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Patient Name: 이미희
Gender: F
Sample ID: N25-287

Primary Tumor Site: Breast
Collection Date: 2024.01.24

Sample Cancer Type: Breast Cancer

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Report Highlights
8 Relevant Biomarkers
56 Therapies Available
259 Clinical Trials

Relevant Breast Cancer Findings

Gene	Finding
BRCA1	None detected
ERBB2	***ERBB2 amplification***

Genomic Alteration	Finding
Tumor Mutational Burden	***9.66 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, 2 / II+] **trastuzumab†** [1] lapatinib + trastuzumab [I, II+] pertuzumab + trastuzumab [I, II+] ado-trastuzumab emtansine	246

*** 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+] ado-trastuzumab emtansine + neratinib		
IIC	*FGFR1 amplification* fibroblast growth factor receptor 1 Locus: chr8:38271452	None*	None*	4
IIC	*CCND1 amplification* cyclin D1 Locus: chr11:69455949	None*	None*	3
IIC	*MYC amplification* MYC proto-oncogene, bHLH transcription factor Locus: chr8:128748847	None*	None*	3
IIC	*SMARCA4 deletion* SWI/SNF related, matrix associated, actin dependent regulator of chromatin, subfamily a, member 4 Locus: chr19:11094814	None*	None*	2
IIC	*BRIP1 p.(S505*) c.1514C>A* BRCA1 interacting protein C-terminal helicase 1 Allele Frequency: 29.66% Locus: chr17:59861745 Transcript: NM_032043.3	None*	None*	1
IIC	*FGF19 amplification* fibroblast growth factor 19 Locus: chr11:69513948	None*	None*	1
IIC	*RB1 deletion* RB transcriptional corepressor 1 Locus: chr13:48877953	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
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Relevant Biomarkers (continued)

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

ERBB2 amplification	**anvatabart opadotin** [1], **GLSI-100** [1]

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

Prevalent cancer biomarkers without relevant evidence based on included data sources

CUL4A deletion, FGF3 amplification, FGF4 amplification, Microsatellite stable, RICTOR amplification, STK11 deletion, TP53 c.376-1G>A, UGT1A1 p.(G71R) c.211G>A, TERT amplification, CTNND2 amplification, IL7R amplification, HLA-A p.(L180) c.539T>A, PRDM1 deletion, HDAC2 deletion, FAM135B amplification, GATA3 p.(T419Hfs*89) c.1254_1255insC, ARID5B deletion, TPP2 deletion, ZFHX3 deletion, RPS6KB1 amplification, ZNF217 amplification, AURKA amplification, Tumor Mutational Burden*

Variant Details

DNA Sequence Variants

Gene	Amino Acid Change	Coding	Variant ID	Locus	Allele Frequency	Transcript	Variant Effect
BRIP1	p.(S505*)	c.1514C>A	.	chr17:59861745	29.66%	NM_032043.3	nonsense
TP53	p.(?)	c.376-1G>A	.	chr17:7578555	77.42%	NM_000546.6	unknown
UGT1A1	p.(G71R)	c.211G>A	COSM4415616	chr2:234669144	99.60%	NM_000463.3	missense
HLA-A	p.(L180*)	c.539T>A	.	chr6:29911240	100.00%	NM_001242758.1	nonsense
GATA3	p.(T419Hfs*89)	c.1254_1255insC	.	chr10:8115903	3.43%	NM_001002295.2	frameshift Insertion
LRRIQ3	p.(Y140D)	c.418T>G	.	chr1:74648377	57.97%	NM_001105659.2	missense
OR6F1	p.(Y252H)	c.754T>C	.	chr1:247875304	11.80%	NM_001005286.1	missense
OR2L13	p.(L129Ifs*6)	c.385_388delCTCT	.	chr1:248263057	64.55%	NM_175911.3	frameshift Deletion
FAM124B	p.(A260G)	c.779C>G	.	chr2:225244879	61.28%	NM_001122779.2	missense
MSH3	p.(A61_P63dup)	c.189_190insGCAGCGCCC	.	chr5:79950735	34.63%	NM_002439.5	nonframeshift Insertion
RUNX1T1	p.(R484W)	c.1450C>T	.	chr8:92983008	5.91%	NM_001198634.2	missense
KMT2A	p.(R1532H)	c.4595G>A	.	chr11:118360863	4.19%	NM_001197104.2	missense
FANCM	p.(Q1715H)	c.5145G>C	.	chr14:45658370	10.61%	NM_020937.4	missense
SPOP	p.(C205R)	c.613T>C	.	chr17:47688687	29.57%	NM_001007228.2	missense
COG1	p.(P410L)	c.1229C>T	.	chr17:71196863	24.49%	NM_018714.3	missense
NOTCH3	p.(P1975S)	c.5923C>T	.	chr19:15272516	84.19%	NM_000435.3	missense
ZMYM3	p.(E639K)	c.1915G>A	.	chrX:70468072	30.84%	NM_201599.3	missense

Copy Number Variations

Gene	Locus	Copy Number	CNV Ratio
ERBB2	chr17:37863255	5.39	2.18
FGFR1	chr8:38271452	8.54	3.29

Variant Details (continued)

Copy Number Variations (continued)

Gene	Locus	Copy Number	CNV Ratio
CCND1	chr11:69455949	9.5	3.62
MYC	chr8:128748847	9.44	3.61
SMARCA4	chr19:11094814	1.13	0.7
FGF19	chr11:69513948	8.71	3.35
RB1	chr13:48877953	0.81	0.58
CUL4A	chr13:113863977	0.86	0.6
FGF3	chr11:69625020	7.19	2.82
FGF4	chr11:69588019	7.46	2.91
RICTOR	chr5:38942342	7.01	2.76
STK11	chr19:1206847	0.71	0.55
TERT	chr5:1253783	6.97	2.74
CTNND2	chr5:10988230	5.89	2.36
IL7R	chr5:35857035	8.29	3.2
PRDM1	chr6:106534408	0.37	0.43
HDAC2	chr6:114262171	0.29	0.4
FAM135B	chr8:139144776	9.46	3.61
ARID5B	chr10:63661463	0.8	0.58
TPP2	chr13:103249399	0.8	0.58
ZFHX3	chr16:72820995	1.1	0.68
RPS6KB1	chr17:57970507	7.3	2.85
ZNF217	chr20:52188253	15.81	5.84
AURKA	chr20:54945190	6.04	2.42
SDHA	chr5:218412	6.83	2.69
CDH10	chr5:24487706	5.97	2.39
ADAMTS12	chr5:33527235	5.59	2.25
FYN	chr6:111982890	0.29	0.4
NBN	chr8:90947783	11.73	4.4
RUNX1T1	chr8:92982878	7.36	2.88
CSMD3	chr8:113237020	10.36	3.92
RECQL4	chr8:145736758	10.29	3.9
FANCM	chr14:45605157	5.66	2.28
CDK12	chr17:37618286	5.73	2.31
SPOP	chr17:47677716	7.39	2.88
RAD51C	chr17:56769933	5.06	2.07

Variant Details (continued)

Copy Number Variations (continued)

Gene	Locus	Copy Number	CNV Ratio
PPM1D	chr17:58677747	12.5	4.67
BRIP1	chr17:59760627	29.03	10.46
AXIN2	chr17:63526027	6.86	2.7
PRKAR1A	chr17:66511464	6.39	2.54
SOX9	chr17:70117435	8.09	3.13
PRKACA	chr19:14204349	0.21	0.37

Biomarker Descriptions

ERBB2 amplification

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[1]. Along with ERBB2/HER2, EGFR/ERBB1/HER1, ERBB3/HER3, and ERBB4/HER4 make up the HER protein family[227]. All ERBB/HER proteins encode transmembrane receptor tyrosine kinases[228]. However, ERBB2/HER2 is an orphan receptor with no known ligand[228]. ERBB2 preferentially binds other ligand-bound ERBB/HER family members to form heterodimers 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[229]. Recurrent focal amplification of the ERBB2 gene leads to increased expression in several cancer types[229]. ERBB2 overexpression in immortalized cell lines is oncogenic and leads to ERBB2 homo-dimerization and activation without ligand binding[230,231,232].

Alterations and prevalence: ERBB2 gene amplification occurs in 10-25% of breast, esophageal, and gastric cancers, 5-10% of bladder, cervical, pancreas, and uterine cancers, and 1-5% of colorectal, lung, and ovarian cancers[4,5,120,165,186,233,234,235]. ERBB2 gene amplification in pediatric population is observed in 2% of peripheral nervous system cancers (2 in 91 patients) and less than 1% of leukemia (1 in 250 cases)[5]. Recurrent somatic activating mutations in ERBB2/HER2 occur at low frequencies (<1%) in diverse cancer types[5,236,237]. 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.

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[238,239]. Trastuzumab[240] 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[241] (2012), a humanized monoclonal antibody that inhibits HER2 dimerization, and ado-trastuzumab emtansine[242] (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[243]. In addition to monoclonal antibodies, the small molecule inhibitor lapatinib[244], 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[245], 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[245] 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[246] 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[88]. In 2024, a bispecific HER2 antibody, zanidatamab[247], was approved for the treatment of adults with previously treated, unresectable or metastatic ERBB2 overexpressing biliary tract cancer. In 2018 fast track designation was granted to the monoclonal antibody margetuximab[248] in patients with ERBB2 positive breast cancer previously treated with an anti-HER2 therapy. Additionally, in 2019, zanidatamab[249], received fast track designation in combination with standard chemotherapy for patients with HER2-overexpressing gastroesophageal adenocarcinoma (GEA). The humanized anti-HER2 antibody drug conjugate disitamab vedotin[250] (2020) received breakthrough designation for adult patients with HER2-positive urothelial cancer after previous platinum-chemotherapy treatment. In 2021, the antibody-drug conjugate ARX788[251] 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. In 2024, a small

Biomarker Descriptions (continued)

molecule inhibitor, BAY-2927088[252], 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[253,254,255,256,257]. ERBB2 kinase domain mutations R896G and V659E both showed response to afatinib in two NSCLC case studies[258,259]. Additionally, acquired HER2 mutations in estrogen receptor-positive (ER+) breast cancer have been shown to confer resistance to hormone therapy[260]. However, this was shown to be overcome by neratinib in combination with therapies targeting ER[260]. Additionally, in 2025, FDA approved zongertinib[261], a kinase inhibitor indicated for the treatment of adult patients with unresectable or metastatic non-squamous non-small cell lung cancer (NSCLC) whose tumors have HER2 tyrosine kinase domain activating mutations. In 2025, a 9 amino acid transmembrane peptide of the HER2/neu protein, GLSI-100 (GP-2)[262], received fast track designation for the prevention of breast cancer recurrence following surgery.

FGFR1 amplification

fibroblast growth factor receptor 1

Background: The FGFR1 gene encodes fibroblast growth receptor 1, a member of the fibroblast growth factor receptor (FGFR) family that also includes FGFR2, 3, and 4[1]. These proteins are single transmembrane receptors composed of three extracellular immunoglobulin (Ig)-type domains and an intracellular kinase domain[1]. Upon FGF-mediated stimulation, FGFRs activate several oncogenic signaling pathways, including the RAS/RAF/MEK/ERK, PI3K/AKT/MTOR, PLCγ/PKC, and JAK/STAT pathways influencing cell proliferation, migration, and survival[60,61,62].

Alterations and prevalence: Recurrent somatic alterations common to the FGFR family include gene amplification, mutation, and chromosomal translocations leading to FGFR fusions[184]. Amplification of FGFR1 is observed in 17% of lung squamous cell carcinoma, 11% of breast invasive carcinoma, 8% of bladder urothelial carcinoma, 7% of uterine carcinosarcoma and head and neck squamous cell carcinoma, 6% of esophageal adenocarcinoma, 5% of sarcoma, 4% of colorectal adenocarcinoma and pancreatic adenocarcinoma, 3% of prostate adenocarcinoma, ovarian serous cystadenocarcinoma, and lung adenocarcinoma, and 2% of uterine corpus endometrial carcinoma[4,5,106,185,186]. The most common recurrent mutations, N546K and K656E, are relatively infrequent (<1%); they activate mutations in the kinase domain and are distributed in diverse cancer types[187]. Somatic mutations in FGFR1 are observed in 7% of skin cutaneous melanoma, 6% of uterine corpus endometrial carcinoma, and 3% of stomach adenocarcinoma and colorectal adenocarcinoma[4,5]. FGFR1 translocations giving rise to expressed fusions are common in certain hematological cancers, but are less common in solid tumors[188,189,190]. Alterations in FGFR1 are rare in pediatric cancers[4,5]. Amplification of FGFR1 is observed in less than 1% of B-lymphoblastic leukemia/lymphoma (2 in 731 cases). Somatic mutations in FGFR1 are observed in 6% of non-Hodgkin Lymphoma, 3% of soft tissue sarcoma, 2% of glioma, and less than 1% of embryonal tumors (2 in 332 cases), B-lymphoblastic leukemia/lymphoma (1 in 252 cases), Wilms tumor (2 in 710 cases), and peripheral nervous system cancers (1 in 1158 cases)[4,5].

Potential relevance: The FGFR kinase inhibitor, pemigatinib[191] (2022) is approved for the treatment of adults with relapsed/refractory myeloid/lymphoid neoplasms (MLNs) with FGFR1 rearrangement. Additionally, the FDA granted fast-track designation to Debio 1347[192] (2018) for solid tumors harboring aberrations in FGFR1, FGFR2, or FGFR3. FDA has approved multi-kinase inhibitors, including regorafenib, ponatinib, lenvatinib, nintedanib, and pazopanib, that are known to inhibit FGFR family members[193]. These inhibitors have demonstrated anti-tumor activity in select cancer types with FGFR alterations[194,195,196,197,198,199,200]. In a phase II clinical trial, dovitinib, a multi-tyrosine kinase inhibitor (TKI), exhibited an overall response rate (ORR) of 11.5% and a disease control rate (DCR) of 50% in patients with advanced squamous cell lung cancer possessing FGFR1 amplification[201]. The patients had a median overall survival (OS) of 5 months and progression-free survival (PFS) of 2.9 months[201]. Likewise, in a phase Ib study testing the FGFR inhibitor AZD4547, the median OS was 4.9 months in patients with FGFR1-amplified advanced squamous cell lung cancer. One of 13 (8%) patients achieved a partial response, 4 (31%) exhibited stable disease, and 2 (13.3%) demonstrated PFS at 12 weeks[202]. Rearrangements in FGFR1 are associated with poor risk pediatric and adult acute lymphoblastic leukemia[17,18,203].

CCND1 amplification

cyclin D1

Background: The CCND1 gene encodes the cyclin D1 protein, a member of the highly conserved D-cyclin family that also includes CCND2 and CCND3[101,102,103]. D-type cyclins are known to regulate cell cycle progression by binding to and activating cyclin dependent kinases (CDKs), specifically CDK4 and CDK6, which leads to the phosphorylation and inactivation of the retinoblastoma (RB1) protein[101,102]. Consequently, RB1 inactivation results in E2F transcription factor activation and cellular G1/S phase transition thereby resulting in cell cycle progression, a common event observed in tumorigenesis[101,102,104]. Aberrations in the D-type cyclins have been observed to promote tumor progression suggesting an oncogenic role for CCND1[103,105].

Alterations and prevalence: Recurrent somatic alterations to CCND1, including mutations, amplifications, and chromosomal translocations, are observed in many cancer types. A common mechanism of these alterations is to increase the expression and nuclear localization of the cyclin D1 protein. Recurrent somatic mutations include missense mutations at codons T286 and P287 and c-terminal truncating mutations that are enriched in about 33% of uterine cancer, and missense mutations at Y44 that are enriched in about 50% of Mantle cell lymphoma (MCL)[4,5,106,107]. These mutations block phosphorylation-dependent nuclear export and

Biomarker Descriptions (continued)

proteolysis[108,109,110,111]. CCND1 is recurrently amplified in many cancer types, including up to 35% of esophageal cancer, 20-30% of head and neck cancer, and 10-20% of breast, squamous lung, and bladder cancers[4,5,112]. MCL is genetically characterized by the t(11;14)(q13;q13) translocation, a rearrangement that juxtaposes CCND1 to the immunoglobulin heavy (IgH) chain gene. This rearrangement leads to constitutive expression of cyclin D1 and plays an important role in MCL pathogenesis[113,114].

Potential relevance: Currently, no therapies are approved for CCND1 aberrations. The t(11;14) translocation involving CCND1 can be used to help diagnose some lymphoma subtypes including non-gastric MALT lymphoma, splenic marginal cell lymphoma, and mantle cell lymphoma[115].

MYC amplification

MYC proto-oncogene, bHLH transcription factor

Background: The MYC gene encodes the MYC proto-oncogene, bHLH transcription factor (c-MYC), a basic helix-loop-helix transcription factor that regulates the expression of numerous genes that control cell cycle progression, apoptosis, metabolic pathways, and cellular transformation[125,126,127,128]. MYC is part of the MYC oncogene family, which includes the related transcription factors, MYCN and MYCL, and regulates transcription in 10-15% of promoter regions[129]. MYC functions as a heterodimer in complex with the transcription factor MAX[126,130].

Alterations and prevalence: Recurrent somatic alterations are observed in both solid and hematological cancers. Recurrent somatic mutations in MYC, including those at codon T58, are infrequent and hypothesized to increase the stability of the MYC protein[131,132]. Amplification of the MYC gene is observed in 15-30% of ovarian serous cystadenocarcinoma, esophageal adenocarcinoma, uterine carcinosarcoma, and breast invasive carcinoma, 10-15% of pancreatic adenocarcinoma, stomach adenocarcinoma, and liver hepatocellular carcinoma, 5-10% of head and neck squamous cell carcinoma, uterine corpus endometrial carcinoma, prostate adenocarcinoma, lung adenocarcinoma, lung squamous cell carcinoma, bladder urothelial carcinoma, and colorectal adenocarcinoma, and 2-5% of skin cutaneous melanoma, brain lower grade glioma, sarcoma, cervical squamous cell carcinoma, uveal melanoma, diffuse B-cell lymphoma, glioblastoma, and kidney chromophobe[4,5]. MYC is the target of the t(8;14)(q24;32) chromosomal translocation in Burkitt lymphoma that places MYC coding sequences adjacent to immunoglobulin region regulatory sequences, resulting in increased MYC expression[133,134]. Overall, MYC translocations are observed in 2% of diffuse large B-cell lymphoma[4,5]. Somatic mutations in MYC are observed in 7% of diffuse large B-cell lymphoma, 4% of uterine carcinosarcoma, 3% of uterine corpus endometrial carcinoma and skin cutaneous melanoma, and 2% of colorectal adenocarcinoma and stomach adenocarcinoma[4,5]. Alterations in MYC are also observed in pediatric cancers[5]. Somatic mutations in MYC have been observed in 59% of non-Hodgkin lymphoma, 2% of leukemia, and less than 1% of bone cancer (2 in 327 cases) and B-lymphoblastic leukemia/lymphoma (1 in 252 cases)[5]. Amplification of MYC is observed in 6% of embryonal tumor, 5% of bone cancer, and less than 1% of B-lymphoblastic leukemia/lymphoma (2 in 731 cases) and MYC translocations are observed in 5% of T-lymphoblastic leukemia/lymphoma[5].

Potential relevance: B-cell lymphoma with MYC translocations that co-occur with BCL2 or BCL6 are referred to as double hit lymphoma, while co-occurrence with BCL2 and BCL6 rearrangements is referred to as triple-hit lymphoma[115,135]. MYC translocations are a diagnostic marker of Burkitt Lymphoma[136,137]. MYC translocations are also indicative of high risk for multiple myeloma and are associated with poor risk in acute lymphoblastic leukemia[17,138]. Currently, no therapies are approved for MYC aberrations. Due to the high frequency of somatic MYC alterations in cancer, many approaches are being investigated in clinical trials including strategies to disrupt complex formation with MAX, including inhibition of MYC expression and synthetic lethality associated with MYC overexpression[125,139,140,141].

SMARCA4 deletion

SWI/SNF related, matrix associated, actin dependent regulator of chromatin, subfamily a, member 4

Background: The SMARCA4 gene encodes the SWI/SNF related, matrix associated, actin dependent regulator of chromatin, subfamily A, member 4 protein[1]. SMARCA4, also known as BRG1, is a core member of ATP-dependent, multisubunit SWI/SNF chromatin-remodeling complex, along with SMARCB1/SNF5, SMARCC1/BAF155, SMARCC2/BAF170, and SMARCA2/BRM[175]. The SWI/SNF complex remodels chromatin at promoter and enhancer elements to alter and regulate gene expression[175,176]. SMARCA4 and SMARCA2 are highly homologous and are mutually exclusive ATPase catalytic subunits for SWI/SNF chromatin remodeling complexes[175,176]. Germline loss of function mutations in SMARCA4 are associated with atypical teratoid/rhabdoid tumors (AT/RT), and a rare form of ovarian cancer called small cell carcinoma of the ovary, hypercalcemic type (SCCOHT), which highlights the tumor suppressor function of SMARCA4.[177,178].

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[176]. Recurrent somatic mutations in SMARCA4 are observed in 10% of skin cutaneous melanoma and uterine corpus endometrial carcinoma, and 7% of esophageal adenocarcinoma[4,5].

Biomarker Descriptions (continued)

Potential relevance: Currently, no therapies are approved for SMARCA4 aberrations. SMARCA4 mutations and deletions are considered a diagnostic marker for the SMARCA4-deficient uterine sarcoma (SDUS) subtype[179].

BRIP1 p.(S505*) c.1514C>A

BRCA1 interacting protein C-terminal helicase 1

Background: The BRIP1 gene encodes the BRCA1 interacting protein C-terminal helicase 1 and is a member of the RecQ DEAH helicase family that plays a role in homologous recombination repair (HRR) of double-stranded breaks (DSBs) in DNA[48]. BRIP1 interacts directly with BRCA1 through the BRCT domain and controls BRCA1-dependent DNA repair and the DNA damage-induced G2-M checkpoint control[49]. BRIP1 is a tumor suppressor gene. Loss of function mutations in BRIP1 are implicated in the BRCAness phenotype, characterized by a defect in HRR, mimicking BRCA1 or BRCA2 loss[50,51]. Germline aberrations in BRIP1 are associated with inherited disorders such as Fanconi anemia (FA)[52]. Specifically, BRIP1 was shown to be biallelically inactivated in FA patients and is also considered a high-risk gene for familial late-onset ovarian cancer[52,53]. BRIP1 germline mutations confer ~ 10% cumulative risk of ovarian cancer and are associated with an increased risk of colorectal cancer[48,54].

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

Potential relevance: The PARP inhibitor, olaparib[55] is approved (2020) for metastatic castration-resistant prostate cancer (mCRPC) with deleterious or suspected deleterious, germline or somatic mutations in HRR genes that includes BRIP1. Consistent with other genes associated with the BRCAness phenotype, BRIP1 mutations may aid in selecting patients likely to respond to PARP inhibitors or platinum therapy[50,56]. In 2022, the FDA granted fast track designation to the small molecule inhibitor, pidnarulex[57], for BRCA1/2, PALB2, or other homologous recombination deficiency (HRD) mutations in breast and ovarian cancers.

FGF19 amplification

fibroblast growth factor 19

Background: The FGF19 gene encodes the fibroblast growth factor 19 protein, a member of the FGF protein family composed of twenty-two members[58,59]. With the exception of four non-signaling FGF memebers (FGF11-14), FGF proteins function as ligands and mediate the activation of the fibroblast growth factor receptor (FGFR) family of tyrosine kinases[58,59]. Upon FGF-mediated stimulation, FGFRs activate several oncogenic signaling pathways, including the RAS/RAF/MEK/ERK, PI3K/AKT/MTOR, PLC/PKC, and JAK/STAT pathways thereby influencing cell proliferation, migration, and survival[60,61,62]. FGF19 is specifically observed to bind FGFR4 with increased affinity in the presence of the transmembrane protein klotho beta (KLB) which functions as a cofactor in FGF19 mediated FGFR4 activation[222,223]. FGF19-mediated aberrant signaling has been identified as an oncogenic driver in hepatocellular carcinoma[222,224].

Alterations and prevalence: FGF19 amplification is observed in about 35% of esophageal cancer, 23% of head and neck cancer, 10-15% of invasive breast carcinoma, cholangiocarcinoma, squamous lung, and bladder cancers as well as 5-7% of melanoma, liver, ovarian, and stomach cancers[4]. FGF19 overexpression is correlated with the development and tumor progression in hepatocellular carcinoma[225].

Potential relevance: Currently, no therapies are approved for FGF19 aberrations. Selective, irreversible FGFR4 inhibitors, including fisogatinib (BLU-554), are under current clinical trial evaluation. In a phase-I clinical study of fisogatinib in patients with advanced hepatocellular carcinoma, 63% of the 115 patients enrolled were FGF19-positive by IHC[226]. Additionally, in 53 patients with tissue available for evaluation, 96% also exhibited mRNA-expression of FGFR4 and KLB. The total overall response rate observed for fisogatinib in FGF19-positive patients evaluable for response was 17% (11/66)[226].

RB1 deletion

RB transcriptional corepressor 1

Background: The RB1 gene encodes the retinoblastoma protein (pRB), and is an early molecular hallmark of cancer. RB1 belongs to the family of pocket proteins that also includes p107 and p130, which play a crucial role in the cell proliferation, apoptosis, and differentiation[20,21]. RB1 is well characterized as a tumor suppressor gene that restrains cell cycle progression from G1 phase to S phase[22]. Specifically, RB1 binds and represses the E2F family of transcription factors that regulate the expression of genes involved in the G1/S cell cycle regulation[20,21,23]. Germline mutations in RB1 are associated with retinoblastoma (a rare childhood tumor) as well as other cancer types such as osteosarcoma, soft tissue sarcoma, and melanoma[24].

Alterations and prevalence: Recurrent somatic alterations in RB1, including mutations and biallelic loss, lead to the inactivation of the RB1 protein. RB1 mutations are observed in urothelial carcinoma (approximately 16%), endometrial cancer (approximately 12%), and sarcomas (approximately 9%)[5]. Similarly, biallelic loss of RB1 is observed in sarcomas (approximately 13%), urothelial carcinoma

Biomarker Descriptions (continued)

(approximately 6%), and endometrial cancer (approximately 1%)[5]. Biallelic loss of the RB1 gene is also linked to the activation of chemotherapy-induced acute myeloid leukemia (AML) and acute lymphoblastic leukemia (ALL)[25,26,27].

Potential relevance: Currently, there are no therapies approved for RB1 aberrations.

CUL4A deletion

cullin 4A

Background: The CUL4A gene encodes cullin 4A, a member of the cullin family, which includes CUL1, CUL2, CUL3, CUL4b, CUL5, CUL7, and Parc[1,6]. CUL4A belongs to the CUL4 subfamily which also includes CUL4B[7]. CUL4A and CUL4B share greater than 80% sequence identity and functional redundancy[7,8]. Cullin proteins share a conserved cullin homology domain and act as molecular scaffolds for RING E3 ubiquitin ligases to assemble into cullin-RING ligase complexes (CRLs)[6]. CUL4A is part of the CRL4 complex which is responsible for ubiquitination and degradation of a variety of substrates where substrate specificity is dependent on the substrate recognition component of the CRL4 complex[8]. CRL4 substrates include oncoproteins, tumor suppressors, nucleotide excision repair proteins, cell cycle promoters, histone methylation proteins, and tumor-related signaling molecules, thereby impacting various processes critical to tumor development and progression and supporting a complex role of CUL4A in oncogenesis[7,8].

Alterations and prevalence: Somatic mutations in CUL4A are observed in 5% of uterine corpus endometrial carcinoma, 3% of skin cutaneous melanoma, and 2% of diffuse large B-cell lymphoma[4,5]. Structural variants of CUL4A are observed in 3% of cholangiocarcinoma[4,5]. Amplification of CUL4A is observed in 4% of sarcoma and uterine carcinosarcoma, 3% of colorectal adenocarcinoma, ovarian serous cystadenocarcinoma, liver hepatocellular carcinoma, and bladder urothelial carcinoma, and 2% of lung squamous cell carcinoma, esophageal adenocarcinoma, stomach adenocarcinoma, breast invasive carcinoma, and head and neck squamous cell carcinoma[4,5]. Biallelic loss of CUL4A is observed in 2% of diffuse large B-cell lymphoma[4,5].

Potential relevance: Currently, no therapies are approved for CUL4A aberrations.

FGF3 amplification

fibroblast growth factor 3

Background: The FGF3 gene encodes the fibroblast growth factor 3 protein, a member of the FGF protein family composed of twenty-two members[58,59]. With the exception of four non-signaling FGF memebers (FGF11-14), FGF proteins function as ligands and mediate the activation of the fibroblast growth factor receptor (FGFR) family of tyrosine kinases[58,59]. Upon FGF-mediated stimulation, FGFRs activate several oncogenic signaling pathways, including the RAS/RAF/MEK/ERK, PI3K/AKT/MTOR, PLC/PKC, and JAK/STAT pathways thereby influencing cell proliferation, migration, and survival[60,61,62]. Specifically, FGF3 has been shown to bind to both FGFR1 and FGFR2[180,181]. Overexpression of FGF3 has been associated with certain tumor types including lung and liver cancers[182,183]. Additionally, constitutive ectopic expression has been suggested to promote tumorigenesis in vitro, supporting an oncogenic role for FGF3[181].

Alterations and prevalence: FGF3 amplification is observed in about 35% of esophageal cancer, 24% of head and neck cancer, 10-15% of invasive breast carcinoma, squamous lung, and bladder cancers as well as 5-10% of cholangiocarcinoma, melanoma, liver, ovarian and stomach cancers[4]. FGF3 overexpression is correlated with non-small cell lung cancer (NSCLC) development as well as tumor metastasis and recurrence in hepatocellular carcinoma[182,183].

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

FGF4 amplification

fibroblast growth factor 4

Background: The FGF4 gene encodes the fibroblast growth factor 4 protein, a member of the FGF protein family, which is composed of 22 members[1,58]. With the exception of four non-signaling FGF members (FGF11-14), FGF proteins function as ligands and mediate the activation of the fibroblast growth factor receptor (FGFR) family of tyrosine kinases[58,59]. Upon FGF-mediated stimulation, FGFRs activate several oncogenic signaling pathways, including the RAS/RAF/MEK/ERK, PI3K/AKT/MTOR, PLC/PKC, and JAK/STAT pathways, thereby influencing cell proliferation, migration, and survival[60,61,62].

Alterations and prevalence: Amplifications in FGF4 are observed in various tumor types, but most frequently are found in up to 35% of esophageal adenocarcinoma, 24% of head and neck squamous cell carcinoma, 14% of breast invasive carcinoma, 12% of lung squamous cell carcinoma, 11% of cholangiocarcinoma, 10% of bladder urothelial carcinoma, 7% of stomach adenocarcinoma, and 5% of liver hepatocellular carcinoma[4,5]. FGF4 overexpression has been associated with Kaposi sarcoma lesions as well as testicular cancer[63,64].

Biomarker Descriptions (continued)

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

Microsatellite stable

Background: Microsatellites are short tandem repeats (STR) of 1 to 6 bases of DNA between 5 to 50 repeat units in length. There are approximately 0.5 million STRs that occupy 3% of the human genome[75]. Microsatellite instability (MSI) is defined as a change in the length of a microsatellite in a tumor as compared to normal tissue[76,77]. 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[78]. 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[79]. 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)[79]. Tumors classified as MSI-L are often phenotypically indistinguishable from MSS tumors and tend to be grouped with MSS[80,81,82,83,84]. 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[77]. LS is associated with an increased risk of developing colorectal cancer, as well as other cancers, including endometrial and stomach cancer[76,77,81,85].

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[76,77,86,87]. 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[86,87].

Potential relevance: Anti-PD-1 immune checkpoint inhibitors including pembrolizumab[88] (2014) and nivolumab[89] (2015) are approved for patients with MSI-H or dMMR colorectal cancer who have progressed following chemotherapy. Pembrolizumab[88] 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[88]. Dostarlimab[90] (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[82,91]. The cytotoxic T-lymphocyte antigen 4 (CTLA-4) blocking antibody, ipilimumab[92] (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[82,93,94]. 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[94]. 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[95,96]. However, checkpoint blockade with the addition of chemotherapy or targeted therapies have demonstrated response in MSS or pMMR cancers[95,96].

RICTOR amplification

RPTOR independent companion of MTOR complex 2

Background: The RICTOR gene encodes the RPTOR independent companion of MTOR complex 2, a core component of the mTOR complex-2 (mTORC2)[1,166]. RICTOR complexes with MTOR, DEPTOR, mSin1 and Protor1/2 to form the mTORC2 complex, which regulates cell proliferation and survival by phosphorylating members of the PKA/PKG/PKC family of protein kinases[167]. The mTORC2 complex is a downstream effector of the PI3K/AKT/MTOR signaling pathway and facilitates integration of the PI3K/AKT/MTOR and RAS/RAF/MEK/ERK signaling pathways[159,168,169]. Independent of mTORC2, RICTOR can interact with integrin-linked kinases and promote phosphorylation of AKT[167,170]. Aberrations in RICTOR can lead to downstream pathway activation promoting cell proliferation and survival, supporting an oncogenic role for RICTOR[171].

Alterations and prevalence: Amplification of RICTOR is observed in several types of solid tumors and has been observed to correlate with protein overexpression[172]. Specifically, RICTOR amplification is observed in 10% of lung squamous cell carcinoma, 8% of esophageal adenocarcinoma, 7% of lung adenocarcinoma, 6% of stomach adenocarcinoma, 5% of adrenocortical carcinoma, bladder urothelial carcinoma, cervical squamous cell carcinoma, ovarian serous cystadenocarcinoma, and sarcoma[4,5]. Somatic mutations in RICTOR are observed in 7% of uterine corpus endometrial carcinoma and skin cutaneous melanoma, 5% of stomach adenocarcinoma and bladder urothelial carcinoma, and 3% of lung adenocarcinoma and lung squamous cell carcinoma[4,5].

Potential relevance: Currently, no therapies are approved for RICTOR aberrations. RICTOR overexpression is associated with poor survival in hepatocellular carcinoma and endometrial carcinoma[173,174].

Biomarker Descriptions (continued)

STK11 deletion

serine/threonine kinase 11

Background: The STK11 gene, also known as liver kinase B1 (LKB1), encodes the serine/threonine kinase 11 protein. STK11 is a tumor suppressor with multiple substrates including AMP-activated protein kinase (AMPK) that regulates cell metabolism, growth, and tumor suppression[116]. Germline mutations in STK11 are associated with Peutz-Jeghers syndrome, an autosomal dominant disorder, characterized by gastrointestinal polyp formation and elevated risk of neoplastic development[117,118].

Alterations and prevalence: Somatic mutations in STK11 have been reported in 10% of lung cancer, 4% of cervical cancer, and up to 3% of cholangiocarcinoma and uterine cancer[4,5,119,120]. Mutations in STK11 are found to co-occur with KEAP1 and KRAS mutations in lung cancer[4,5]. Copy number deletion leads to inactivation of STK11 in cervical, ovarian, and lung cancers, among others[4,5,117,120,121].

Potential relevance: Currently, no therapies are approved for STK11 aberrations. However, in 2023, the FDA granted fast track designation to a first-in-class inhibitor of the CoREST complex (Co-repressor of Repressor Element-1 Silencing Transcription), TNG-260[122] in combination with an anti-PD-1 antibody, for advanced non-small cell lung cancer harboring STK11-mutations. The presence of STK11 mutations may be a mechanism of resistance to immunotherapies. Mutations in STK11 are associated with reduced expression of PD-L1, which may contribute to the ineffectiveness of anti-PD-1 immunotherapy in STK11 mutant tumors[123]. In a phase III clinical trial of nivolumab in lung adenocarcinoma, patients with KRAS and STK11 co-mutations demonstrated a worse (0/6) objective response rate (ORR) in comparison to patients with KRAS and TP53 co-mutations (4/7) or KRAS mutations only (2/11) (ORR= 0% vs 57.1% vs 18.25%, respectively)[124].

TP53 c.376-1G>A

tumor protein p53

Background: The TP53 gene encodes the tumor suppressor protein p53, which binds to DNA and activates transcription in response to diverse cellular stresses to induce cell cycle arrest, apoptosis, or DNA repair[1]. In unstressed cells, TP53 is kept inactive by targeted degradation via MDM2, a substrate recognition factor for ubiquitin-dependent proteolysis[204]. Alterations in TP53 are required for oncogenesis as they result in loss of protein function and gain of transforming potential[205]. Germline mutations in TP53 are the underlying cause of Li-Fraumeni syndrome, a complex hereditary cancer predisposition disorder associated with early-onset cancers[206,207].

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%)[4,5,112,119,185,208]. 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[209,210,211,212]. 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[213] (2020), received a fast track designation by the FDA for advanced tumors harboring a TP53 Y220C mutation. In addition to investigational therapies aimed at restoring wild-type TP53 activity, compounds that induce synthetic lethality are also under clinical evaluation[214,215]. TP53 mutation are a diagnostic marker of SHH-activated, TP53-mutant medulloblastoma[216]. 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)[17,217,218,219,220]. In mantle cell lymphoma, TP53 mutations are associated with poor prognosis when treated with conventional therapy including hematopoietic cell transplant[115]. 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[221].

UGT1A1 p.(G71R) c.211G>A

UDP glucuronosyltransferase family 1 member A1

Background: The UGT1A1 gene encodes UDP glucuronosyltransferase family 1 member A1, a member of the UDP-glucuronosyltransferase 1A (UGT1A) subfamily of the UGT protein superfamily[1,28]. UGTs are microsomal membrane-bound enzymes that catalyze the glucuronidation of endogenous and xenobiotic compounds and transform the lipophilic molecules into excretable, hydrophilic metabolites[28,29]. UGTs play an important role in drug metabolism, detoxification, and metabolite homeostasis. Differential expression of UGTs can promote cancer development, disease progression, as well as drug resistance[30]. Specifically,

Biomarker Descriptions (continued)

elevated expression of UGT1As are associated with resistance to many anti-cancer drugs due to drug inactivation and lower active drug concentrations. However, reduced expression and downregulation of UGT1As are implicated in bladder and hepatocellular tumorigenesis and progression due to toxin accumulation[30,31,32,33]. Furthermore, UGT1A1 polymorphisms, such as UGT1A1*28, UGT1A1*93, and UGT1A1*6, confer an increased risk of severe toxicity to irinotecan-based chemotherapy treatment of solid tumors, due to reduced glucuronidation of the irinotecan metabolite, SN-38[34].

Alterations and prevalence: Biallelic deletion of UGT1A1 has been observed in 6% of sarcoma, 3% of brain lower grade glioma and uveal melanoma, and 2% of thymoma, cervical squamous cell carcinoma, bladder urothelial carcinoma, head and neck squamous cell carcinoma, and esophageal adenocarcinoma[4,5].

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

TERT amplification

telomerase reverse transcriptase

Background: The TERT gene encodes telomerase reverse transcriptase, a component of the telomerase core enzyme along with the internal telomerase RNA template (TERC)[43]. TERT is repressed in most differentiated cells, resulting in telomerase silencing[43]. In cancer, telomerase reactivation is known to contribute to cellular immortalization[43,44]. Increased TERT expression results in telomerase activation, allowing for unlimited cancer cell proliferation through telomere stabilization[43]. In addition to its role in telomere maintenance, TERT has RNA-dependent RNA polymerase activity, which, when deregulated, can promote oncogenesis by facilitating mitotic progression and cancer cell stemness[43].

Alterations and prevalence: Somatic mutations are observed in 4% of skin cutaneous melanoma and uterine corpus endometrial carcinoma, 3% of kidney renal papillary cell carcinoma, and 2% of pancreatic adenocarcinoma, stomach adenocarcinoma, and sarcoma[4,5]. Additionally, TERT promoter mutations causing upregulation are observed in many cancer types, especially non-aural cutaneous melanoma (80% of cases), and glioblastoma (70% of cases)[44]. Specifically, TERT promoter mutations at C228T and C250T are recurrent and result in de novo binding sites for ETS transcription factors, leading to enhanced TERT transcription[43]. Amplification of TERT is observed in 15% of lung squamous cell carcinoma, 14% of esophageal adenocarcinoma, 13% of adrenocortical carcinoma and lung adenocarcinoma, and 10% of bladder urothelial carcinoma, 9% of ovarian serous cystadenocarcinoma, 6% of cervical squamous cell carcinoma, 5% of liver hepatocellular carcinoma, sarcoma, skin cutaneous melanoma, stomach adenocarcinoma, head and neck squamous cell carcinoma, 4% of uterine carcinosarcoma, 3% of uterine corpus endometrial carcinoma, breast invasive carcinoma, and 2% of diffuse large B-cell lymphoma[4,5]. TERT is overexpressed in over 85% of tumors and is considered a universal tumor associated antigen[45]. Alterations in TERT are rare in pediatric cancers[4,5]. Somatic mutations are observed in less than 1% of B-lymphoblastic leukemia/lymphoma (2 in 252 cases), glioma (2 in 297 cases), bone cancer (1 in 327 cases), and Wilms tumor (1 in 710 cases)[4,5]. TERT amplification is observed in 1-2% of peripheral nervous system cancers (2 in 91 cases), leukemia (2 in 250 cases), and B-lymphoblastic leukemia/lymphoma (5 in 731 cases)[4,5].

Potential relevance: Currently, no therapies are approved for TERT aberrations. TERT promoter mutations are diagnostic of oligodendroglioma IDH-mutant with 1p/19q co-deletion, while the absence of promoter mutations combined with an IDH mutation is characteristic of astrocytoma[46,47]. Due to its immunogenicity and near-universal expression on cancer cells, TERT has been a focus of immunotherapy research, including peptide, dendritic, and DNA vaccines as well as T-cell therapy[45].

CTNND2 amplification

catenin delta 2

Background: The CTNND2 gene encodes catenin delta 2 protein[1]. CTNND2, also known as NPRAP and δ-catenin, belongs to the delta subfamily of the β-catenin superfamily along with CTNND1[9]. Due to its interaction with the cell junction protein, E-cadherin, CTNND2 overexpression has been observed to disrupt E-cadherin distribution and promote tumor growth[9,10,11]. Additionally, CTNND2 alteration, particularly overexpression, is observed in several cancer types, supporting an oncogenic role for CTNND2[9,10,11].

Alterations and prevalence: Somatic mutations in CTNND2 are observed in 14% of skin cutaneous melanoma, 11% of lung adenocarcinoma, 10% of lung squamous cell carcinoma, 9% of stomach adenocarcinoma and uterine corpus endometrial carcinoma, and 6% of head and neck squamous cell carcinoma, and colorectal adenocarcinoma[4,5]. Amplification of CTNND2 is observed in 13% of lung squamous cell carcinoma, 10% of lung adenocarcinoma, esophageal adenocarcinoma, and bladder urothelial carcinoma, and 7% of ovarian serous cystadenocarcinoma, sarcoma, adrenocortical adenocarcinoma[4,5].

Potential relevance: Currently, no therapies are approved for CTNND2 aberrations.

Biomarker Descriptions (continued)

IL7R amplification

interleukin 7 receptor

Background: The IL7R gene encodes the interleukin 7 receptor[1]. IL7R is commonly expressed in immune cells and plays a critical role in the development and homeostasis of the immune system, including the regulation of cell development, survival, and differentiation of T-cells[13,14]. IL7R may also play a role in the development of B-cells by controlling downstream signaling pathways, including the JAK/PI3K/AKT pathways[14]. Mutations and other aberrations in IL7R result in a gain-of-function, thereby supporting its oncogenic role[15].

Alterations and prevalence: Somatic mutations in IL7R are observed in 13% of skin cutaneous melanoma, 6% of lung squamous cell carcinoma, and 4% of uterine corpus endometrial carcinoma, lung adenocarcinoma, and stomach adenocarcinoma[4,5]. Amplification of IL7R is observed in 10% of lung squamous cell carcinoma, 9% of lung adenocarcinoma, 8% of esophageal adenocarcinoma, 7% of bladder urothelial carcinoma, 6% of stomach adenocarcinoma, and 5% of cervical squamous cell carcinoma and ovarian serous cystadenocarcinoma[4,5]. Alterations in IL7R are also observed in pediatric cancers[4,5]. Somatic mutations are observed in 5% of T-lymphoblastic leukemia/lymphoma, 3% of soft tissue sarcoma (1 in 38 cases), 2% of B- lymphoblastic leukemia/lymphoma (4 in 252 cases), and less than 1% of embryonal tumor (3 in 332 cases), glioma (2 in 297 cases), leukemia (2 in 311 cases), bone cancer (2 in 327 cases), and peripheral nervous system cancers (1 in 1158 cases)[4,5,16]. Amplification of IL7R is observed in about 5% of pediatric bone cancer[4,5].

Potential relevance: Currently, no therapies are approved for IL7R aberrations. The Philadelphia-chromosome-like (Ph-like) phenotype of acute lymphoblastic leukemia (ALL) is associated with mutations in tyrosine kinase pathway genes, including IL7R[16,17,18]. Testing for these abnormalities at diagnosis may aid in risk stratification[17]. Notably, mutations in IL7R are associated with unfavorable-risk features in pediatric acute lymphoblastic leukemia[18,19].

HLA-A p.(L180*) c.539T>A

major histocompatibility complex, class I, A

Background: The HLA-A gene encodes the major histocompatibility complex, class I, A[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[35]. MHC class I molecules are heterodimers composed of two polypeptide chains, α and B2M[36]. 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[37,38,39]. Downregulation of MHC class I promotes tumor evasion of the immune system, suggesting a tumor suppressor role for HLA-A[40].

Alterations and prevalence: Somatic mutations in HLA-A are observed in 7% of diffuse large B-cell lymphoma (DLBCL), 4% of cervical squamous cell carcinoma and head and neck squamous cell carcinoma, 3% of colorectal adenocarcinoma, and 2% of uterine corpus endometrial carcinoma and stomach adenocarcinoma[4,5]. Biallelic loss of HLA-A is observed in 4% of DLBCL[4,5].

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

PRDM1 deletion

PR/SET domain 1

Background: The PRDM1 gene encodes the PR/SET domain 1 protein, also known as BLIMP1[1]. PRDM1 is a transcriptional repressor that regulates B- and T-cell differentiation[97,98,99]. PRDM1 drives the differentiation of mature B-cells to antibody-secreting cells (ASCs) and is commonly expressed in ASCs[100]. PRDM1, along with other transcription factors, also regulates the expression of IL-2, IL-21, and IL-10 in effector T-cells, resulting in T-cell mediated immunosuppression through IL repression[99]. Dysregulation of B-cell terminal differentiation, as a result of PRDM1 mutations, has been observed to contribute to lymphoma development, supporting a tumor suppressor role for PRDM1[100].

Alterations and prevalence: Somatic mutations in PRDM1 are observed in 7% of skin cutaneous melanoma, 6% of uterine corpus endometrial carcinoma, 5% diffuse large B-cell lymphoma (DLBCL), and 3% of cholangiocarcinoma[4,5]. Additionally, PRDM1 mutations have been reported in 25% of activated B-cell phenotype diffuse large B-cell lymphoma (ABC-DLBCL)[100]. PRDM1 biallelic deletions are observed in 10% of DLBCL, 9% of prostate adenocarcinoma, and 6% of uveal melanoma[4,5].

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

Biomarker Descriptions (continued)

HDAC2 deletion

histone deacetylase 2

Background: The HDAC2 gene encodes the histone deacetylase 2 protein[1]. HDAC2 is part of the histone deacetylase (HDAC) family consisting of 18 different isoforms categorized into four classes (I-IV)[151]. Specifically, HDAC2 is a member of class I, along with HDAC1, HDAC3, and HDAC8[151]. HDACs, including HDAC2, function by removing acetyl groups on histone lysines resulting in chromatin condensation, transcriptional repression, and regulation of cell proliferation and differentiation[151,152]. HDAC2 negatively regulates antigen presentation by inhibiting CIITA, which regulates MHC class II genes[151]. Further, HDAC2 and HDAC1 are essential for B-cell proliferation during development and antigen stimulation in mature B-cells[151]. HDAC deregulation, including overexpression, is observed in a variety of tumor types, which is proposed to affect the expression of genes involved in cellular regulation and promote tumor development[151,153].

Alterations and prevalence: Somatic mutations in HDAC2 are observed in 4% of uterine corpus endometrial carcinoma, 2% of diffuse large B-cell lymphoma (DLBCL) and colorectal adenocarcinoma[4,5]. Biallelic deletions in HDAC2 are observed in 8% of prostate adenocarcinoma and DLBCL, and 6% of uveal melanoma[4,5].

Potential relevance: Currently, no therapies are approved for HDAC2 aberrations. Although not approved for specific HDAC2 alterations, the pan-HDAC inhibitor vorinostat (2006) is approved for the treatment of progressive, persistent, or recurrent cutaneous T-cell lymphoma (CTCL) following treatment with two systemic therapies[154]. The pan-HDAC inhibitor, romidepsin (2009), is approved for the treatment of CTCL and peripheral T-cell lymphoma (PTCL) having received at least one prior systemic therapy[155]. The pan-HDAC inhibitor, belinostat (2014), is approved for the treatment of relapsed or refractory PTCL[156]. The pan-HDAC inhibitor, panobinostat (2015), is approved for the treatment of multiple myeloma in combination of bortezomib and dexamethasone having received at least 2 prior regimens[157].

FAM135B amplification

family with sequence similarity 135 member B

Background: The FAM135B gene encodes the family with sequence similarity 135 member B protein[1]. While the function of FAM135B is not well characterized, FAM135B has been proposed to contribute to the activation of the PIK3CA/AKT/MTOR pathway and has been suggested to contribute to tumor progression, proliferation, and migration in esophageal squamous cell carcinoma (ESCC)[41,42].

Alterations and prevalence: Somatic mutations of FAM135B are observed in 28% of skin cutaneous melanoma, 24% of lung squamous cell carcinoma, 15% lung adenocarcinoma, 14% of uterine corpus endometrial carcinoma, 10% of head and neck squamous cell carcinoma, 8% of stomach adenocarcinoma, 7% of colorectal adenocarcinoma and uterine carcinosarcoma, 5% of esophageal adenocarcinoma, and bladder urothelial carcinoma, 4% of cervical squamous cell carcinoma, 3% of adrenocortical carcinoma and pancreatic adenocarcinoma, and 2% of diffuse large B-cell lymphoma, ovarian serous cystadenocarcinoma, breast invasive carcinoma, glioblastoma multiforme, liver hepatocellular carcinoma, and sarcoma[4,5]. Amplification of FAM135B is observed in 27% of ovarian serous cystadenocarcinoma, 12% of esophageal adenocarcinoma, 10% of breast invasive carcinoma and liver hepatocellular carcinoma, 9% of pancreatic adenocarcinoma, 7% of head and neck squamous cell carcinoma and uterine carcinosarcoma, 6% of prostate adenocarcinoma, 5% of lung adenocarcinoma, and stomach adenocarcinoma, 4% of skin cutaneous melanoma and lung squamous cell carcinoma, 3% of uterine corpus endometrial carcinoma, colorectal adenocarcinoma, brain lower grade glioma, bladder urothelial carcinoma, and uveal melanoma, and 2% of cervical squamous cell carcinoma and sarcoma[4,5].

Potential relevance: Currently, no therapies are approved for FAM135B aberrations.

GATA3 p.(T419Hfs*89) c.1254_1255insC

GATA binding protein 3

Background: The GATA3 gene encodes GATA binding protein 3, a member of the GATA family of zinc-finger transcription factors, which also includes GATA1, GATA2, and GATA4-6[1,146,147]. The GATA family regulates transcription of many genes by binding to the DNA consensus sequence T/A(GATA)A/G[147]. GATA3 functions in the differentiation of immune cells and tissue development[148,149]. As GATA3 also functions in luminal cell development and cell function, it is a common marker of the gene expression profile in luminal breast cancer[148].

Alterations and prevalence: Somatic mutations in GATA3 are observed in 12% of breast invasive carcinoma, 4% of uterine corpus endometrial carcinoma and stomach adenocarcinoma, and 3% of colorectal adenocarcinoma and skin cutaneous melanoma[4,5]. Biallelic loss of GATA3 is observed in 2% of diffuse large B-cell lymphoma (DLBCL)[4,5]. Alterations in GATA3 are also observed in the pediatric population[5]. Somatic mutations are observed in 6% of non-Hodgkin lymphoma (1 in 17 cases), 3% of soft tissue sarcoma (1 in 38 cases), 2% of T-lymphoblastic leukemia/lymphoma (1 in 41 cases) and Hodgkin lymphoma (1 in 61 cases), and less than 1% of bone cancer (3 in 327 cases), embryonal tumor (3 in 332 cases), and leukemia (1 in 311 cases)[5]. Biallelic deletion is observed in 1% of

Biomarker Descriptions (continued)

peripheral nervous system cancers (1 in 91 cases), less than 1% of leukemia (1 in 250 cases) and B-lymphoblastic leukemia/lymphoma (1 in 731 cases)[5].

Potential relevance: Currently, no therapies are approved for GATA3 aberrations. Low GATA3 expression is associated with invasion and poor prognosis in breast cancer[148,150].

ARID5B deletion

AT-rich interaction domain 5B

Background: The ARID5B gene encodes the AT-rich interaction domain 5B protein[1]. ARID5B, also known as MRF2, belongs to the ARID superfamily that also includes ARID1A, ARID1B, and ARID2[2,3]. ARID5B forms a complex with PHF2, which is capable of histone demethylation leading to transcriptional activation of target genes[3]. ARID5B is known to be essential for the development of hematopoietic cells[3]. Several single-nucleotide polymorphisms (SNPs) in ARID5B have been associated with susceptibility of acute lymphoblastic leukemia (ALL)[3].

Alterations and prevalence: Somatic mutations in ARID5B are observed in 15% of uterine corpus endometrial carcinoma, 6% of skin cutaneous melanoma, 5% of diffuse large B-cell lymphoma, 4% of stomach adenocarcinoma[4,5]. Biallelic loss of ARID5B is observed in 1% of kidney chromophobe, lung squamous cell carcinoma, and skin cutaneous melanoma[4,5].

Potential relevance: Currently, no therapies are approved for ARID5B aberrations.

TPP2 deletion

tripeptidyl peptidase 2

Background: The TPP2 gene encodes the tripeptidyl peptidase 2[1]. TPP2 is a serine peptidase that becomes activated upon homopolymer complex formation[12]. Upon activation, TPP2 cleaves amino terminal tripeptides from substrates[12]. TPP2 is involved in antigen processing, cell growth, DNA damage repair, and carcinogenesis, potentially through its control of ERK1/2 phosphorylation[12].

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

Potential relevance: Currently, no therapies are approved for TPP2 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[1,65,66]. Functionally, ZFHX3 is found to be necessary for neuronal and myogenic differentiation[66,67]. ZFHX3 is capable of binding and repressing transcription of α-fetoprotein (AFP), thereby negatively regulating the expression of MYB and cancer cell growth[68,69,70,71,72]. In addition, ZFHX3 has been observed to be altered in several cancer types, supporting a tumor suppressor role for ZFHX3[68,71,73,74].

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.

Biomarker Descriptions (continued)

RPS6KB1 amplification

ribosomal protein S6 kinase B1

Background: The RPS6KB1 gene encodes ribosomal protein S6 kinase B1[1]. RPS6KB1, also known as S6K1, belongs to the AGC kinase family along with AKT, PKA, PKC, and PKG[158]. RPS6KB1 is a downstream target of mTORC1 phosphorylation which results in activation of RPS6KB1 and subsequent phosphorylation of the 40S ribosomal protein S6[159,160]. Aberrations including amplification and overexpression of RPS6KB1 have been associated with various cancer types including breast, kidney, and hepatocellular carcinoma, supporting an oncogenic role for RPS6KB1[159,161].

Alterations and prevalence: Somatic mutations in RPS6KB1 are observed in 2% uterine corpus endometrial carcinoma[4,5]. Amplification of RPS6KB1 is observed in 9% of breast invasive carcinoma, 5% of liver hepatocellular carcinoma and mesothelioma, and 4% uterine carcinosarcoma[4,5].

Potential relevance: Currently, no therapies are approved for RPS6KB1 aberrations.

ZNF217 amplification

zinc finger protein 217

Background: ZNF217 encodes zinc finger protein 217, a member of the Krüppel-like family of transcription factors[1,142]. While ZNF217 positively regulates gene expression, it also interacts with corepressors and histone-modifying proteins demonstrating its complexity as a transcriptional regulator[142,143,144]. ZNF217 coordinates several cellular processes involved in tumorigenesis, such as proliferation, survival, invasion, and metastasis[144]. In breast cancer, functional crosstalk between the estrogen receptor and ZNF217 has been a suggested mechanism for endocrine therapy resistance and high expression of ZNF217 may confer poor prognosis[145].

Alterations and prevalence: Somatic mutations in ZNF217 are observed in 7% of uterine corpus endometrial carcinoma, 5% of diffuse large B-cell lymphoma, 4% of skin cutaneous melanoma, 3% of stomach adenocarcinoma, colorectal adenocarcinoma, and bladder urothelial carcinoma, and 2% of lung squamous cell carcinoma, lung adenocarcinoma, and head and neck squamous cell carcinoma[4,5]. Amplification of ZNF217 is found in 9% of uterine carcinosarcoma, 8% of stomach adenocarcinoma, 7% of colorectal adenocarcinoma and breast invasive carcinoma, 5% of esophageal adenocarcinoma and lung adenocarcinoma, 4% of ovarian serous cystadenocarcinoma, 3% of uterine corpus endometrial carcinoma, and 2% of sarcoma, pancreatic adenocarcinoma, and liver hepatocellular carcinoma[4,5].

Potential relevance: Currently, no therapies are approved for ZNF217 aberrations.

AURKA amplification

aurora kinase A

Background: The AURKA gene encodes aurora kinase A[1]. AURKA, along with AURKB and AURKC, is a member of the Aurora kinase family[162]. AURKA is a serine threonine kinase involved in several important biological processes, including G2/M transition, mitosis, meiosis, and DNA replication[162,163]. Aurora kinase-mediated phosphorylation has been observed to regulate a number of molecular targets. Deregulation, due to amplification and overexpression, has been observed in various tumor types, supporting a potential oncogenic role for AURKA[162,163,164].

Alterations and prevalence: Somatic mutations in AURKA are observed in 2% of uterine corpus endometrial carcinoma and cervical squamous cell carcinoma[4,5,165]. AURKA amplification is observed in 7% of colorectal adenocarcinoma, 5% of ovarian serous cystadenocarcinoma, 4% of breast invasive carcinoma, uterine carcinosarcoma, 3% of esophageal adenocarcinoma, lung adenocarcinoma, and stomach adenocarcinoma, and 2% of sarcoma and pancreatic adenocarcinoma[4,5,165].

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

Alerts Informed By Public Data Sources

Current FDA Information

Contraindicated Not recommended Resistance Breakthrough Fast Track

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

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

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

GLSI-100

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

Supporting Statement:
The FDA has granted Fast Track designation to the immunotherapy, GLSI-100, for the treatment of patients with HLA-A*02 genotype and HER2-positive breast cancer who have completed treatment with standard of care HER2/neu targeted therapy to improve invasive breast cancer free survival.

Reference:

https://investor.greenwichlifesciences.com/news-events/press-releases/detail/102/us-fda-fast-track-designation

ERBB2 amplification (continued)

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/

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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

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Current ESMO Information

Contraindicated Not recommended Resistance Breakthrough Fast Track

ESMO information is current as of 2025-09-02. 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	●	✖	✖	✖	✖
zanidatamab	○	○	○	○	● (II)
trastuzumab + capecitabine + cisplatin	○	○	○	✖	✖
trastuzumab + cisplatin + fluorouracil	○	○	○	✖	✖
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	✖	●	✖	✖	✖
ado-trastuzumab emtansine + neratinib	✖	●	✖	✖	✖
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	✖	●	✖	✖	✖

* 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 + vinorelbine	✖	●	✖	✖	✖
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 (CuraTeQ Biologics)	✖	✖	●	✖	✖
trastuzumab (CuraTeQ Biologics) + anastrozole	✖	✖	●	✖	✖
trastuzumab (CuraTeQ Biologics) + carboplatin + docetaxel	✖	✖	●	✖	✖
trastuzumab (CuraTeQ Biologics) + docetaxel	✖	✖	●	✖	✖
trastuzumab (CuraTeQ Biologics) + paclitaxel	✖	✖	●	✖	✖

* 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 (EirGenix)	✖	✖	●	✖	✖
trastuzumab (EirGenix) + anastrozole	✖	✖	●	✖	✖
trastuzumab (EirGenix) + carboplatin + docetaxel	✖	✖	●	✖	✖
trastuzumab (EirGenix) + docetaxel	✖	✖	●	✖	✖
trastuzumab (EirGenix) + paclitaxel	✖	✖	●	✖	✖
trastuzumab (Henlius) + anastrozole	✖	✖	●	✖	✖
trastuzumab (Henlius) + carboplatin + docetaxel	✖	✖	●	✖	✖
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 (CuraTeQ Biologics) + capecitabine + cisplatin	✖	✖	○	✖	✖
trastuzumab (CuraTeQ Biologics) + cisplatin + fluorouracil	✖	✖	○	✖	✖
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	✖	✖	○	✖	✖

* 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 + 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, pertuzumab, pyrotinib, chemotherapy	✖	✖	✖	✖	● (IV)
pertuzumab, trastuzumab (Henlius), chemotherapy	✖	✖	✖	✖	● (IV)
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)
antiHER2 therapy, radiation therapy	✖	✖	✖	✖	● (III)
BL-M07D1, ado-trastuzumab emtansine	✖	✖	✖	✖	● (III)
chemotherapy, pertuzumab, trastuzumab	✖	✖	✖	✖	● (III)
chemotherapy, trastuzumab, pertuzumab	✖	✖	✖	✖	● (III)
disitamab vedotinaide, pyrotinib	✖	✖	✖	✖	● (III)
DP-303c, trastuzumab, chemotherapy	✖	✖	✖	✖	● (III)
Hemay022, hormone therapy, lapatinib, chemotherapy	✖	✖	✖	✖	● (III)

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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*
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	✖	✖	✖	✖	● (III)
pertuzumab (Biocon Biologics), trastuzumab, chemotherapy	✖	✖	✖	✖	● (III)
pertuzumab, trastuzumab, KM-118, chemotherapy	✖	✖	✖	✖	● (III)
pyrotinib, hormone therapy, chemotherapy	✖	✖	✖	✖	● (III)
TQB-2102, ado-trastuzumab emtansine	✖	✖	✖	✖	● (III)
TQB-2102, chemotherapy, trastuzumab, pertuzumab	✖	✖	✖	✖	● (III)
TQB-2930, trastuzumab, chemotherapy	✖	✖	✖	✖	● (III)
trastuzumab deruxtecan, ado-trastuzumab emtansine, olaparib, trastuzumab, pertuzumab, chemotherapy, neratinib, CDK 4/6 inhibitor	✖	✖	✖	✖	● (III)
trastuzumab rezetecan, pertuzumab, trastuzumab, chemotherapy	✖	✖	✖	✖	● (III)
trastuzumab, chemotherapy	✖	✖	✖	✖	● (III)
trastuzumab, pertuzumab, chemotherapy, pyrotinib, palbociclib, ado-trastuzumab emtansine, everolimus, hormone therapy, sintilimab	✖	✖	✖	✖	● (III)
trastuzumab, pyrotinib, chemotherapy	✖	✖	✖	✖	● (III)
tucatinib, ado-trastuzumab emtansine	✖	✖	✖	✖	● (III)
zanidatamab, trastuzumab, chemotherapy	✖	✖	✖	✖	● (III)
MRG-002	✖	✖	✖	✖	● (II/III)
pertuzumab, BL-M07D1, trastuzumab, chemotherapy	✖	✖	✖	✖	● (II/III)
A-166	✖	✖	✖	✖	● (II)
AdHER2DC vaccine, trastuzumab, pertuzumab, chemotherapy	✖	✖	✖	✖	● (II)
ado-trastuzumab emtansine, neratinib	✖	✖	✖	✖	● (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*
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, 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)
disitamab vedotinaide, bevacizumab, pyrotinib	✖	✖	✖	✖	● (II)
disitamab vedotinaide, toripalimab, pertuzumab	✖	✖	✖	✖	● (II)
disitamab vedotinaide, tucatinib	✖	✖	✖	✖	● (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)

* 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, atezolizumab + pertuzumab/trastuzumab/hyaluronidase-zzxf, trastuzumab + tucatinib	✖	✖	✖	✖	● (II)
pertuzumab, trastuzumab, chemotherapy	✖	✖	✖	✖	● (II)
pertuzumab/trastuzumab/hyaluronidase-zzxf, chemotherapy	✖	✖	✖	✖	● (II)
pertuzumab/trastuzumab/hyaluronidase-zzxf, hormone therapy	✖	✖	✖	✖	● (II)
pyrotinib, anvatabart opadotin	✖	✖	✖	✖	● (II)
pyrotinib, dalpiciclib, hormone therapy	✖	✖	✖	✖	● (II)
pyrotinib, pertuzumab, chemotherapy, trastuzumab	✖	✖	✖	✖	● (II)
pyrotinib, pertuzumab, trastuzumab	✖	✖	✖	✖	● (II)
pyrotinib, trastuzumab rezetecan, pertuzumab, trastuzumab, chemotherapy	✖	✖	✖	✖	● (II)
radiation therapy, pyrotinib, chemotherapy	✖	✖	✖	✖	● (II)
sacituzumab govitecan, trastuzumab, trastuzumab and hyaluronidase-oysk	✖	✖	✖	✖	● (II)
TAP-11, sargramostim, ado-trastuzumab emtansine, trastuzumab, pertuzumab	✖	✖	✖	✖	● (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)
trastuzumab deruxtecan, pertuzumab/trastuzumab/ hyaluronidase-zzxf	✖	✖	✖	✖	● (II)
trastuzumab deruxtecan, radiation therapy	✖	✖	✖	✖	● (II)
trastuzumab rezetecan, pertuzumab, chemotherapy, trastuzumab	✖	✖	✖	✖	● (II)
trastuzumab rezetecan, pyrotinib	✖	✖	✖	✖	● (II)
trastuzumab rezetecan, pyrotinib, bevacizumab	✖	✖	✖	✖	● (II)
trastuzumab, hormone therapy, pirotinib	✖	✖	✖	✖	● (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*
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, 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	✖	✖	✖	✖	● (I/II)
E01001	✖	✖	✖	✖	● (I/II)
evorpacept, trastuzumab, chemotherapy	✖	✖	✖	✖	● (I/II)
fadraciclib	✖	✖	✖	✖	● (I/II)
GQ1001, pyrotinib, chemotherapy	✖	✖	✖	✖	● (I/II)
hormone therapy, steroid, chemotherapy	✖	✖	✖	✖	● (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*
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)
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)
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)
YH32367	✖	✖	✖	✖	● (I/II)
zongertinib, ado-trastuzumab emtansine, trastuzumab deruxtecan, trastuzumab, chemotherapy	✖	✖	✖	✖	● (I/II)
zotatifin, trastuzumab	✖	✖	✖	✖	● (I/II)
ZV-0203	✖	✖	✖	✖	● (I/II)
177Lu-ABY-271	✖	✖	✖	✖	● (I)
177Lu-RAD202	✖	✖	✖	✖	● (I)
ado-trastuzumab emtansine (Shanghai Fosun Pharma)	✖	✖	✖	✖	● (I)
anti-HER-2 MAb (Anke Biotechnology)	✖	✖	✖	✖	● (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*
antiemetic agent, chemotherapy, trastuzumab, pertuzumab	✖	✖	✖	✖	● (I)
BC004	✖	✖	✖	✖	● (I)
BL-M17D1	✖	✖	✖	✖	● (I)
BM-230	✖	✖	✖	✖	● (I)
CART-HER2	✖	✖	✖	✖	● (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)
ENT-H-1, trastuzumab	✖	✖	✖	✖	● (I)
EX-101 (Excelmab)	✖	✖	✖	✖	● (I)
GB251	✖	✖	✖	✖	● (I)
GQ-1005	✖	✖	✖	✖	● (I)
GQ1001	✖	✖	✖	✖	● (I)
HF-50	✖	✖	✖	✖	● (I)
HS-630	✖	✖	✖	✖	● (I)
inetetamab, pyrotinib, chemotherapy	✖	✖	✖	✖	● (I)
IPH-5301, trastuzumab, chemotherapy	✖	✖	✖	✖	● (I)
MBS301	✖	✖	✖	✖	● (I)
micvotabart pelidotin	✖	✖	✖	✖	● (I)
MVF-HER-2 (266-296), MVF-HER-2(597-626)	✖	✖	✖	✖	● (I)
NC-18	✖	✖	✖	✖	● (I)
palbociclib, avelumab	✖	✖	✖	✖	● (I)
pyrotinib, chemotherapy, trastuzumab	✖	✖	✖	✖	● (I)
SPH5030	✖	✖	✖	✖	● (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*
SYS-6023	✖	✖	✖	✖	● (I)
TAS0728	✖	✖	✖	✖	● (I)
TL-938	✖	✖	✖	✖	● (I)
trastuzumab deruxtecan, azenosertib	✖	✖	✖	✖	● (I)
tucatinib, trastuzumab, pertuzumab, hormone therapy	✖	✖	✖	✖	● (I)
VRN-10	✖	✖	✖	✖	● (I)
VVD-159642	✖	✖	✖	✖	● (I)
XMT-2056	✖	✖	✖	✖	● (I)

FGFR1 amplification

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
pemigatinib	✖	✖	✖	✖	● (II)
regorafenib	✖	✖	✖	✖	● (II)
sunitinib	✖	✖	✖	✖	● (II)
BBI-355, futibatinib	✖	✖	✖	✖	● (I/II)

CCND1 amplification

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
abemaciclib	✖	✖	✖	✖	● (II)
palbociclib	✖	✖	✖	✖	● (II)
zotatifin, hormone therapy	✖	✖	✖	✖	● (I/II)

MYC amplification

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
entinostat, nivolumab	✖	✖	✖	✖	● (I/II)
nedisertib, tuvusertib	✖	✖	✖	✖	● (I)
talazoparib, palbociclib	✖	✖	✖	✖	● (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

SMARCA4 deletion

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
tucidinostat, catequentinib, PD-1 Inhibitor, anti-PD-L1 antibody	✖	✖	✖	✖	● (II)
tazemetostat, nivolumab, ipilimumab	✖	✖	✖	✖	● (I/II)

BRIP1 p.(S505*) c.1514C>A

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

FGF19 amplification

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
TYRA-430	✖	✖	✖	✖	● (I)

RB1 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
Not Detected	***Not Applicable***

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

Thermo Fisher Scientific's Ion Torrent Oncomine Reporter software was used in generation of this report. Software was developed and designed internally by Thermo Fisher Scientific. The analysis was based on Oncomine Reporter (6.1.1 data version 2025.10(006)). The data presented here are from a curated knowledge base of publicly available information, but may not be exhaustive. FDA information was sourced from www.fda.gov and is current as of 2025-09-17. NCCN information was sourced from www.nccn.org and is current as of 2025-09-02. EMA information was sourced from www.ema.europa.eu and is current as of 2025-09-17. ESMO information was sourced from www.esmo.org and is current as of 2025-09-02. Clinical Trials information is current as of 2025-09-02. For the most up-to-date information regarding a particular trial, search www.clinicaltrials.gov by NCT ID or search local clinical trials authority website by local identifier listed in 'Other identifiers.' Variants are reported according to HGVS nomenclature and classified following AMP/ASCO/CAP guidelines (Li et al. 2017). Based on the data sources selected, variants, therapies, and trials listed in this report are listed in order of potential clinical significance but not for predicted efficacy of the therapies.

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