome and then transported into the endoplasmic reticulum where ERAP1 and ERAP2 excise peptide N-terminal extensions to generate mature antigen peptides for presentation on MHC class I molecules[350,352]. The polymorphic variability in ERAP2 is hypothesized to affect the severity of cytotoxic responses to transformed cells and potentially influence their chances to gain mutations that evade the immune system and become tumorigenic[350].

Alterations and prevalence: Somatic mutations in ERAP2 are observed in 7% of uterine corpus endometrial carcinoma and skin cutaneous melanoma, and 2% of colorectal adenocarcinoma, uterine carcinosarcoma, head and neck squamous cell carcinoma, and stomach adenocarcinoma[4,5]. Deletions are observed in 2% of ovarian serous cystadenocarcinoma, prostate adenocarcinoma, and 1% of colorectal adenocarcinoma, mesothelioma, esophageal adenocarcinoma, and lung squamous cell carcinoma[4,5].

Potential relevance: Currently, no therapies are approved for ERAP2 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[320]. MHC class I molecules are heterodimers composed of two polypeptide chains, α and B2M[321]. 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[322,323,324]. Downregulation of MHC class I promotes tumor evasion of the immune system, suggesting a tumor suppressor role for HLA-B[325].

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[4,5]. Biallelic loss of HLA-B is observed in 5% of DLBCL[4,5].

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

JAK2 deletion

Janus kinase 2

Background: The JAK2 gene encodes Janus kinase 2, a non-receptor protein tyrosine kinase (PTK)[1,11]. JAK2 is a member of the Janus kinase (JAK) family, which includes JAK1, JAK2, JAK3, and TYK2[11]. Janus kinases are characterized by the presence of a second phosphotransferase-related or pseudokinase domain immediately N-terminal to the PTK domain[12]. JAK kinases function with signal transducer and activator of transcription (STAT) proteins to facilitate intracellular signal transduction required for cytokine receptor and interferon-alpha/beta/gamma signaling[12,13,14]. Since JAK2 functions in interferon receptor signaling, inactivation of JAK2 is proposed to inhibit the presentation of tumor antigens and contribute to immune evasion[15,16].

Alterations and prevalence: Clonal expansion of hematopoietic cells in myeloproliferative neoplasms (MPNs) is associated with loss of heterozygosity on chromosome 9p and subsequently the acquisition of a dominant somatic gain-of-function V617F mutation in the pseudokinase domain of JAK2[17,18]. The JAK2 V617F mutation is rarely observed in acute myeloid leukemia (AML)[19,20]. Mutations in the pseudokinase domain of JAK2, including R683G, have been detected in 8% of ALL[21,22]. JAK2 fusions are observed in myeloid and lymphoid leukemias with partner genes including TEL, PCM1, and BCR[23,24,25,26]. JAK2 fusions are infrequently observed in solid tumors[4]. As with JAK1, truncating mutations in JAK2 are common in solid tumors and particularly enriched in uterine cancers[4]. JAK2 is amplified in 4% of sarcoma, diffuse large B-cell lymphoma, and head and neck squamous cell carcinoma, 3% of ovarian serous cystadenocarcinoma, and 2% of esophageal adenocarcinoma, uterine corpus endometrial carcinoma, stomach adenocarcinoma, bladder urothelial carcinoma, and uterine carcinosarcoma[4,5]. Alterations in JAK2 are also observed in pediatric cancers[4,5]. Somatic mutations are observed in 6% of B-lymphoblastic leukemia/lymphoma, 3% of soft tissue sarcoma, 2% of T-lymphoblastic leukemia/lymphoma, and less than 1% of leukemia (3 in 354 cases), bone cancer (2 in 327 cases), glioma (1 in 297 cases), Wilms tumor (1 in 710 cases), and peripheral nervous system tumors (1 in 1158 cases)[4,5]. JAK2 fusions are observed in 10% of B-lymphoblastic leukemia/lymphoma and 1% of leukemia (1 in 107 cases)[4,5]. JAK2 is amplified in 1% of Wilms tumor (2 in 136 cases) and less than 1% of B-lymphoblastic leukemia/lymphoma (4 in 731 cases)[4,5].

Biomarker Descriptions (continued)

Potential relevance: Currently, no therapies are approved for JAK2 aberrations. JAK2 V617F and JAK2 exon 12 mutations are considered major diagnostic criteria of polycythemia vera (PV)[27,28]. Ruxolitinib[29] (2011) is a JAK1/2 inhibitor FDA approved for PMF and PV, although specific JAK2 alterations are not indicated. Other JAK inhibitors including tofacitinib (2012) and baricitinib (2018) are approved for the treatment of rheumatoid arthritis. JAK2 mutations and fusions are associated with poor risk in acute lymphoblastic leukemia[30]. Clinical cases associated with high tumor mutational burden (TMB) but failure to respond to anti-PD1 therapy were associated with loss of function mutations in JAK1/2[31]. Some case studies report efficacy with ruxolitinib in myeloid and lymphoid leukemias, although duration of complete response was limited[23,24,25,26].

PTCH1 deletion

patched 1

Background: The PTCH1 gene encodes the patched 1 protein, a transmembrane protein that along with PTCH2, belongs to the patched gene family[1]. PTCH1 is involved in the Hedgehog (Hh) signaling pathway that plays a significant role in embryonic development, cell proliferation, and cell differentiation[407,408]. PTCH1 is a tumor suppressor gene that inhibits the transmembrane receptor Smoothened (SMO) and prevents downstream Hh signaling pathway activation[407,408]. The Hh pathway is activated when one of the Hh ligands including Sonic hedgehog (SHh), Indian hedgehog (IHh), or Desert Hedgehog (DHh) bind to PTCH1 and disrupt SMO inhibition[408]. Inactivating mutations in PTCH1 lead to ligand-independent signaling of Hh, as PTCH1 no longer prevents SMO activity[408]. Germline mutations in PTCH1 are associated with basal cell nevus syndrome (BCNS) or Gorlin Syndrome with a predisposition to non-cancerous and cancerous tumors including basal cell carcinoma[408,409].

Alterations and prevalence: Inactivating mutations in PTCH1 are observed in 85% of sporadic basal cell carcinomas[409]. Somatic mutations in PTCH1 are also observed in 11% of uterine corpus endometrial carcinoma and 4-5% of stomach adenocarcinoma, skin cutaneous melanoma, cholangiocarcinoma, esophagus adenocarcinoma, colorectal adenocarcinoma, and mesothelioma[4,5].

Potential relevance: Currently, no therapies are approved for PTCH1 aberrations.

MAPK8 deletion

mitogen-activated protein kinase 8

Background: The MAPK8 gene encodes the mitogen-activated protein kinase 8, also known as JNK1[1]. MAPK8 is involved in the JNK signaling pathway along with MAP3K4, MAP3K12, MAP2K4, MAP2K7, MAPK9, and MAPK10[294,295,296]. Activation of MAPK proteins occurs through a kinase signaling cascade[294,295,297]. Specifically, MAP3Ks are responsible for phosphorylation of MAP2K family members[294,295,297]. 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[294,295,297].

Alterations and prevalence: Somatic mutations in MAPK8 are observed in 4% of uterine corpus endometrial carcinoma, 3% of skin cutaneous melanoma, and 2% of colorectal adenocarcinoma[4,5]. Biallelic deletions are observed in 1% of bladder urothelial carcinoma, esophageal adenocarcinoma, adrenocortical carcinoma, and skin cutaneous melanoma[4,5].

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

MEN1 deletion

menin 1

Background: The MEN1 gene encodes the menin 1 protein[1]. MEN1 is a tumor suppressor that functions as a scaffold protein and is known to play a role in histone modification and epigenetic gene regulation through alteration of chromatin structure[1,235]. MEN1 also interacts with several proteins involved in transcription, signaling pathways, and cell division, including JUND, NF-κB, SMAD3, and estrogen receptor α[235,236,237]. Germline mutations in MEN1 result in multiple endocrine neoplasia type 1 (also referred to as MEN1), which is an inherited familial cancer syndrome that causes a predisposition to endocrine tumors, including pituitary, parathyroid, and pancreatic cancer[236,237].

Alterations and prevalence: Somatic mutations in MEN1 are observed in 8% of adrenocortical carcinoma, 5% of uterine corpus endometrial carcinoma, and 3% of stomach adenocarcinoma and skin cutaneous melanoma[4,5]. Biallelic deletion of MEN1 is observed in 1% of adrenocortical carcinoma and esophageal adenocarcinoma[4,5].

Potential relevance: Currently, no therapies are approved for MEN1 aberrations.

Biomarker Descriptions (continued)

SDHD deletion

succinate dehydrogenase complex subunit D

Background: The SDHD gene encodes succinate dehydrogenase complex subunit D of the succinate dehydrogenase (SDH) enzyme complex[1,74]. The SDH enzyme complex, also known as complex II of the mitochondrial respiratory chain, is composed of four subunits encoded by SDHA, SDHB, SDHC, and SDHD[75,76]. SDH is a key mitochondrial enzyme complex that catalyzes the oxidation of succinate to fumarate in the tricarboxylic acid cycle and transfers the electrons to ubiquinone in the electron transport chain[75,76]. SDHD, along with SDHC, anchors SDHA and SDHB to the inner mitochondrial membrane and provides a binding site for ubiquinone[74]. Mutations in SDH genes lead to abnormal stabilization of hypoxia-inducible factors and pseudo-hypoxia, thereby promoting cell proliferation, angiogenesis, and tumorigenesis[74,75,76]. Inherited pathogenic mutations in SDHD have been associated with paragangliomas and gastrointestinal stromal tumors[1,74,77].

Alterations and prevalence: Somatic mutations in SDHD are observed in 1% of mesothelioma, uterine corpus endometrial carcinoma, adrenocortical carcinoma, esophageal adenocarcinoma, colorectal adenocarcinoma, and lung adenocarcinoma[4,5]. Biallelic loss of SDHD is observed in 3% of testicular germ cell tumors, skin cutaneous melanoma, cervical squamous cell carcinoma, and uveal melanoma, and 2% of sarcoma and uterine carcinosarcoma[4,5].

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

ACVR1B deletion

activin A receptor type 1B

Background: The ACVR1B gene encodes the activin A type 1B receptor protein, a transmembrane serine-threonine kinase receptor and member of the bone morphogenic protein (BMP)/transforming growth factor-beta (TGFβ) receptor family[1,298]. ACVR1B is a type I receptor that forms a heterotetrametric complex with at least two type I receptors (including ACVR1) and two type II receptors (including BMPR2, ACVR2A, and ACVR2B)[298,299]. When ligands, such as activin A or BMPs, dimerize and bind to the heterotetrametric complex, type II receptors transphosphorylate and activate type I receptors leading to phosphorylation of SMAD proteins and downstream signaling[298,299]. Loss of function mutations and homozygous deletion in ACVR1B has been observed in pancreatic cancer and is associated with increased cell growth, colony formation, and tumorigenicity[300,301].

Alterations and prevalence: Somatic mutations of ACVR1B are observed in 5% of uterine corpus endometrial carcinoma, 4% of colorectal adenocarcinoma, 3% of stomach adenocarcinoma, 2% of lung adenocarcinoma, skin cutaneous melanoma, lung squamous cell carcinoma, uterine carcinosarcoma, esophageal adenocarcinoma, and kidney chromophobe, and 1% of head and neck squamous cell carcinoma, kidney renal clear cell carcinoma, breast invasive carcinoma, brain lower grade glioma, ovarian serous cystadenocarcinoma, pancreatic adenocarcinoma, liver hepatocellular carcinoma, and acute myeloid leukemia[4,5]. Biallelic deletion of ACRV1B is observed in 1% of stomach adenocarcinoma, brain lower grade glioma, and pancreatic adenocarcinoma[4,5].

Potential relevance: Currently, no therapies are approved for ACVR1B aberrations.

DICER1 deletion

dicer 1, ribonuclease III

Background: The DICER1 gene encodes the dicer 1, ribonuclease III protein[1]. DICER1 is a member of the ribonuclease (RNase) III family that also includes DROSHA[314]. Both DICER and DROSHA are responsible for the processing of precursor non-coding RNA (primary miRNA) into micro-RNA (miRNA)[314,315]. Following primary miRNA processing to hairpin precursor miRNA (pre-miRNA) by DROSHA and DGCR8, pre-miRNA is then cleaved by DICER1 resulting in the production of mature miRNA[314]. Once processed, mature miRNA is capable of post-transcriptional gene repression by recognizing complimentary target sites on messenger RNA (mRNA)[314,315]. miRNAs are frequently dysregulated in cancer, potentially through DGCR8, DICER1, or DROSHA aberrations that impact miRNA processing[315,316,317,318]. Germline DICER1 mutations result in DICER1 syndrome, a rare genetic disorder that predisposes affected individuals to tumor development[319].

Alterations and prevalence: Somatic mutations in DICER1 are observed in 13% of uterine corpus endometrial carcinoma, 11% of skin cutaneous melanoma, and 4% of colorectal adenocarcinoma, bladder urothelial carcinoma, and uterine carcinosarcoma[4,5]. Biallelic loss of DICER1 is observed in 3% of cholangiocarcinoma and 2% kidney chromophobe[4,5].

Potential relevance: Currently, no therapies are approved for DICER1 aberrations.

Biomarker Descriptions (continued)

CYLD deletion

CYLD lysine 63 deubiquitinase

Background: The CYLD gene encodes CYLD lysine 63 deubiquitinase, which is a deubiquitinating enzyme (DUB) and a member of the ubiquitin-specific protease (USP) family of deubiquitinases[1,6]. DUBs are responsible for protein deubiquitination, thereby counter-regulating the post-transcriptional ubiquitin modification of proteins within the cell[7]. CLYD contains a USP domain with a catalytic triad formed by Cys601, His871, and Asp889 that selectively hydrolyses K63-linked ubiquitin chains from signaling molecules and regulates cell survival, proliferation, and tumorigenesis[8,9]. CYLD plays a tumor suppressor role by negatively regulating NF-κB activation by deubiquitinating multiple NF-κB signaling components, including NEMO, Tak1, TRAF2, TRAF6, and RIP1[10]. Mutations in CYLD were originally identified in patients with familial cylindromatosis, a genetic condition that predisposes patients to the development of skin appendage tumors[9,10]. CYLD has also been found to be downregulated in melanoma, salivary gland tumors, head and neck cancer, colon and hepatocellular carcinoma, cervical cancer, lung cancer, and renal cell carcinoma[9].

Alterations and prevalence: Somatic mutations in CYLD have been observed in 6% of uterine corpus endometrial carcinoma, 3% of stomach adenocarcinoma, skin cutaneous melanoma, colorectal adenocarcinoma, head and neck squamous cell carcinoma, and lung squamous cell carcinoma, and 2% of thymoma, esophageal adenocarcinoma, lung adenocarcinoma, and kidney chromophobe[4,5]. Biallelic loss of CYLD has been observed in 2% of prostate adenocarcinoma, diffuse large B-cell lymphoma, sarcoma, and uterine carcinosarcoma[4,5].

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

CBFB deletion

core-binding factor beta subunit

Background: The CBFB gene encodes the core-binding factor subunit beta, a member of the PEBP2/CBF transcription factor family[1]. CBFB is capable of heterodimerization with the RUNX protein family (RUNX1, RUNX2, and RUNX3) which results in the formation of the core binding factor (CFB) complex, a transcription factor complex responsible for the regulation of many critical functions in hematopoiesis and osteogenesis[340,341,342]. Although possessing no DNA-binding activity, CBFB has been observed to enhance stability and transcriptional activity of RUNX proteins, thereby exhibiting a critical role in RUNX mediated transcriptional regulation[341,342]. In cancer, mutations in CBFB have been implicated in decreased protein stability and loss of function, supporting a tumor suppressor role for CBFB[342]

Alterations and prevalence: Somatic mutations in CBFB are observed in 2% of diffuse large B-cell lymphoma, breast invasive carcinoma, and uterine corpus endometrial carcinoma[4]. Biallelic deletions in CBFB are found in 2% of ovarian serous cystadenocarcinoma, prostate adenocarcinoma, and breast invasive carcinoma[4]. Translocations including inv(16) and t(16;16) have been observed to be recurrent in de novo AML, occurring in 7-10% of patients, and have been associated with the AML M4 with bone barrow eosinophilia (M4Eo) subtype[343]. Translocations often result in CBFB::MYH11 fusion, which can exist as one of multiple transcripts, depending on the exons fused[343].

Potential relevance: Currently, no therapies are approved for CBFB aberrations. In AML, CBFB translocations, including inv(16) and t(16;16) which result in CBFB::MYH11 fusion, are associated with favorable prognosis and define a distinct molecular subtype of AML according to the World Health Organization (WHO)[28,115,116].

CTCF deletion

CCCTC-binding factor

Background: The CTCF gene encodes the CCCTC-binding factor, a member of the BORIS + CTCF gene family[1]. CTCF promotes the formation of cohesion-mediated loops, the formation of which organizes chromatin into self-interacting topologically associated domains (TADs) and influences gene expression[125]. Additionally, CTCF has been observed to function as a transcription factor through the binding of transcriptional start sites (TSS), but may also play a role in transcriptional repression[125,126,127]. CTCF mutations lead to disruption of TAD boundaries which alters gene expression and may promote oncogenesis[125].

Alterations and prevalence: Somatic mutations in CTCF are observed in 25% of uterine corpus endometrial carcinoma, 5% of stomach adenocarcinoma and uterine carcinosarcoma, 4% of colorectal adenocarcinoma, and 3% of bladder urothelial carcinoma, head and neck squamous cell carcinoma, and cholangiocarcinoma[4,5].

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

Biomarker Descriptions (continued)

CDH1 deletion

cadherin 1

Background: The CDH1 gene encodes epithelial cadherin or E-cadherin, a member of the cadherin superfamily that includes the classical cadherins: neural cadherin (N-cadherin), retinal cadherin (R-cadherin), and placental cadherin (P-cadherin)[1,372]. E-cadherin proteins, composed of 5 extracellular cadherin repeats, a single transmembrane domain, and conserved cytoplasmic tail, are calcium-dependent transmembrane glycoproteins expressed in epithelial cells[1]. Extracellular E-cadherin monomers form homodimers with those on adjacent cells to form adherens junctions. Adherens junctions are reinforced by intracellular complexes formed between the cytoplasmic tail of E-cadherin and catenins, proteins which directly anchor cadherins to actin filaments[373]. E-cadherin is a critical tumor suppressor and when lost, results in epithelial-mesenchymal transition (EMT), anchorage-independent cell growth, loss of cell polarity, and tumor metastasis[374,375]. Germline mutations in CDH1 are enriched in a rare autosomal-dominant genetic malignancies such as hereditary diffuse gastric cancer, lobular breast cancer, and colorectal cancer[376].

Alterations and prevalence: Mutations in CDH1 are predominantly missense or truncating and have been observed to result in loss of function[4,5,377,378]. In cancer, somatic mutation of CDH1 is observed in 12% of invasive breast carcinoma, 10% of stomach adenocarcinoma, 7% of uterine corpus endometrial carcinoma, 4% of colorectal adenocarcinoma and skin cutaneous melanoma, 3% of bladder urothelial carcinomas, and 2% of lung squamous cell and liver hepatocelluar carcinomas[4,5]. Biallelic deletion of CDH1 is observed in 3% of prostate adenocarcinoma and ovarian serous cystadenocarcinoma, and 2% of esophageal adenocarcinoma, diffuse large B-cell lymphoma, and breast invasive carcinoma[4,5].

Potential relevance: Currently, no therapies are approved for CDH1 aberrations.

ZFHX3 deletion

zinc finger homeobox 3

Background: ZFHX3 encodes zinc finger homeobox 3, a large transcription factor composed of several DNA binding domains, including seventeen zinc finger domains and four homeodomains[1,326,327]. Functionally, ZFHX3 is found to be necessary for neuronal and myogenic differentiation[327,328]. ZFHX3 is capable of binding and repressing transcription of α-fetoprotein (AFP), thereby negatively regulating the expression of MYB and cancer cell growth[329,330,331,332,333]. In addition, ZFHX3 has been observed to be altered in several cancer types, supporting a tumor suppressor role for ZFHX3[329,332,334,335].

Alterations and prevalence: Somatic mutations in ZFHX3 are observed in 24% of uterine corpus endometrial carcinoma, 14% of skin cutaneous melanoma, 10% of colorectal adenocarcinoma, 9% of stomach adenocarcinoma, 8% of lung squamous cell carcinoma, 6% of cervical squamous cell carcinoma, 5% of uterine carcinosarcoma, bladder urothelial carcinoma, and lung adenocarcinoma, 3% of head and neck squamous cell carcinoma, adrenocortical carcinoma, cholangiocarcinoma, esophageal adenocarcinoma, and prostate adenocarcinoma, and 2% of diffuse large B-cell lymphoma, glioblastoma multiforme, pancreatic adenocarcinoma, liver hepatocellular carcinoma, thyroid carcinoma, breast invasive carcinoma, ovarian serous cystadenocarcinoma, thymoma, sarcoma, and acute myeloid leukemia[4,5]. Biallelic loss of ZFHX3 is observed in 6% of prostate adenocarcinoma, 4% of uterine carcinosarcoma, 3% of ovarian serous cystadenocarcinoma, and 2% of uterine corpus endometrial carcinoma, breast invasive carcinoma, and esophageal adenocarcinoma[4,5].

Potential relevance: Currently, no therapies are approved for ZFHX3 aberrations.

GPS2 deletion

G protein pathway suppressor 2

Background: GPS2 encodes G protein pathway suppressor 2[1]. GPS2 is a core subunit regulating transcription and suppresses G protein-activated MAPK signaling[353]. GPS2 plays a role in several cellular processes including transcriptional regulation, cell cycle regulation, metabolism, proliferation, apoptosis, cytoskeleton architecture, DNA repair, and brain development[353,354]. Dysregulation of GPS2 through decreased expression, somatic mutation, and deletion is associated with oncogenic pathway activation and tumorigenesis, supporting a tumor suppressor role for GPS2[355,356,357].

Alterations and prevalence: Somatic mutations in GPS2 are predominantly splice site or truncating mutations and have been observed in 3% of cholangiocarcinoma, and 2% of uterine corpus endometrial carcinoma, bladder urothelial carcinoma, and colorectal adenocarcinoma[4,5]. Biallelic loss of GPS2 is observed in 4% of prostate adenocarcinoma, and 2% of liver hepatocellular carcinoma and diffuse large B-cell lymphoma[4,5]. Isolated GSP2 fusions have been reported in cancer with various fusion partners[4,5,358]. In one case, MLL4::GPS2 fusion was observed to drive anchorage independent growth in a spindle cell sarcoma[358].

Potential relevance: Currently, no therapies are approved for GPS2 aberrations.

Biomarker Descriptions (continued)

NCOR1 deletion

nuclear receptor corepressor 1

Background: NCOR1 encodes nuclear receptor corepressor 1, which serves as a scaffold protein for large corepressor including transducin beta like 1 X-linked (TBL1X), TBL1X/Y related 1 (TBL1XR1), the G-protein-pathway suppressor 2 (GPS2), and protein deacetylases such as histone deacetylase 3 (HDAC3)[1,344,345]. NCOR1 plays a key role in several processes including embryonal development, metabolism, glucose homeostasis, inflammation, cell fate, chromatin structure and genomic stability[344,345,346,347]. NCOR1 has been shown exhibit a tumor suppressor role by inhibiting invasion and metastasis in various cancer models[345]. Inactivation of NCOR1 through mutation or deletion is observed in several cancer types including colorectal cancer, bladder cancer, hepatocellular carcinomas, lung cancer, and breast cancer[345,348].

Alterations and prevalence: Somatic mutations in NCOR1 are observed in 13% of uterine corpus endometrial carcinoma, 11% of skin cutaneous melanoma, 8% of bladder urothelial carcinoma, 7% of stomach adenocarcinoma, 6% of colorectal adenocarcinoma, 5% of lung squamous cell carcinoma and breast invasive carcinoma, 4% of cervical squamous cell carcinoma and lung adenocarcinoma, 3% of mesothelioma, head and neck squamous cell carcinoma, cholangiocarcinoma, and kidney renal papillary cell carcinoma, and 2% of esophageal adenocarcinoma, glioblastoma multiforme, and ovarian serous cystadenocarcinoma[4,5]. Biallelic loss of NCOR1 are observed in 3% of liver hepatocellular carcinoma, and 2% of uterine carcinosarcoma, stomach adenocarcinoma, diffuse large B-cell lymphoma, and bladder urothelial carcinoma[4,5]. Structural variants of NCOR1 are observed in 3% of cholangiocarcinoma and 2% of uterine carcinosarcoma[4,5].

Potential relevance: Currently, no therapies are approved for NCOR1 aberrations.

RUNX1 deletion

RUNX family transcription factor 1

Background: The RUNX1 gene encodes the runt-related transcription factor (RUNX) 1, part of the RUNX family of transcription factors, which also includes RUNX2 and RUNX3[194]. All RUNX proteins share several conserved regions with similar functionality, including a highly conserved N-terminal ‘runt’ domain responsible for binding DNA, a C-terminal region composed of an activation domain, inhibitory domain, protein-interacting motifs, and a nuclear matrix targeting signal[195]. Each of these proteins interacts with core binding factor beta (CBFβ) to form the core binding factor (CFB) complex[195]. Consequently, RUNX1, RUNX2, and RUNX3 are collectively known as core binding factor alpha (CBFα) since they can each function as the alpha subunit of CBF[196]. Specifically, CBFβ binds to the 'runt' domain of RUNX1, leading to RUNX1 stabilization and increased affinity of the CFB complex for promoters involved in hematopoietic differentiation and cell cycle regulation[197,198]. RUNX1 is frequently mutated in various hematological malignancies[198]. Germline mutations in RUNX1 result in a rare autosomal dominant condition known as familial platelet disorder with predisposition to acute myeloid leukemia (FPD/AML)[199,200]. Somatic mutations and chromosomal translocations in RUNX1 are often observed in myelodysplastic syndrome (MDS), acute myeloid leukemia (AML), acute lymphoblastic leukemia (ALL), and chronic myelomonocytic leukemia (CMML)[198].

Alterations and prevalence: RUNX1 is frequently rearranged in hematological malignancies with over 50 different observed translocations[201]. RUNX1 translocations occur in 4% of all AML[4,5]. A recurrent translocation, t(8;21)(q22;q22), results in RUNX1::RUNX1T1 fusion and is observed in 5-10% of AML[202]. The RUNX1::RUNX1T1 fusion, consists of the runt-homology domain (RHD) of RUNX1 and the majority of RUNX1T1, which promotes oncogenesis by altering transcriptional regulation of RUNX1 target genes[198,202]. Another translocation, t(12;21)(q34;q11), results in ETV6::RUNX1 fusion and is observed in 2% of adult ALL[203]. Somatic mutations in RUNX1 include missense, nonsense, and frameshift mutations resulting in loss of function or dominant negative effects[198]. RUNX1 somatic mutations are observed in approximately 10% of AML, 10-15% of MDS, 5% of uterine corpus endometrial carcinoma, 4% of breast invasive carcinoma, 3% of bladder urothelial carcinoma, and 2% of colorectal adenocarcinoma[4,5,198]. Biallelic deletion of RUNX1 is observed in 7% of esophageal adenocarcinoma and 2% of stomach adenocarcinoma[4,5]. Alterations in RUNX1 are common in pediatric cancers, particularly the ETV6::RUNX1 fusion, which is observed in 20-25% of childhood ALL[203,204]. Overall, RUNX1 fusions are observed in 12% of B-lymphoblastic leukemia/lymphoma[4,5]. Somatic mutations in RUNX1 are observed in 5% of T-lymphoblastic leukemia/lymphoma, and less than 1% of bone cancer (3 in 327 cases), B-lymphoblastic leukemia/lymphoma (1 in 252 cases), glioma (1 in 297 cases), and embryonal tumor (1 in 332 cases)[4,5]. Biallelic deletion of RUNX1 is observed in 5% of leukemia and less than 1% of B-lymphoblastic leukemia/lymphoma (5 in 731 cases)[4,5].

Potential relevance: AML with RUNX1::RUNX1T1 fusions is considered a distinct molecular subtype by the World Health Organization (WHO)[28]. Translocations involving RUNX1, specifically t(8;21)(q22;q22)/RUNX1::RUNX1T1, is associated with favorable risk in AML[116]. The translocation t(12;21)(q34;q11) that results in ETV6::RUNX1 fusion is associated with standard risk in adult ALL and favorable risk in pediatric ALL[30,120,205]. On the other hand, mutations in RUNX1 confer poor prognosis in AML, MDS, and systemic mastocytosis (SM)[116,206,207].

Alerts Informed By Public Data Sources

Current FDA Information

Contraindicated Not recommended Resistance Breakthrough Fast Track

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

ERBB2 amplification

trastuzumab pamirtecan

Cancer type: Endometrial Carcinoma **Variant class:** ERBB2 overexpression

Supporting Statement:
The FDA has granted Breakthrough Therapy designation to antibody-drug conjugate, trastuzumab pamirtecan (DB-1303), for the treatment of patients with HER2-expressing advanced endometrial cancer.

Reference:

https://investors.biontech.de//news-releases/news-release-details/biontech-and-dualitybio-receive-fda-breakthrough-therapy

disitamab vedotinaide

Cancer type: Bladder Urothelial Carcinoma **Variant class:** ERBB2 positive

Supporting Statement:
The FDA has granted Breakthrough Therapy designation to the humanized anti-HER2 antibody drug conjugate (ADC), disitamab vedotin, for the second-line treatment of HER2 positive locally advanced or metastatic urothelial cancer (UC) after previous platinum-containing chemotherapy treatment.

Reference:

https://www.prnewswire.com/news-releases/remegen-announces-us-fda-has-granted-breakthrough-therapy-designation-for-disitamab-vedotin-rc48-in-urothelial-cancer-301138315.html

CT-0508

Cancer type: Solid Tumor **Variant class:** ERBB2 overexpression

Supporting Statement:

The FDA has granted Fast Track designation to the HER2 targeted chimeric antigen receptor macrophage (CAR-M), CT-0508, for HER2-overexpressing solid tumors.

Reference:

https://www.prnewswire.com/news-releases/carisma-therapeutics-announces-us-food-and-drug-administration-grants-fast-track-designation-to-ct-0508-for-the-treatment-of-patients-with-solid-tumors-301381843.html

ERBB2 amplification (continued)

CT-0525

Cancer type: Solid Tumor

Variant class: ERBB2 overexpression

Supporting Statement:
The FDA has granted Fast Track designation to the ex vivo gene-modified autologous chimeric antigen receptor-monocyte (CAR-Monocyte) cellular therapy, CT-0525, for the treatment of patients with human epidermal growth factor receptor 2 (HER2) overexpressing solid tumours.

Reference:

https://www.prnewswire.com/news-releases/carisma-therapeutics-granted-fda-fast-track-designation-for-ct-0525-for-the-treatment-of-her2overexpressing-solid-tumors-302180804.html

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anvatabart opadotin

Cancer type: Breast Cancer

Variant class: ERBB2 positive

Supporting Statement:
The FDA has granted Fast Track designation to the HER2-targeting antibody drug conjugate, anvatabart opadotin (ARX-788), for HER2-positive metastatic breast cancer.

Reference:

https://ir.ambrx.com/news/news-details/2023/ACE-Breast-02-Pivotal-Phase-3-Study-of-Ambrxs-ARX788-for-the-Treatment-of-HER2-Positive-Metastatic-Breast-Cancer-Achieves-Positive-Results/default.aspx

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zanidatamab + chemotherapy

Cancer type: Gastroesophageal Junction Adenocarcinoma

Variant class: ERBB2 overexpression

Supporting Statement:
The FDA has granted Fast Track designation to the HER2 targeted bispecific antibody, zanidatamab, for HER2-overexpressing gastroesophageal adenocarcinoma (GEA) to be used in combination with standard-of-care chemotherapy.

Reference:

https://www.targetedonc.com/view/her2targeted-antibody-zw25-earns-fda-fast-track-designation-in-gea

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CYNK-101 + pembrolizumab + trastuzumab + chemotherapy

Cancer type: Gastric Cancer, Gastroesophageal Junction Adenocarcinoma

Variant class: ERBB2 positive

Supporting Statement:
The FDA has granted Fast Track designation to the genetically modified cryopreserved human placental hematopoietic stem cell-derived natural killer (NK) cell therapy, CYNK-101, in combination with standard chemotherapy, trastuzumab, and pembrolizumab for the treatment of HER2/neu positive gastric or gastroesophageal junction (G/GEJ) adenocarcinoma.

Reference:

https://celularity.com/celularity-receives-fast-track-designation-from-u-s-fda-for-its-nk-cell-therapy-cynk-101/

ERBB2 amplification (continued)

evorpacept

Cancer type: Gastric Cancer, Gastroesophageal Junction Adenocarcinoma

Variant class: ERBB2 positive

Supporting Statement:
The FDA has granted Fast Track designation to the CD47 checkpoint inhibitor, ALX148, for the second-line treatment of patients with HER2-positive gastric or gastroesophageal junction carcinoma.

Reference:

https://www.targetedonc.com/view/two-fda-fast-track-designations-granted-to-alx148-for-hnscc-and-gastricgej-adenocarcinomas

ERBB2 p.(L755S) c.2264T>C

BAY-2927088

Cancer type: Non-Small Cell Lung Cancer

Variant class: ERBB2 activating mutation

Supporting Statement:
The FDA has granted Breakthrough Therapy designation to an oral small molecule tyrosine kinase inhibitor, BAY 2927088, for the treatment of patients with HER2 activating mutation in non-small cell lung cancer (NSCLC).

Reference:

https://www.biospace.com/article/releases/bayer-receives-u-s-fda-breakthrough-therapy-designation-for-bay-2927088-for-non-small-cell-lung-cancer-harboring-her2-activating-mutations

zongertinib

Cancer type: Non-Small Cell Lung Cancer

Variant class: ERBB2 activating mutation

Supporting Statement:
The FDA has granted Breakthrough Therapy designation to the tyrosine kinase inhibitor, zongertinib (BI 1810631), for the treatment of adult patients with advanced, unresectable or metastatic non-small cell lung cancer (NSCLC) whose tumors have activating HER2 mutations and who have received prior systemic therapy.

Reference:

https://www.boehringer-ingelheim.com/us/human-health/cancer/boehringer-ingelheim-unveil-oncology-research-wclc

Current ESMO Information

Contraindicated Not recommended Resistance Breakthrough Fast Track

ESMO information is current as of 2025-05-01. For the most up-to-date information, search www.esmo.org.

ERBB2 amplification

hormone therapy

Cancer type: Breast Cancer **Variant class:** ERBB2 positive

Other criteria: Hormone receptor positive

ESMO Level of Evidence/Grade of Recommendation: III / C

Summary:

ESMO™ Clinical Practice Guidelines include the following supporting statement:

- "The use of single-agent ET without a HER2-targeted therapy is not routinely recommended unless cardiac disease precludes the safe use of HER2-directed therapies [III, C]"

Reference: ESMO Clinical Practice Guidelines - ESMO-Metastatic Breast Cancer [Ann Oncol (2021) VOLUME 32, ISSUE 12, P1475-1495, DECEMBER 01, 2021; DOI:https://doi.org/10.1016/j.annonc.2021.09.019]

trastuzumab

Cancer type: Gastric Cancer **Variant class:** ERBB2 overexpression

Summary:

ESMO Clinical Practice Guidelines include the following supporting statement:

- "Treatment with trastuzumab is not recommended after first-line therapy in HER2-positive advanced gastric cancer [I, D]."

Reference: ESMO Clinical Practice Guidelines - ESMO-Gastric Cancer [Ann Oncol (2022), doi: https://doi.org/10.1016/j.annonc.2022.07.004.]

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,

Genes Assayed (continued)

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

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

ERBB2 amplification

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
trastuzumab deruxtecan	◑	◑	◑	◑	● (IV)
trastuzumab (Henlius)	◑	✖	●	✖	✖

* 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

ERBB2 amplification (continued)

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
ado-trastuzumab emtansine	●	◑	●	◑	● (II)
trastuzumab + paclitaxel	●	◑	●	●	✖
trastuzumab + docetaxel	●	◑	●	○	✖
trastuzumab	●	◑	●	✖	● (IV)
lapatinib + capecitabine	●	●	●	●	✖
neratinib	●	●	●	●	✖
pertuzumab + trastuzumab + chemotherapy	●	●	●	●	✖
pertuzumab + trastuzumab + docetaxel	●	●	●	●	✖
trastuzumab + tucatinib + capecitabine	●	●	●	●	✖
trastuzumab + carboplatin + docetaxel	●	●	●	✖	✖
neratinib + capecitabine	●	●	✖	✖	✖
lapatinib + letrozole	●	✖	●	✖	✖
pertuzumab/trastuzumab/hyaluronidase-zzxf + cyclophosphamide + doxorubicin	●	✖	●	✖	✖
pertuzumab/trastuzumab/hyaluronidase-zzxf + docetaxel	●	✖	●	✖	✖
trastuzumab (Biocon)	●	✖	●	✖	✖
trastuzumab (Biocon) + carboplatin + docetaxel	●	✖	●	✖	✖
trastuzumab (Biocon) + docetaxel	●	✖	●	✖	✖
trastuzumab (Biocon) + paclitaxel	●	✖	●	✖	✖
trastuzumab (Celltrion)	●	✖	●	✖	✖
trastuzumab (Celltrion) + carboplatin + docetaxel	●	✖	●	✖	✖
trastuzumab (Celltrion) + docetaxel	●	✖	●	✖	✖
trastuzumab (Celltrion) + paclitaxel	●	✖	●	✖	✖
trastuzumab (Pfizer)	●	✖	●	✖	✖
trastuzumab (Pfizer) + carboplatin + docetaxel	●	✖	●	✖	✖
trastuzumab (Pfizer) + docetaxel	●	✖	●	✖	✖
trastuzumab (Pfizer) + paclitaxel	●	✖	●	✖	✖
trastuzumab (Samsung Bioepis)	●	✖	●	✖	✖
trastuzumab (Samsung Bioepis) + carboplatin + docetaxel	●	✖	●	✖	✖

* 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

ERBB2 amplification (continued)

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
trastuzumab (Samsung Bioepis) + docetaxel	●	✖	●	✖	✖
trastuzumab (Samsung Bioepis) + paclitaxel	●	✖	●	✖	✖
trastuzumab (Synthon)	●	✖	●	✖	✖
trastuzumab (Synthon) + carboplatin + docetaxel	●	✖	●	✖	✖
trastuzumab (Synthon) + docetaxel	●	✖	●	✖	✖
trastuzumab (Synthon) + paclitaxel	●	✖	●	✖	✖
margetuximab + chemotherapy	●	✖	✖	●	✖
trastuzumab and hyaluronidase-oysk	●	✖	✖	✖	✖
trastuzumab and hyaluronidase-oysk + carboplatin + docetaxel	●	✖	✖	✖	✖
trastuzumab and hyaluronidase-oysk + docetaxel	●	✖	✖	✖	✖
trastuzumab and hyaluronidase-oysk + paclitaxel	●	✖	✖	✖	✖
trastuzumab + capecitabine + cisplatin	○	○	○	✖	✖
trastuzumab + cisplatin + fluorouracil	○	○	○	✖	✖
zanidatamab	○	○	✖	○	● (II)
trastuzumab + tucatinib	○	○	✖	✖	✖
pembrolizumab + trastuzumab + chemotherapy + fluoropyrimidine	○	✖	○	✖	✖
trastuzumab (Biocon) + capecitabine + cisplatin	○	✖	○	✖	✖
trastuzumab (Biocon) + cisplatin + fluorouracil	○	✖	○	✖	✖
trastuzumab (Celltrion) + capecitabine + cisplatin	○	✖	○	✖	✖
trastuzumab (Celltrion) + cisplatin + fluorouracil	○	✖	○	✖	✖
trastuzumab (Pfizer) + capecitabine + cisplatin	○	✖	○	✖	✖
trastuzumab (Pfizer) + cisplatin + fluorouracil	○	✖	○	✖	✖
trastuzumab (Samsung Bioepis) + capecitabine + cisplatin	○	✖	○	✖	✖
trastuzumab (Samsung Bioepis) + cisplatin + fluorouracil	○	✖	○	✖	✖
trastuzumab (Synthon) + capecitabine + cisplatin	○	✖	○	✖	✖
trastuzumab (Synthon) + cisplatin + fluorouracil	○	✖	○	✖	✖
lapatinib + trastuzumab	✖	◑	●	◑	✖

* 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

ERBB2 amplification (continued)

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
pertuzumab + trastuzumab	✖	◑	✖	◑	● (II/III)
trastuzumab + capecitabine	✖	◑	✖	✖	✖
trastuzumab + carboplatin + paclitaxel	✖	◑	✖	✖	✖
trastuzumab + chemotherapy	✖	●	✖	◑	✖
pertuzumab + trastuzumab + hormone therapy	✖	●	✖	●	✖
pertuzumab + trastuzumab + paclitaxel	✖	●	✖	●	✖
trastuzumab + hormone therapy	✖	●	✖	●	✖
abemaciclib + trastuzumab + fulvestrant	✖	●	✖	✖	✖
aromatase inhibitor	✖	●	✖	✖	✖
fulvestrant	✖	●	✖	✖	✖
hormone therapy	✖	●	✖	✖	✖
lapatinib + aromatase inhibitor	✖	●	✖	✖	✖
lapatinib + trastuzumab + aromatase inhibitor	✖	●	✖	✖	✖
margetuximab + capecitabine	✖	●	✖	✖	✖
margetuximab + eribulin	✖	●	✖	✖	✖
margetuximab + gemcitabine	✖	●	✖	✖	✖
margetuximab + vinorelbine	✖	●	✖	✖	✖
neratinib + paclitaxel	✖	●	✖	✖	✖
pertuzumab + trastuzumab + carboplatin + docetaxel	✖	●	✖	✖	✖
pertuzumab + trastuzumab + carboplatin + paclitaxel	✖	●	✖	✖	✖
pertuzumab + trastuzumab + hormone therapy + chemotherapy	✖	●	✖	✖	✖
tamoxifen	✖	●	✖	✖	✖
trastuzumab + aromatase inhibitor	✖	●	✖	✖	✖
trastuzumab + chemotherapy (non-anthracycline)	✖	●	✖	✖	✖
trastuzumab + cyclophosphamide + docetaxel	✖	●	✖	✖	✖
trastuzumab + fulvestrant	✖	●	✖	✖	✖
trastuzumab + hormone therapy + chemotherapy	✖	●	✖	✖	✖
trastuzumab + tamoxifen	✖	●	✖	✖	✖
trastuzumab + vinorelbine	✖	●	✖	✖	✖

* 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

ERBB2 amplification (continued)

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
pembrolizumab + trastuzumab + capecitabine + cisplatin	✖	○	✖	✖	✖
pembrolizumab + trastuzumab + capecitabine + oxaliplatin	✖	○	✖	✖	✖
pembrolizumab + trastuzumab + cisplatin + fluorouracil	✖	○	✖	✖	✖
pembrolizumab + trastuzumab + fluorouracil + oxaliplatin	✖	○	✖	✖	✖
trastuzumab + capecitabine + oxaliplatin	✖	○	✖	✖	✖
trastuzumab + cisplatin + docetaxel	✖	○	✖	✖	✖
trastuzumab + cisplatin + docetaxel + fluorouracil	✖	○	✖	✖	✖
trastuzumab + cisplatin + paclitaxel	✖	○	✖	✖	✖
trastuzumab + docetaxel + fluorouracil + oxaliplatin	✖	○	✖	✖	✖
trastuzumab + fluorouracil	✖	○	✖	✖	✖
trastuzumab + fluorouracil + irinotecan	✖	○	✖	✖	✖
trastuzumab + fluorouracil + oxaliplatin	✖	○	✖	✖	✖
pertuzumab/trastuzumab/hyaluronidase-zzxf + carboplatin + docetaxel	✖	✖	●	✖	✖
pertuzumab/trastuzumab/hyaluronidase-zzxf + cyclophosphamide + doxorubicin + fluorouracil	✖	✖	●	✖	✖
pertuzumab/trastuzumab/hyaluronidase-zzxf + cyclophosphamide + epirubicin	✖	✖	●	✖	✖
pertuzumab/trastuzumab/hyaluronidase-zzxf + paclitaxel	✖	✖	●	✖	✖
trastuzumab (Biocon) + anastrozole	✖	✖	●	✖	✖
trastuzumab (Celltrion) + anastrozole	✖	✖	●	✖	✖
trastuzumab (EirGenix)	✖	✖	●	✖	✖
trastuzumab (EirGenix) + anastrozole	✖	✖	●	✖	✖
trastuzumab (EirGenix) + carboplatin + docetaxel	✖	✖	●	✖	✖
trastuzumab (EirGenix) + docetaxel	✖	✖	●	✖	✖
trastuzumab (EirGenix) + paclitaxel	✖	✖	●	✖	✖
trastuzumab (Henlius) + anastrozole	✖	✖	●	✖	✖
trastuzumab (Henlius) + carboplatin + docetaxel	✖	✖	●	✖	✖

* 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

ERBB2 amplification (continued)

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
trastuzumab (Henlius) + docetaxel	✖	✖	●	✖	✖
trastuzumab (Henlius) + paclitaxel	✖	✖	●	✖	✖
trastuzumab (Pfizer) + anastrozole	✖	✖	●	✖	✖
trastuzumab (Prestige BioPharma)	✖	✖	●	✖	✖
trastuzumab (Prestige BioPharma) + anastrozole	✖	✖	●	✖	✖
trastuzumab (Prestige BioPharma) + carboplatin + docetaxel	✖	✖	●	✖	✖
trastuzumab (Prestige BioPharma) + docetaxel	✖	✖	●	✖	✖
trastuzumab (Prestige BioPharma) + paclitaxel	✖	✖	●	✖	✖
trastuzumab (Samsung Bioepis) + anastrozole	✖	✖	●	✖	✖
trastuzumab (Synthon) + anastrozole	✖	✖	●	✖	✖
trastuzumab + anastrozole	✖	✖	●	✖	✖
trastuzumab (EirGenix) + capecitabine + cisplatin	✖	✖	○	✖	✖
trastuzumab (EirGenix) + cisplatin + fluorouracil	✖	✖	○	✖	✖
trastuzumab (Henlius) + capecitabine + cisplatin	✖	✖	○	✖	✖
trastuzumab (Henlius) + cisplatin + fluorouracil	✖	✖	○	✖	✖
trastuzumab (Prestige BioPharma) + capecitabine + cisplatin	✖	✖	○	✖	✖
trastuzumab (Prestige BioPharma) + cisplatin + fluorouracil	✖	✖	○	✖	✖
ado-trastuzumab emtansine + hormone therapy	✖	✖	✖	●	✖
lapatinib + hormone therapy	✖	✖	✖	●	✖
lapatinib + trastuzumab + hormone therapy	✖	✖	✖	●	✖
margetuximab	✖	✖	✖	●	✖
neratinib + chemotherapy	✖	✖	✖	●	✖
pertuzumab + trastuzumab + nab-paclitaxel	✖	✖	✖	●	✖
chemotherapy, trastuzumab	✖	✖	✖	✖	● (IV)
hormone therapy, pyrotinib, trastuzumab	✖	✖	✖	✖	● (IV)
inetetamab, chemotherapy	✖	✖	✖	✖	● (IV)
inetetamab, pertuzumab, pyrotinib, chemotherapy	✖	✖	✖	✖	● (IV)
pertuzumab, trastuzumab (Henlius), chemotherapy	✖	✖	✖	✖	● (IV)

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Relevant Therapy Summary (continued)

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

ERBB2 amplification (continued)

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
pyrotinib	✖	✖	✖	✖	● (IV)
pyrotinib, chemotherapy	✖	✖	✖	✖	● (IV)
pyrotinib, trastuzumab, chemotherapy	✖	✖	✖	✖	● (IV)
pyrotinib, trastuzumab, pertuzumab, chemotherapy	✖	✖	✖	✖	● (IV)
trastuzumab (Samsung Bioepis), chemotherapy, pertuzumab	✖	✖	✖	✖	● (IV)
trastuzumab, chemotherapy, pertuzumab	✖	✖	✖	✖	● (IV)
trastuzumab, pertuzumab, chemotherapy	✖	✖	✖	✖	● (IV)
trastuzumab, piperacillin, hormone therapy	✖	✖	✖	✖	● (IV)
ado-trastuzumab emtansine (Shanghai Fosun Pharma), ado-trastuzumab emtansine	✖	✖	✖	✖	● (III)
ado-trastuzumab emtansine, radiation therapy	✖	✖	✖	✖	● (III)
ado-trastuzumab emtansine, trastuzumab rezetecan	✖	✖	✖	✖	● (III)
BL-M07D1, ado-trastuzumab emtansine	✖	✖	✖	✖	● (III)
chemotherapy, trastuzumab, pertuzumab	✖	✖	✖	✖	● (III)
disitamab vedotinaide, pyrotinib	✖	✖	✖	✖	● (III)
DP-303c, ado-trastuzumab emtansine	✖	✖	✖	✖	● (III)
Hemay022, hormone therapy, lapatinib, chemotherapy	✖	✖	✖	✖	● (III)
hormone therapy, pertuzumab/trastuzumab/hyaluronidase-zzxf, chemotherapy	✖	✖	✖	✖	● (III)
IAH-0968, chemotherapy	✖	✖	✖	✖	● (III)
JSKN-003, ado-trastuzumab emtansine	✖	✖	✖	✖	● (III)
KN026, pertuzumab, trastuzumab, chemotherapy	✖	✖	✖	✖	● (III)
KN026, trastuzumab, pertuzumab, chemotherapy	✖	✖	✖	✖	● (III)
nilotinib, trastuzumab, pertuzumab	✖	✖	✖	✖	● (III)
pertuzumab, trastuzumab, KM-118, chemotherapy	✖	✖	✖	✖	● (III)
pyrotinib, hormone therapy, chemotherapy	✖	✖	✖	✖	● (III)
trastuzumab pamirtecan, ado-trastuzumab emtansine	✖	✖	✖	✖	● (III)
trastuzumab rezetecan, pertuzumab, trastuzumab, chemotherapy	✖	✖	✖	✖	● (III)

* 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

ERBB2 amplification (continued)

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
trastuzumab, pertuzumab, chemotherapy, pyrotinib, palbociclib, ado-trastuzumab emtansine, everolimus, hormone therapy, sintilimab	✖	✖	✖	✖	● (III)
trastuzumab, pyrotinib, chemotherapy	✖	✖	✖	✖	● (III)
trastuzumab, radiation therapy	✖	✖	✖	✖	● (III)
tucatinib, ado-trastuzumab emtansine	✖	✖	✖	✖	● (III)
zanidatamab, trastuzumab, chemotherapy	✖	✖	✖	✖	● (III)
MRG-002	✖	✖	✖	✖	● (II/III)
trastuzumab, chemotherapy	✖	✖	✖	✖	● (II/III)
A-166	✖	✖	✖	✖	● (II)
AdHER2DC vaccine, trastuzumab, pertuzumab, chemotherapy	✖	✖	✖	✖	● (II)
ado-trastuzumab emtansine, neratinib	✖	✖	✖	✖	● (II)
ado-trastuzumab emtansine, pyrotinib	✖	✖	✖	✖	● (II)
afatinib, ado-trastuzumab emtansine	✖	✖	✖	✖	● (II)
antiHER2 therapy, trastuzumab, pertuzumab/ trastuzumab/hyaluronidase-zzxf, trastuzumab deruxtecan, ado-trastuzumab emtansine	✖	✖	✖	✖	● (II)
anvatabart opadotin	✖	✖	✖	✖	● (II)
atezolizumab, trastuzumab, chemotherapy	✖	✖	✖	✖	● (II)
atezolizumab, trastuzumab, pertuzumab	✖	✖	✖	✖	● (II)
BL-M07D1, pertuzumab, chemotherapy	✖	✖	✖	✖	● (II)
CART-HER2, chemotherapy	✖	✖	✖	✖	● (II)
chemoradiation therapy, trastuzumab, chemotherapy, radiation therapy	✖	✖	✖	✖	● (II)
chemotherapy, trastuzumab, pertuzumab, pertuzumab/trastuzumab/hyaluronidase-zzxf	✖	✖	✖	✖	● (II)
dalpiciclib, hormone therapy, pyrotinib	✖	✖	✖	✖	● (II)
dalpiciclib, hormone therapy, trastuzumab, pyrotinib	✖	✖	✖	✖	● (II)
dalpiciclib, pyrotinib, chemotherapy	✖	✖	✖	✖	● (II)
dalpiciclib, pyrotinib, hormone therapy, inetetamab	✖	✖	✖	✖	● (II)
dalpiciclib, trastuzumab, pertuzumab, chemotherapy	✖	✖	✖	✖	● (II)

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Relevant Therapy Summary (continued)

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

ERBB2 amplification (continued)

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
disitamab vedotinaide, toripalimab, pertuzumab	✖	✖	✖	✖	● (II)
DX126-262	✖	✖	✖	✖	● (II)
envafolimab, trastuzumab, chemotherapy	✖	✖	✖	✖	● (II)
FDA022-BB05	✖	✖	✖	✖	● (II)
inetetamab, chemotherapy, hormone therapy	✖	✖	✖	✖	● (II)
neratinib, hormone therapy, trastuzumab	✖	✖	✖	✖	● (II)
palbociclib, hormone therapy, trastuzumab, tucatinib	✖	✖	✖	✖	● (II)
palbociclib, trastuzumab, pyrotinib, hormone therapy	✖	✖	✖	✖	● (II)
pembrolizumab, anti-HER2/HER3 dendritic cell vaccine	✖	✖	✖	✖	● (II)
pertuzumab + trastuzumab, atezolizumab + pertuzumab/trastuzumab/hyaluronidase-zzxf, trastuzumab + tucatinib	✖	✖	✖	✖	● (II)
pertuzumab/trastuzumab/hyaluronidase-zzxf, chemotherapy	✖	✖	✖	✖	● (II)
pertuzumab/trastuzumab/hyaluronidase-zzxf, hormone therapy	✖	✖	✖	✖	● (II)
pyrotinib, anvatabart opadotin	✖	✖	✖	✖	● (II)
pyrotinib, pertuzumab, chemotherapy, trastuzumab	✖	✖	✖	✖	● (II)
pyrotinib, pertuzumab, trastuzumab	✖	✖	✖	✖	● (II)
radiation therapy, pyrotinib, chemotherapy	✖	✖	✖	✖	● (II)
sacituzumab govitecan, trastuzumab, trastuzumab and hyaluronidase-oysk	✖	✖	✖	✖	● (II)
TAP-11, sargramostim, ado-trastuzumab emtansine, trastuzumab, pertuzumab	✖	✖	✖	✖	● (II)
TQB-2102	✖	✖	✖	✖	● (II)
trastuzumab (Henlius), pertuzumab, palbociclib, hormone therapy	✖	✖	✖	✖	● (II)
trastuzumab (Samsung Bioepis), chemotherapy	✖	✖	✖	✖	● (II)
trastuzumab and hyaluronidase-oysk, chemotherapy, ado-trastuzumab emtansine	✖	✖	✖	✖	● (II)
trastuzumab deruxtecan, durvalumab	✖	✖	✖	✖	● (II)
trastuzumab deruxtecan, pertuzumab, trastuzumab, chemotherapy, ribociclib, hormone therapy	✖	✖	✖	✖	● (II)

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Relevant Therapy Summary (continued)

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

ERBB2 amplification (continued)

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
trastuzumab deruxtecan, pertuzumab/trastuzumab/ hyaluronidase-zzxf	✖	✖	✖	✖	● (II)
trastuzumab rezetecan, pyrotinib	✖	✖	✖	✖	● (II)
trastuzumab rezetecan, pyrotinib, bevacizumab	✖	✖	✖	✖	● (II)
trastuzumab, hormone therapy, pirotinib	✖	✖	✖	✖	● (II)
trastuzumab, pertuzumab	✖	✖	✖	✖	● (II)
trastuzumab, pertuzumab, chemotherapy, trastuzumab deruxtecan, ado-trastuzumab emtansine, tucatinib, pertuzumab/trastuzumab/ hyaluronidase-zzxf	✖	✖	✖	✖	● (II)
trastuzumab, pyrotinib, dalpiciclib, hormone therapy, pertuzumab, chemotherapy	✖	✖	✖	✖	● (II)
trastuzumab, pyrotinib, palbociclib, hormone therapy	✖	✖	✖	✖	● (II)
trastuzumab, pyrotinib, pertuzumab, chemotherapy	✖	✖	✖	✖	● (II)
trilaciclib, chemotherapy	✖	✖	✖	✖	● (II)
tucatinib, chemotherapy	✖	✖	✖	✖	● (II)
tucatinib, chemotherapy, trastuzumab	✖	✖	✖	✖	● (II)
tucatinib, pembrolizumab, trastuzumab	✖	✖	✖	✖	● (II)
tucatinib, trastuzumab, chemotherapy	✖	✖	✖	✖	● (II)
zongertinib	✖	✖	✖	✖	● (II)
AAA-614, 68Ga-FAP-2286, chemotherapy	✖	✖	✖	✖	● (I/II)
AP-402	✖	✖	✖	✖	● (I/II)
atezolizumab, tivozanib	✖	✖	✖	✖	● (I/II)
AZD-9574, trastuzumab deruxtecan	✖	✖	✖	✖	● (I/II)
BAT-8010, BAT-1006	✖	✖	✖	✖	● (I/II)
BL-M07D1	✖	✖	✖	✖	● (I/II)
CART-MUC1 (Minerva)	✖	✖	✖	✖	● (I/II)
catequentinib, pyrotinib, chemotherapy	✖	✖	✖	✖	● (I/II)
DB-1310, trastuzumab	✖	✖	✖	✖	● (I/II)
DF-1001, nivolumab	✖	✖	✖	✖	● (I/II)
disitamab vedotinaide, tucatinib	✖	✖	✖	✖	● (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

ERBB2 amplification (continued)

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
E01001	✖	✖	✖	✖	● (I/II)
fadraciclib	✖	✖	✖	✖	● (I/II)
GQ1001, pyrotinib, chemotherapy	✖	✖	✖	✖	● (I/II)
hormone therapy, steroid, chemotherapy	✖	✖	✖	✖	● (I/II)
HRS-8080, trastuzumab rezetecan, SHR-A2009, adebrelimab	✖	✖	✖	✖	● (I/II)
HypoSti.CART-HER2, chemotherapy	✖	✖	✖	✖	● (I/II)
IAH-0968	✖	✖	✖	✖	● (I/II)
IBI-354	✖	✖	✖	✖	● (I/II)
JIN-A-04	✖	✖	✖	✖	● (I/II)
JSKN-003	✖	✖	✖	✖	● (I/II)
JSKN-033	✖	✖	✖	✖	● (I/II)
patritumab deruxtecan, olaparib	✖	✖	✖	✖	● (I/II)
patritumab deruxtecan, trastuzumab, trastuzumab (Genor Biopharma), tucatinib, pertuzumab	✖	✖	✖	✖	● (I/II)
pertuzumab/trastuzumab/hyaluronidase-zzxf + hormone therapy, abemaciclib + pertuzumab/ trastuzumab/hyaluronidase-zzxf + hormone therapy, palbociclib + pertuzumab/trastuzumab/ hyaluronidase-zzxf + hormone therapy	✖	✖	✖	✖	● (I/II)
PF-07220060, midazolam	✖	✖	✖	✖	● (I/II)
radiation therapy, trastuzumab, pertuzumab	✖	✖	✖	✖	● (I/II)
ribociclib, tucatinib, trastuzumab, chemotherapy, pertuzumab	✖	✖	✖	✖	● (I/II)
ST-1703	✖	✖	✖	✖	● (I/II)
TQB-2930, chemotherapy, hormone therapy	✖	✖	✖	✖	● (I/II)
trastuzumab deruxtecan, neratinib	✖	✖	✖	✖	● (I/II)
trastuzumab pamirtecan, pertuzumab	✖	✖	✖	✖	● (I/II)
trastuzumab rezetecan, pyrotinib, pertuzumab, adebrelimab, chemotherapy	✖	✖	✖	✖	● (I/II)
trastuzumab, ribociclib, hormone therapy	✖	✖	✖	✖	● (I/II)
YH32367	✖	✖	✖	✖	● (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

ERBB2 amplification (continued)

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
zongertinib, ado-trastuzumab emtansine, trastuzumab deruxtecan, trastuzumab, chemotherapy	✖	✖	✖	✖	● (I/II)
zotatifin, trastuzumab	✖	✖	✖	✖	● (I/II)
ZV-0203	✖	✖	✖	✖	● (I/II)
177Lu-RAD202	✖	✖	✖	✖	● (I)
ado-trastuzumab emtansine (Shanghai Fosun Pharma)	✖	✖	✖	✖	● (I)
anti-HER-2 MAb (Anke Biotechnology)	✖	✖	✖	✖	● (I)
antiemetic agent, chemotherapy, trastuzumab, pertuzumab	✖	✖	✖	✖	● (I)
BC004	✖	✖	✖	✖	● (I)
BL-M17D1	✖	✖	✖	✖	● (I)
BM-230	✖	✖	✖	✖	● (I)
CART-HER2/PD-L1	✖	✖	✖	✖	● (I)
ceralasertib, trastuzumab deruxtecan	✖	✖	✖	✖	● (I)
D3L-001	✖	✖	✖	✖	● (I)
dendritic cell vaccine, trastuzumab, pepinemab, T-cell therapy	✖	✖	✖	✖	● (I)
DM-002	✖	✖	✖	✖	● (I)
doxorubicin (Hangzhou HighField Biopharma)	✖	✖	✖	✖	● (I)
DP-303c	✖	✖	✖	✖	● (I)
ELVN-002, ado-trastuzumab emtansine	✖	✖	✖	✖	● (I)
ELVN-002, trastuzumab	✖	✖	✖	✖	● (I)
ELVN-002, trastuzumab, chemotherapy	✖	✖	✖	✖	● (I)
ENT-H-1, trastuzumab	✖	✖	✖	✖	● (I)
EX-101 (Excelmab)	✖	✖	✖	✖	● (I)
GB251	✖	✖	✖	✖	● (I)
GQ-1005	✖	✖	✖	✖	● (I)
GQ1001	✖	✖	✖	✖	● (I)
HS-630	✖	✖	✖	✖	● (I)
inetetamab, pyrotinib, chemotherapy	✖	✖	✖	✖	● (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

ERBB2 amplification (continued)

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
IPH-5301, trastuzumab, chemotherapy	✖	✖	✖	✖	● (I)
MBS301	✖	✖	✖	✖	● (I)
micvotabart pelidotin	✖	✖	✖	✖	● (I)
MVF-HER-2 (266-296), MVF-HER-2(597-626)	✖	✖	✖	✖	● (I)
natural killer cell therapy, trastuzumab, pertuzumab, chemotherapy, interleukin-2 (Ajinomoto)	✖	✖	✖	✖	● (I)
NC-18	✖	✖	✖	✖	● (I)
palbociclib, avelumab	✖	✖	✖	✖	● (I)
pyrotinib, chemotherapy, trastuzumab	✖	✖	✖	✖	● (I)
SPH5030	✖	✖	✖	✖	● (I)
TAS0728	✖	✖	✖	✖	● (I)
TL-938	✖	✖	✖	✖	● (I)
trastuzumab deruxtecan, azenosertib	✖	✖	✖	✖	● (I)
trastuzumab deruxtecan, olaparib	✖	✖	✖	✖	● (I)
trastuzumab, BBO-10203	✖	✖	✖	✖	● (I)
tucatinib, trastuzumab, pertuzumab, hormone therapy	✖	✖	✖	✖	● (I)
VVD-159642	✖	✖	✖	✖	● (I)
XMT-2056	✖	✖	✖	✖	● (I)
ZN-A-1041, ado-trastuzumab emtansine, trastuzumab deruxtecan, trastuzumab, pertuzumab, pertuzumab/ trastuzumab/hyaluronidase-zzxf	✖	✖	✖	✖	● (I)

ERBB2 p.(L755S) c.2264T>C

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
trastuzumab deruxtecan	○	○	○	✖	● (II)
pertuzumab + trastuzumab	✖	✖	✖	✖	● (II/III)
BAY-2927088	✖	✖	✖	✖	● (II)
pertuzumab/trastuzumab/hyaluronidase-zzxf	✖	✖	✖	✖	● (II)
tucatinib, ado-trastuzumab emtansine	✖	✖	✖	✖	● (II)
zongertinib	✖	✖	✖	✖	● (II)
DF-1001, nivolumab	✖	✖	✖	✖	● (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

ERBB2 p.(L755S) c.2264T>C (continued)

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
JSKN-003	✖	✖	✖	✖	● (I/II)
trastuzumab deruxtecan, neratinib	✖	✖	✖	✖	● (I/II)
ado-trastuzumab emtansine (Shanghai Fosun Pharma)	✖	✖	✖	✖	● (I)
ENT-H-1, trastuzumab	✖	✖	✖	✖	● (I)
XMT-2056	✖	✖	✖	✖	● (I)

BRCA2 deletion

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

MTAP deletion

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
AMG 193	✖	✖	✖	✖	● (I/II)
TNG-456, abemaciclib	✖	✖	✖	✖	● (I/II)
TNG-462	✖	✖	✖	✖	● (I/II)
GTA-182	✖	✖	✖	✖	● (I)
ISM-3412	✖	✖	✖	✖	● (I)
MRTX-1719	✖	✖	✖	✖	● (I)
PH020-803	✖	✖	✖	✖	● (I)
S-095035	✖	✖	✖	✖	● (I)
SYH-2039	✖	✖	✖	✖	● (I)

ATM deletion

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

ATM deletion (continued)

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

CDKN2A deletion

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

ARID1A deletion

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
pamiparib, tislelizumab	✖	✖	✖	✖	● (II)
tucidinostat, catequentinib, PD-1 Inhibitor, anti-PD-L1 antibody	✖	✖	✖	✖	● (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)

FANCA 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

FANCA p.(E1240Dfs*36) c.3719_3723delAAAAC

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

FBXW7 deletion

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
ARTS-021	✖	✖	✖	✖	● (I/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	***36.34%***
BRCA2	***CNV, CN:1.0***
BRCA2	***LOH, 13q13.1(32890491-32972932)x1***
ATM	***CNV, CN:1.0***
ATM	***LOH, 11q22.3(108098341-108236285)x1***
BRIP1	***LOH, 17q23.2(59760627-59938976)x2***
CHEK1	***CNV, CN:1.0***
CHEK1	***LOH, 11q24.2(125496639-125525271)x1***
RAD51B	***CNV, CN:1.0***
RAD51B	***LOH, 14q24.1(68290164-69061406)x1***
RAD51C	***LOH, 17q22(56769933-56811619)x2***
RAD54L	***CNV, CN:1.0***
RAD54L	***LOH, 1p34.1(46714017-46743978)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 2025.06(006)). The data presented here are from a curated knowledge base of publicly available information, but may not be exhaustive. FDA information was sourced from www.fda.gov and is current as of 2025-05-14. NCCN information was sourced from www.nccn.org and is current as of 2025-05-01. EMA information was sourced from www.ema.europa.eu and is current as of 2025-05-14. ESMO information was sourced from www.esmo.org and is current as of 2025-05-01. Clinical Trials information is current as of 2025-05-01. For the most up-to-date information regarding a particular trial, search www.clinicaltrials.gov by NCT ID or search local clinical trials authority website by local identifier listed in 'Other identifiers.' Variants are reported according to HGVS nomenclature and classified following AMP/ASCO/CAP guidelines (Li et al. 2017). Based on the data sources selected, variants, therapies, and trials listed in this report are listed in order of potential clinical significance but not for predicted efficacy of the therapies.

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