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Patient Name: 이민정
Gender: F
Sample ID: N25-319

Primary Tumor Site: Lung
Collection Date: 2025.11.13.

Sample Cancer Type: Lung Cancer

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Report Highlights

2 Relevant Biomarkers
57 Therapies Available
85 Clinical Trials

Relevant Lung Cancer Findings

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

Genomic Alteration	Finding
Tumor Mutational Burden	***5.68 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	**trastuzumab deruxtecan** [1 / II+]	**lapatinib + hormone therapy** [1, 2 / I, II+] **lapatinib + trastuzumab** [2 / I, II+] **pertuzumab + trastuzumab + chemotherapy** [1, 2 / I, II+] **trastuzumab + tucatinib** [1 / I, II+] **trastuzumab deruxtecan** [1, 2 / I, II+] **trastuzumab† + chemotherapy** [1, 2 / I, II+] **trastuzumab† + hormone therapy** [2 / I, II+] **pembrolizumab + trastuzumab + chemotherapy** [1, 2 / I] **ado-trastuzumab emtansine** [1, 2 / II+] **lapatinib + chemotherapy** [1, 2 / II+] **margetuximab + chemotherapy** [1 / II+]	71

*** 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.

Disclaimer: The data presented here are from a curated knowledge base of publicly available information, but may not be exhaustive. The data version is 2025.10(006). The content of this report has not been evaluated or approved by the FDA, EMA or other regulatory agencies.

Relevant Biomarkers (continued)

Tier	Genomic Alteration	Relevant Therapies (In this cancer type)	Relevant Therapies (In other cancer type)	Clinical Trials
			neratinib [1, 2 / II+] **neratinib + chemotherapy** [1 / II+] **trastuzumab + tucatinib + chemotherapy** [1, 2 / II+] **trastuzumab†** [1, 2 / II+] **zanidatamab** [1, 2 / II+] **pertuzumab/trastuzumab/ hyaluronidase-zzxf + chemotherapy** [1, 2] **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	
IA	*ERBB2 exon 20 insertion* erb-b2 receptor tyrosine kinase 2 Allele Frequency: 68.51% Locus: chr17:37880981 Transcript: NM_004448.4	**trastuzumab deruxtecan** [1, 2 / II+] **zongertinib** [1 / II+]	None*	32

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

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

ERBB2 exon 20 insertion	**sevabertinib** [1]

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

Prevalent cancer biomarkers without relevant evidence based on included data sources

CDKN2A p.(R58) c.172C>T, Microsatellite stable, TP53 p.(R306*) c.916C>T, UGT1A1 p.(G71R) c.211G>A, ADAMTS12 deletion, RARA amplification, Tumor Mutational Burden*

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Variant Details

DNA Sequence Variants

Gene	Amino Acid Change	Coding	Variant ID	Locus	Allele Frequency	Transcript	Variant Effect
ERBB2	p.(Y772_A775dup)	c.2313_2324dup	COSM20959	chr17:37880981	68.51%	NM_004448.4	nonframeshift Insertion
CDKN2A	p.(R58*)	c.172C>T	COSM12473	chr9:21971186	53.64%	NM_001195132.2	nonsense
TP53	p.(R306*)	c.916C>T	COSM10663	chr17:7577022	45.67%	NM_000546.6	nonsense
UGT1A1	p.(G71R)	c.211G>A	COSM4415616	chr2:234669144	43.04%	NM_000463.3	missense
USP40	p.(R1105I)	c.3314G>T	.	chr2:234394504	57.97%	NM_018218.4	missense
MAML3	p.(Q488_Q494delinsHDS)	c.1455_1506delACAGCAACAGCAACAGCAGCAGCAGCAGCAGCAGCAGCAGCAGCAGCAGCAGinsGCAGCAACACGACAGCCAGCAGCAGCAGCAGCAGCAGCAA	.	chr4:140811084	16.38%	NM_018717.5	nonframeshift Block Substitution
MAML3	p.(Q491Pfs*32)	c.1455_1506delACAGCAACAGCAACAGCAGCAGCAGCAGCAGCAGCAGCAGCAGCAGCAGCAGinsGCAGCAACAGCAACAGCCAGCAGCAGCAGCAGCAGCAGCAA	.	chr4:140811084	83.62%	NM_018717.5	frameshift Block Substitution
HLA-A	p.(C125S)	c.373T>A	.	chr6:29911074	24.15%	NM_001242758.1	missense
CCND1	p.(T12A)	c.34A>G	.	chr11:69456115	14.64%	NM_053056.3	missense

Copy Number Variations

Gene	Locus	Copy Number	CNV Ratio
ERBB2	chr17:37863255	10.4	2.68
ADAMTS12	chr5:33527235	0.48	0.7
RARA	chr17:38487425	11.18	2.83
CDK12	chr17:37618286	14	2.34

Biomarker Descriptions

ERBB2 amplification, ERBB2 exon 20 insertion

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[86]. All ERBB/HER proteins encode transmembrane receptor tyrosine kinases[87]. However, ERBB2/HER2 is an orphan receptor with no known ligand[87]. 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[88]. Recurrent focal amplification of the ERBB2 gene leads to increased expression in several cancer types[88]. ERBB2 overexpression in immortalized cell lines is oncogenic and leads to ERBB2 homo-dimerization and activation without ligand binding[89,90,91].

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[6,7,92,93,94,95,96,97]. ERBB2 gene amplification in

Biomarker Descriptions (continued)

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)[6]. Recurrent somatic activating mutations in ERBB2/HER2 occur at low frequencies (<1%) in diverse cancer types[6,98,99]. 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[100,101]. Trastuzumab[102] 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[103] (2012), a humanized monoclonal antibody that inhibits HER2 dimerization, and ado-trastuzumab emtansine[104] (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[105]. In addition to monoclonal antibodies, the small molecule inhibitor lapatinib[106], 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[107], 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[107] 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[108] 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[40]. In 2024, a bispecific HER2 antibody, zanidatamab[109], 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[110] in patients with ERBB2 positive breast cancer previously treated with an anti-HER2 therapy. Additionally, in 2019, zanidatamab[111], 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[112] (2020) received breakthrough designation for adult patients with HER2-positive urothelial cancer after previous platinum-chemotherapy treatment. In 2021, the antibody-drug conjugate ARX788[113] 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 molecule inhibitor, BAY-2927088[114], 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[115,116,117,118,119]. ERBB2 kinase domain mutations R896G and V659E both showed response to afatinib in two NSCLC case studies[120,121]. Additionally, acquired HER2 mutations in estrogen receptor-positive (ER+) breast cancer have been shown to confer resistance to hormone therapy[122]. However, this was shown to be overcome by neratinib in combination with therapies targeting ER[122]. Additionally, in 2025, FDA approved zongertinib[123], 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)[124], received fast track designation for the prevention of breast cancer recurrence following surgery.

CDKN2A p.(R58*) c.172C>T

cyclin dependent kinase inhibitor 2A

Background: CDKN2A encodes cyclin dependent kinase inhibitor 2A, a cell cycle regulator that controls G1/S progression[1]. CDKN2A, also known as p16/INK4A, belongs to a family of INK4 cyclin-dependent kinase inhibitors, which also includes CDKN2B (p15/INK4B), CDKN2C (p18/INK4C), and CDKN2D (p19/INK4D)[64]. The INK4 family regulates cell cycle progression by inhibiting CDK4 or CDK6, thereby preventing the phosphorylation of Rb[65,66,67]. CDKN2A encodes two alternative transcript variants, namely p16 and p14ARF, both of which exhibit differential tumor suppressor functions[68]. Specifically, the CDKN2A/p16 transcript inhibits cell cycle kinases CDK4 and CDK6, whereas the CDKN2A/p14ARF transcript stabilizes the tumor suppressor protein p53 to prevent its degradation[1,68,69]. CDKN2A aberrations commonly co-occur with CDKN2B[64]. Loss of CDKN2A/p16 results in downstream inactivation of the Rb and p53 pathways, leading to uncontrolled cell proliferation[70]. Germline mutations of CDKN2A are known to confer a predisposition to melanoma and pancreatic cancer[71,72].

Alterations and prevalence: Somatic alterations in CDKN2A often result in loss of function (LOF) which is attributed to copy number loss, truncating, or missense mutations[73]. Somatic mutations in CDKN2A are observed in 20% of head and neck squamous cell carcinoma and pancreatic adenocarcinoma, 15% of lung squamous cell carcinoma, 13% of skin cutaneous melanoma, 8% of esophageal adenocarcinoma, 7% of bladder urothelial carcinoma, 6% of cholangiocarcinoma, 4% of lung adenocarcinoma and stomach adenocarcinoma, and 2% of liver hepatocellular carcinoma, uterine carcinosarcoma, and cervical squamous cell carcinoma[6,7]. Biallelic deletion of CDKN2A is observed in 56% of glioblastoma multiforme, 45% of mesothelioma, 39% of esophageal adenocarcinoma, 32% of bladder urothelial carcinoma, 31% of skin cutaneous melanoma and head and neck squamous cell carcinoma, 28% of pancreatic adenocarcinoma, 27% of diffuse large B-cell lymphoma, 26% of lung squamous cell carcinoma, 17% of lung adenocarcinoma and cholangiocarcinoma, 15% of sarcoma, 11% of stomach adenocarcinoma and of brain lower grade glioma, 7% of adrenocortical

Biomarker Descriptions (continued)

carcinoma, 6% of liver hepatocellular carcinoma, 4% of breast invasive carcinoma, kidney renal papillary cell carcinoma and thymoma, 3% of ovarian serous cystadenocarcinoma and kidney renal clear cell carcinoma, and 2% of uterine carcinosarcoma and kidney chromophobe[6,7]. Alterations in CDKN2A are also observed in pediatric cancers[6]. Biallelic deletion of CDKN2A is observed in 68% of T-lymphoblastic leukemia/lymphoma, 40% of B-lymphoblastic leukemia/lymphoma, 25% of glioma, 19% of bone cancer, and 6% of embryonal tumors[6]. Somatic mutations in CDKN2A are observed in less that 1.5% of bone cancer (5 in 327 cases), B-lymphoblastic leukemia/lymphoma (3 in 252 cases), and leukemia (1 in 354 cases)[6].

Potential relevance: Loss of CDKN2A can be useful in the diagnosis of mesothelioma, and mutations in CDKN2A are ancillary diagnostic markers of malignant peripheral nerve sheath tumors[74,75,76]. Additionally, deletion of CDKN2B is a molecular marker used in staging Grade 4 pediatric IDH-mutant astrocytoma[77]. Currently, no therapies are approved for CDKN2A aberrations. However, CDKN2A LOF leading to CDK4/6 activation may confer sensitivity to CDK inhibitors such as palbociclib and abemaciclib[78,79,80]. Alternatively, CDKN2A expression and Rb inactivation demonstrate resistance to palbociclib in cases of glioblastoma multiforme[81]. CDKN2A (p16) expression is associated with a favorable prognosis for progression-free survival (PFS) and overall survival (OS) in p16/HPV positive head and neck cancer[82,83,84,85].

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[27]. Microsatellite instability (MSI) is defined as a change in the length of a microsatellite in a tumor as compared to normal tissue[28,29]. 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[30]. 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[31]. 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)[31]. Tumors classified as MSI-L are often phenotypically indistinguishable from MSS tumors and tend to be grouped with MSS[32,33,34,35,36]. 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[29]. LS is associated with an increased risk of developing colorectal cancer, as well as other cancers, including endometrial and stomach cancer[28,29,33,37].

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[28,29,38,39]. 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[38,39].

Potential relevance: Anti-PD-1 immune checkpoint inhibitors including pembrolizumab[40] (2014) and nivolumab[41] (2015) are approved for patients with MSI-H or dMMR colorectal cancer who have progressed following chemotherapy. Pembrolizumab[40] 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[40]. Dostarlimab[42] (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[34,43]. The cytotoxic T-lymphocyte antigen 4 (CTLA-4) blocking antibody, ipilimumab[44] (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[34,45,46]. 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[46]. 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[47,48]. However, checkpoint blockade with the addition of chemotherapy or targeted therapies have demonstrated response in MSS or pMMR cancers[47,48].

TP53 p.(R306*) c.916C>T

tumor protein p53

Background: The TP53 gene encodes the tumor suppressor protein p53, which binds to DNA and activates transcription in response to diverse cellular stresses to induce cell cycle arrest, apoptosis, or DNA repair[1]. In unstressed cells, TP53 is kept inactive by targeted degradation via MDM2, a substrate recognition factor for ubiquitin-dependent proteolysis[2]. Alterations in TP53 are required for oncogenesis as they result in loss of protein function and gain of transforming potential[3]. Germline mutations in TP53 are the underlying cause of Li-Fraumeni syndrome, a complex hereditary cancer predisposition disorder associated with early-onset cancers[4,5].

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

Biomarker Descriptions (continued)

rates (60-90%)[6,7,8,9,10,11]. 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[6,7]. Invariably, recurrent missense mutations in TP53 inactivate its ability to bind DNA and activate transcription of target genes[12,13,14,15]. Alterations in TP53 are also observed in pediatric cancers[6,7]. 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)[6,7]. 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)[6,7].

Potential relevance: The small molecule p53 reactivator, PC14586[16] (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[17,18]. TP53 mutation are a diagnostic marker of SHH-activated, TP53-mutant medulloblastoma[19]. 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)[20,21,22,23,24]. In mantle cell lymphoma, TP53 mutations are associated with poor prognosis when treated with conventional therapy including hematopoietic cell transplant[25]. 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[26].

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[1,125]. UGTs are microsomal membrane-bound enzymes that catalyze the glucuronidation of endogenous and xenobiotic compounds and transform the lipophilic molecules into excretable, hydrophilic metabolites[125,126]. 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[127]. Specifically, elevated expression of UGT1As are associated with resistance to many anti-cancer drugs due to drug inactivation and lower active drug concentrations. However, reduced expression and downregulation of UGT1As are implicated in bladder and hepatocellular tumorigenesis and progression due to toxin accumulation[127,128,129,130]. 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[131].

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[6,7].

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

RARA amplification

retinoic acid receptor alpha

Background: The RARA gene encodes the retinoic acid receptor alpha, a transcription factor and a member of the retinoic acid (RA) nuclear receptor family[49]. RARA binds DNA as a heterodimer with its cofactor, the retinoid X receptor alpha (RXRA), and the binding of the RARA/RXRA complex to specific RA response elements (RAREs) activates transcription[49]. RARA is also involved in lymphoid and myeloid lineage specification and differentiation[50,51]. RARA translocations are the genetic driver of acute promyelocytic leukemia (APL), where the 3' region of the RARA gene is translocated to the 5' region of partner genes such as the promyelocytic leukemia (PML) gene[52]. The PML::RARA fusion protein contributes to the pathogenesis of APL by blocking differentiation and promoting aberrant self-renewal of APL cells, leading to an accumulation of immature white blood cells in the blood and bone marrow[53].

Alterations and prevalence: More than 95% of APL patients harbor the t(15;17)(q22;q21) translocation that results in PML::RARA fusion[49,54]. Other RARA fusion partners, including PLZF, NPM, NUMA, STAT5b, PRKAR1A, FIP1L1, TBLXR1, FNDC3B, GTF2I, IRF2BP2, account for the remainder[54,55,56,57,58,59]. Overall, RARA fusions are found in 10-15% of APL and 2% of breast invasive carcinoma and uterine carcinosarcoma[6,7]. RARA amplification is observed in 9% of esophageal adenocarcinoma, 8% of stomach adenocarcinoma, 6% of breast invasive carcinoma, 4% of uterine carcinosarcoma, and 2% of colorectal adenocarcinoma, bladder urothelial carcinoma, pancreatic adenocarcinoma, uterine corpus endometrial carcinoma, lung squamous cell carcinoma, and head and neck squamous cell carcinoma[6,7]. RARA mutations occur in 3% of uterine corpus endometrial carcinoma, cholangiocarcinoma, and skin cutaneous melanoma, and 2% of colorectal adenocarcinoma[6,7]. RARA alterations are rare in pediatric cancers[6,7]. Somatic mutations are observed in less than 1% of glioma (1 in 297 cases) and leukemia (1 in 311 cases)[6,7]. RARA amplification is observed in 2% of peripheral nervous system cancers and less than 1% of leukemia (1 in 250 cases)[6,7].

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Biomarker Descriptions (continued)

Potential relevance: The presence of PML::RARA fusion, characterized by the t(15;17)(q24;q21) translocation, is a diagnostic marker of APL, a subtype of AML[21,60,61]. Arsenic trioxide[62] (2000) is approved as a monotherapy for children and adults with APL with PML::RARA fusions, and or in combination with tretinoin (ATRA) for the treatment of adults with APL harboring PML::RARA fusions[60]. Somatic missense mutations in PML::RARA fusion, including A216V, S214L, A216T, L217F, and S220G, are associated with acquired resistance to treatment with arsenic trioxide[63].

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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

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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

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zanidatamab + chemotherapy

Cancer type: Gastroesophageal Junction Adenocarcinoma

Variant class: ERBB2 overexpression

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

Reference:

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

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anvatabart opadotin

Cancer type: Breast Cancer

Variant class: ERBB2 positive

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

Reference:

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

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ERBB2 amplification (continued)

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/

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

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 exon 20 insertion

sevabertinib

Cancer type: Non-Small Cell Lung Cancer

Variant class: ERBB2 activating mutation

Supporting Statement:
The FDA has granted Breakthrough Therapy designation to an oral, reversible tyrosine kinase inhibitor and EGFR antagonist, sevabertinib (BAY 2927088), for the treatment of adult patients with unresectable or metastatic non-small cell lung cancer (NSCLC) whose tumors have activating HER2 (ERBB2) mutations, and who have received a prior systemic therapy.

Reference:

https://www.bayer.com/en/us/news-stories/sevabertinib

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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

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.]

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]

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,

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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	◑	◑	○	◑	● (II)
zanidatamab	○	○	○	○	● (II)

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

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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*
ado-trastuzumab emtansine	○	○	○	○	✖
lapatinib + capecitabine	○	○	○	○	✖
neratinib	○	○	○	○	✖
pertuzumab + trastuzumab + chemotherapy	○	○	○	○	✖
pertuzumab + trastuzumab + docetaxel	○	○	○	○	✖
trastuzumab + docetaxel	○	○	○	○	✖
trastuzumab + paclitaxel	○	○	○	○	✖
trastuzumab + tucatinib + capecitabine	○	○	○	○	✖
trastuzumab	○	○	○	✖	● (II)
trastuzumab + capecitabine + cisplatin	○	○	○	✖	✖
trastuzumab + carboplatin + docetaxel	○	○	○	✖	✖
trastuzumab + cisplatin + fluorouracil	○	○	○	✖	✖
neratinib + capecitabine	○	○	✖	✖	✖
trastuzumab + tucatinib	○	○	✖	✖	✖
lapatinib + letrozole	○	✖	○	✖	✖
pembrolizumab + trastuzumab + chemotherapy + fluoropyrimidine	○	✖	○	✖	✖
pertuzumab/trastuzumab/hyaluronidase-zzxf + cyclophosphamide + doxorubicin	○	✖	○	✖	✖
pertuzumab/trastuzumab/hyaluronidase-zzxf + docetaxel	○	✖	○	✖	✖
trastuzumab (Biocon)	○	✖	○	✖	✖
trastuzumab (Biocon) + capecitabine + cisplatin	○	✖	○	✖	✖
trastuzumab (Biocon) + carboplatin + docetaxel	○	✖	○	✖	✖
trastuzumab (Biocon) + cisplatin + fluorouracil	○	✖	○	✖	✖
trastuzumab (Biocon) + docetaxel	○	✖	○	✖	✖
trastuzumab (Biocon) + paclitaxel	○	✖	○	✖	✖
trastuzumab (Celltrion)	○	✖	○	✖	✖
trastuzumab (Celltrion) + capecitabine + cisplatin	○	✖	○	✖	✖
trastuzumab (Celltrion) + carboplatin + docetaxel	○	✖	○	✖	✖
trastuzumab (Celltrion) + cisplatin + fluorouracil	○	✖	○	✖	✖

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Relevant Therapy Summary (continued)

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

ERBB2 amplification (continued)

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
trastuzumab (Celltrion) + docetaxel	○	✖	○	✖	✖
trastuzumab (Celltrion) + paclitaxel	○	✖	○	✖	✖
trastuzumab (Henlius)	○	✖	○	✖	✖
trastuzumab (Pfizer)	○	✖	○	✖	✖
trastuzumab (Pfizer) + capecitabine + cisplatin	○	✖	○	✖	✖
trastuzumab (Pfizer) + carboplatin + docetaxel	○	✖	○	✖	✖
trastuzumab (Pfizer) + cisplatin + fluorouracil	○	✖	○	✖	✖
trastuzumab (Pfizer) + docetaxel	○	✖	○	✖	✖
trastuzumab (Pfizer) + paclitaxel	○	✖	○	✖	✖
trastuzumab (Samsung Bioepis)	○	✖	○	✖	✖
trastuzumab (Samsung Bioepis) + capecitabine + cisplatin	○	✖	○	✖	✖
trastuzumab (Samsung Bioepis) + carboplatin + docetaxel	○	✖	○	✖	✖
trastuzumab (Samsung Bioepis) + cisplatin + fluorouracil	○	✖	○	✖	✖
trastuzumab (Samsung Bioepis) + docetaxel	○	✖	○	✖	✖
trastuzumab (Samsung Bioepis) + paclitaxel	○	✖	○	✖	✖
trastuzumab (Synthon)	○	✖	○	✖	✖
trastuzumab (Synthon) + capecitabine + cisplatin	○	✖	○	✖	✖
trastuzumab (Synthon) + carboplatin + docetaxel	○	✖	○	✖	✖
trastuzumab (Synthon) + cisplatin + fluorouracil	○	✖	○	✖	✖
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	○	✖	✖	✖	✖
lapatinib + trastuzumab	✖	○	○	○	✖

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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*
pertuzumab + trastuzumab	✖	○	✖	○	● (II/III)
pertuzumab + trastuzumab + hormone therapy	✖	○	✖	○	✖
pertuzumab + trastuzumab + paclitaxel	✖	○	✖	○	✖
trastuzumab + chemotherapy	✖	○	✖	○	✖
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	✖	○	✖	✖	✖
pembrolizumab + trastuzumab + capecitabine + cisplatin	✖	○	✖	✖	✖
pembrolizumab + trastuzumab + capecitabine + oxaliplatin	✖	○	✖	✖	✖
pembrolizumab + trastuzumab + cisplatin + fluorouracil	✖	○	✖	✖	✖
pembrolizumab + trastuzumab + fluorouracil + oxaliplatin	✖	○	✖	✖	✖
pertuzumab + trastuzumab + carboplatin + docetaxel	✖	○	✖	✖	✖
pertuzumab + trastuzumab + carboplatin + paclitaxel	✖	○	✖	✖	✖
pertuzumab + trastuzumab + hormone therapy + chemotherapy	✖	○	✖	✖	✖
tamoxifen	✖	○	✖	✖	✖
trastuzumab + aromatase inhibitor	✖	○	✖	✖	✖

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Relevant Therapy Summary (continued)

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

ERBB2 amplification (continued)

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
trastuzumab + capecitabine	✖	○	✖	✖	✖
trastuzumab + capecitabine + oxaliplatin	✖	○	✖	✖	✖
trastuzumab + carboplatin + paclitaxel	✖	○	✖	✖	✖
trastuzumab + chemotherapy (non-anthracycline)	✖	○	✖	✖	✖
trastuzumab + cisplatin + docetaxel	✖	○	✖	✖	✖
trastuzumab + cisplatin + docetaxel + fluorouracil	✖	○	✖	✖	✖
trastuzumab + cisplatin + paclitaxel	✖	○	✖	✖	✖
trastuzumab + cyclophosphamide + docetaxel	✖	○	✖	✖	✖
trastuzumab + docetaxel + fluorouracil + oxaliplatin	✖	○	✖	✖	✖
trastuzumab + fluorouracil	✖	○	✖	✖	✖
trastuzumab + fluorouracil + irinotecan	✖	○	✖	✖	✖
trastuzumab + fluorouracil + oxaliplatin	✖	○	✖	✖	✖
trastuzumab + fulvestrant	✖	○	✖	✖	✖
trastuzumab + hormone therapy + chemotherapy	✖	○	✖	✖	✖
trastuzumab + tamoxifen	✖	○	✖	✖	✖
trastuzumab + vinorelbine	✖	○	✖	✖	✖
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) + capecitabine + cisplatin	✖	✖	○	✖	✖
trastuzumab (CuraTeQ Biologics) + carboplatin + docetaxel	✖	✖	○	✖	✖

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Relevant Therapy Summary (continued)

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

ERBB2 amplification (continued)

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
trastuzumab (CuraTeQ Biologics) + cisplatin + fluorouracil	✖	✖	○	✖	✖
trastuzumab (CuraTeQ Biologics) + docetaxel	✖	✖	○	✖	✖
trastuzumab (CuraTeQ Biologics) + paclitaxel	✖	✖	○	✖	✖
trastuzumab (EirGenix)	✖	✖	○	✖	✖
trastuzumab (EirGenix) + anastrozole	✖	✖	○	✖	✖
trastuzumab (EirGenix) + capecitabine + cisplatin	✖	✖	○	✖	✖
trastuzumab (EirGenix) + carboplatin + docetaxel	✖	✖	○	✖	✖
trastuzumab (EirGenix) + cisplatin + fluorouracil	✖	✖	○	✖	✖
trastuzumab (EirGenix) + docetaxel	✖	✖	○	✖	✖
trastuzumab (EirGenix) + paclitaxel	✖	✖	○	✖	✖
trastuzumab (Henlius) + anastrozole	✖	✖	○	✖	✖
trastuzumab (Henlius) + capecitabine + cisplatin	✖	✖	○	✖	✖
trastuzumab (Henlius) + carboplatin + docetaxel	✖	✖	○	✖	✖
trastuzumab (Henlius) + cisplatin + fluorouracil	✖	✖	○	✖	✖
trastuzumab (Henlius) + docetaxel	✖	✖	○	✖	✖
trastuzumab (Henlius) + paclitaxel	✖	✖	○	✖	✖
trastuzumab (Pfizer) + anastrozole	✖	✖	○	✖	✖
trastuzumab (Prestige BioPharma)	✖	✖	○	✖	✖
trastuzumab (Prestige BioPharma) + anastrozole	✖	✖	○	✖	✖
trastuzumab (Prestige BioPharma) + capecitabine + cisplatin	✖	✖	○	✖	✖
trastuzumab (Prestige BioPharma) + carboplatin + docetaxel	✖	✖	○	✖	✖
trastuzumab (Prestige BioPharma) + cisplatin + fluorouracil	✖	✖	○	✖	✖
trastuzumab (Prestige BioPharma) + docetaxel	✖	✖	○	✖	✖
trastuzumab (Prestige BioPharma) + paclitaxel	✖	✖	○	✖	✖
trastuzumab (Samsung Bioepis) + anastrozole	✖	✖	○	✖	✖
trastuzumab (Synthon) + anastrozole	✖	✖	○	✖	✖
trastuzumab + anastrozole	✖	✖	○	✖	✖

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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*
ado-trastuzumab emtansine + hormone therapy	✖	✖	✖	○	✖
lapatinib + hormone therapy	✖	✖	✖	○	✖
lapatinib + trastuzumab + hormone therapy	✖	✖	✖	○	✖
margetuximab	✖	✖	✖	○	✖
neratinib + chemotherapy	✖	✖	✖	○	✖
pertuzumab + trastuzumab + nab-paclitaxel	✖	✖	✖	○	✖
pyrotinib	✖	✖	✖	✖	● (IV)
IAH-0968, chemotherapy	✖	✖	✖	✖	● (III)
allitinib	✖	✖	✖	✖	● (II)
CART-HER2, chemotherapy	✖	✖	✖	✖	● (II)
disitamab vedotinaide, tislelizumab, bevacizumab	✖	✖	✖	✖	● (II)
FDA022-BB05	✖	✖	✖	✖	● (II)
neratinib, neratinib + palbociclib	✖	✖	✖	✖	● (II)
pertuzumab + trastuzumab, atezolizumab + pertuzumab/trastuzumab/hyaluronidase-zzxf, trastuzumab + tucatinib	✖	✖	✖	✖	● (II)
pyrotinib, chemotherapy	✖	✖	✖	✖	● (II)
trastuzumab (Samsung Bioepis), chemotherapy	✖	✖	✖	✖	● (II)
tucatinib, ado-trastuzumab emtansine	✖	✖	✖	✖	● (II)
tucatinib, trastuzumab	✖	✖	✖	✖	● (II)
zongertinib	✖	✖	✖	✖	● (II)
AP-402	✖	✖	✖	✖	● (I/II)
AZD-9574, trastuzumab deruxtecan	✖	✖	✖	✖	● (I/II)
BAT-8010, BAT-1006	✖	✖	✖	✖	● (I/II)
BL-M07D1	✖	✖	✖	✖	● (I/II)
DF-1001, nivolumab	✖	✖	✖	✖	● (I/II)
disitamab vedotinaide, catequentinib	✖	✖	✖	✖	● (I/II)
E01001	✖	✖	✖	✖	● (I/II)
HypoSti.CART-HER2, chemotherapy	✖	✖	✖	✖	● (I/II)
IAH-0968	✖	✖	✖	✖	● (I/II)

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Relevant Therapy Summary (continued)

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

ERBB2 amplification (continued)

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
IBI-354	✖	✖	✖	✖	● (I/II)
JIN-A-04	✖	✖	✖	✖	● (I/II)
ST-1703	✖	✖	✖	✖	● (I/II)
trastuzumab deruxtecan, neratinib	✖	✖	✖	✖	● (I/II)
trastuzumab pamirtecan, pertuzumab	✖	✖	✖	✖	● (I/II)
YH32367	✖	✖	✖	✖	● (I/II)
ZV-0203	✖	✖	✖	✖	● (I/II)
177Lu-RAD202	✖	✖	✖	✖	● (I)
ado-trastuzumab emtansine (Shanghai Fosun Pharma)	✖	✖	✖	✖	● (I)
anti-HER-2 MAb (Anke Biotechnology)	✖	✖	✖	✖	● (I)
BC004	✖	✖	✖	✖	● (I)
BL-M17D1	✖	✖	✖	✖	● (I)
BM-230	✖	✖	✖	✖	● (I)
CART-HER2	✖	✖	✖	✖	● (I)
CART-HER2/PD-L1	✖	✖	✖	✖	● (I)
ceralasertib, trastuzumab deruxtecan	✖	✖	✖	✖	● (I)
D3L-001	✖	✖	✖	✖	● (I)
doxorubicin (Hangzhou HighField Biopharma)	✖	✖	✖	✖	● (I)
DP-303c	✖	✖	✖	✖	● (I)
DX126-262	✖	✖	✖	✖	● (I)
ENT-H-1, trastuzumab	✖	✖	✖	✖	● (I)
GQ-1005	✖	✖	✖	✖	● (I)
GQ1001	✖	✖	✖	✖	● (I)
HF-50	✖	✖	✖	✖	● (I)
MBS301	✖	✖	✖	✖	● (I)
NC-18	✖	✖	✖	✖	● (I)
NVL-330	✖	✖	✖	✖	● (I)
SPH5030	✖	✖	✖	✖	● (I)
TAS0728	✖	✖	✖	✖	● (I)

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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*
TL-938	✖	✖	✖	✖	● (I)
trastuzumab deruxtecan, azenosertib	✖	✖	✖	✖	● (I)
VVD-159642	✖	✖	✖	✖	● (I)
XMT-2056	✖	✖	✖	✖	● (I)

ERBB2 exon 20 insertion

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
trastuzumab deruxtecan	●	●	●	●	● (II)
zongertinib	●	●	✖	✖	● (II)
sevabertinib, pembrolizumab, chemotherapy	✖	✖	✖	✖	● (III)
trastuzumab deruxtecan, pembrolizumab, chemotherapy	✖	✖	✖	✖	● (III)
zongertinib, pembrolizumab, chemotherapy	✖	✖	✖	✖	● (III)
pertuzumab + trastuzumab	✖	✖	✖	✖	● (II/III)
anti-PD-L1 antibody, pyrotinib	✖	✖	✖	✖	● (II)
pyrotinib	✖	✖	✖	✖	● (II)
pyrotinib, chemotherapy	✖	✖	✖	✖	● (II)
pyrotinib, thalidomide	✖	✖	✖	✖	● (II)
sevabertinib	✖	✖	✖	✖	● (II)
sintilimab	✖	✖	✖	✖	● (II)
toripalimab, chemotherapy	✖	✖	✖	✖	● (II)
tucatinib, ado-trastuzumab emtansine	✖	✖	✖	✖	● (II)
tucatinib, trastuzumab	✖	✖	✖	✖	● (II)
ABT-101	✖	✖	✖	✖	● (I/II)
AZD-9574, trastuzumab deruxtecan	✖	✖	✖	✖	● (I/II)
BH-30643	✖	✖	✖	✖	● (I/II)
DF-1001, sacituzumab govitecan	✖	✖	✖	✖	● (I/II)
HS-10376	✖	✖	✖	✖	● (I/II)
JIN-A-04	✖	✖	✖	✖	● (I/II)
ORIC-114	✖	✖	✖	✖	● (I/II)

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Relevant Therapy Summary (continued)

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

ERBB2 exon 20 insertion (continued)

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
STX-721	✖	✖	✖	✖	● (I/II)
trastuzumab deruxtecan, neratinib	✖	✖	✖	✖	● (I/II)
ado-trastuzumab emtansine (Shanghai Fosun Pharma)	✖	✖	✖	✖	● (I)
BL-M07D1	✖	✖	✖	✖	● (I)
BM-230	✖	✖	✖	✖	● (I)
ENT-H-1, trastuzumab	✖	✖	✖	✖	● (I)
GQ-1005	✖	✖	✖	✖	● (I)
NVL-330	✖	✖	✖	✖	● (I)

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

HRR Details

Gene/Genomic Alteration	Finding
LOH percentage	***14.88%***
BRCA2	***LOH, 13q13.1(32890491-32972932)x4***
BRIP1	***LOH, 17q23.2(59760627-59938976)x4***
RAD51C	***LOH, 17q22(56769933-56811619)x4***

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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