Taipei Veterans General Hospital

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## Sample Information

**Patient Name:** 陳鳳蘭
**Gender:** Female
**ID No.:** R200015893
**History No.:** 30466183
**Age:** 76

**Ordering Doctor:** DOC2716L 許瀚水
**Ordering REQ.:** C2GG38P
**Signing in Date:** 2022/11/16

**Path No.:** M111-00010
**MP No.:** F22126
**Assay:** Oncomine Focus Assay
**Sample Type:** FFPE
**Block No.:** S111-71479A
**Percentage of tumor cells:** 60%

**Reporting Doctor:** DOC5466K 葉奕成 (Phone: 8#5466)

**Note:**

## Sample Cancer Type: Non-Small Cell Lung Cancer

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### Report Highlights

4 Relevant Biomarkers
54 Therapies Available
12 Clinical Trials

## Relevant Non-Small Cell Lung Cancer Variants

| Gene | Finding | Gene | Finding |
|---|---|---|---|
| ALK | None detected | NTRK1 | None detected |
| BRAF | None detected | NTRK2 | None detected |
| EGFR | ***EGFR exon 19 deletion, EGFR p.(T790M) c.2369C>T*** | NTRK3 | None detected |
| ERBB2 | ***ERBB2 amplification*** | RET | None detected |
| KRAS | None detected | ROS1 | None detected |
| MET | None detected | | |

## Relevant Biomarkers

| Tier | Genomic Alteration | Relevant Therapies (In this cancer type) | Relevant Therapies (In other cancer type) | Clinical Trials |
|---|---|---|---|---|
| IA | *EGFR exon 19 deletion*<br>epidermal growth factor receptor<br>Allele Frequency: 47.01% | **bevacizumab* + erlotinib** [2]<br>**erlotinib + ramucirumab** [1]<br>**gefitinib*** [2]<br>**osimertinib** [1, 2]<br>atezolizumab + bevacizumab + chemotherapy<br>bevacizumab + gefitinib<br>gefitinib + chemotherapy<br>osimertinib + chemotherapy | None | 9 |
| IA | *EGFR p.(T790M) c.2369C>T*<br>epidermal growth factor receptor<br>Allele Frequency: 7.10% | **osimertinib** [1, 2] | None | 6 |
| IIC | *ERBB2 amplification*<br>erb-b2 receptor tyrosine kinase 2 | None | **ado-trastuzumab emtansine** [1, 2]<br>**irbinitinib + trastuzumab + chemotherapy** [1, 2]<br>**lapatinib + chemotherapy** [1, 2]<br>**lapatinib + hormone therapy** [1, 2]<br>**lapatinib + trastuzumab** [2]<br>**margetuximab + chemotherapy** [1]<br>**neratinib** [1, 2]<br>**neratinib + chemotherapy** [1]<br>**pembrolizumab + trastuzumab + chemotherapy** [1]<br>**pertuzumab + trastuzumab + chemotherapy** [1, 2]<br>**pertuzumab/trastuzumab/ hyaluronidase-zzxf + chemotherapy** [1, 2]<br>**trastuzumab and hyaluronidase-oysk** [1]<br>**trastuzumab and hyaluronidase-oysk + chemotherapy** [1]<br>**trastuzumab deruxtecan** [1, 2]<br>**trastuzumab*** [1, 2]<br>**trastuzumab* + chemotherapy** [1, 2]<br>**trastuzumab* + hormone therapy** [2]<br>hormone therapy<br>lapatinib + trastuzumab + hormone therapy<br>margetuximab<br>pertuzumab + trastuzumab<br>pertuzumab + trastuzumab + hormone therapy<br>pertuzumab + trastuzumab + hormone therapy + chemotherapy<br>trastuzumab + hormone therapy + chemotherapy | 2 |
| IIC | *PIK3CA p.(E545K) c.1633G>A*<br>phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha<br>Allele Frequency: 11.31% | None | None | 1 |

**Public data sources included in relevant therapies: FDA**1, NCCN, **EMA**2, ESMO
**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.
*** Includes biosimilars**

## Relevant Biomarkers (continued)

**Alerts informed by public data sources:** ⊘ Contraindicated, Resistance

*EGFR p.(T790M) c.2369C>T*
⊘ **gefitinib*** [2]
afatinib, dacomitinib, erlotinib, gefitinib

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

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

## Variants (Exclude variant in Taiwan BioBank with >1% allele frequency)

### DNA Sequence Variants

| Gene | Amino Acid Change | Coding | Variant ID | Locus | Allele Frequency | Transcript | Variant Effect | Coverage |
|---|---|---|---|---|---|---|---|---|
| PIK3CA | p.(E545K) | c.1633G>A | COSM763 | chr3:178936091 | 11.31% | NM_006218.4 | missense | 1998 |
| EGFR | p.(E746_A750del) | c.2235_2249delGGAATTAAGAGAAGC | COSM6223 | chr7:55242464 | 47.01% | NM_005228.5 | nonframeshift Deletion | 1972 |
| EGFR | p.(T790M) | c.2369C>T | COSM6240 | chr7:55249071 | 7.10% | NM_005228.5 | missense | 2000 |

### Copy Number Variations

| Gene | Locus | Copy Number |
|---|---|---|
| MYC | chr8:128748885 | 8.98 |
| ERBB2 | chr17:37868126 | 33.57 |

## Biomarker Descriptions

**EGFR (epidermal growth factor receptor)**

Background: The EGFR gene encodes the epidermal growth factor receptor (EGFR) tyrosine kinase, a member of the ERBB/human epidermal growth factor receptor (HER) family. In addition to EGFR/ERBB1/HER1, other members of the ERBB/HER family include ERBB2/HER2, ERBB3/HER3, and ERBB4/HER4[1]. EGFR ligand induced dimerization results in kinase activation and leads to stimulation of oncogenic signaling pathways including the PI3K/AKT/MTOR and RAS/RAF/MEK/ERK pathways. Activation of these pathways promote cell proliferation, differentiation, and survival[2,3].

Alterations and prevalence: Recurrent somatic mutations in the tyrosine kinase domain (TKD) of EGFR are observed in approximately 10-20% of lung adenocarcinoma, and at higher frequencies in never-smoker, female, and Asian populations[4,5,6,7]. The most common mutations occur near the ATP-binding pocket of the TKD and include short in-frame deletions in exon 19 (EGFR exon 19 deletion) and the L858R amino acid substitution in exon 21[8]. These mutations constitutively activate EGFR resulting in downstream signaling, and represent 80% of the EGFR mutations observed in lung cancer. A second group of less prevalent activating mutations include E709K, G719X, S768I, L861Q, and short in-frame insertion mutations in exon 20[9,10,11,12]. EGFR activating mutations in lung cancer tend to be mutually exclusive to KRAS activating mutations[13]. In contrast, a different set of recurrent activating EGFR mutations in the extracellular domain include R108K, A289V and G598V and are primarily observed in glioblastoma[8,14]. Amplification of EGFR is observed in several cancer types including 30% of glioblastoma, 12% of esophageal cancer, 10% of head and neck cancer, 5% of bladder cancer, and 5% of lung squamous cell carcinoma[5,6,7,14,15]. Deletion of exons 2-7, encoding the extracellular domain of EGFR (EGFRvIII), results in overexpression of a ligand-independent constitutively active protein and is observed in approximately 30% of glioblastoma[16,17,18].

Potential relevance: Approved first-generation EGFR tyrosine kinase inhibitors (TKIs) include erlotinib[19] (2004) and gefitinib[20] (2015), which block the activation of downstream signaling by reversible interaction with the ATP-binding site. Although initially approved for advanced lung cancer, the discovery that drug sensitivity was associated with exon 19 and exon 21 activating mutations allowed first-generation TKIs to become subsequently approved for front-line therapy in lung cancer tumors containing exon 19 or exon

## Biomarker Descriptions (continued)

21 activating mutations. Second-generation TKIs afatinib[21] (2013) and dacomitinib[22] (2018) bind EGFR and other ERBB/HER gene family members irreversibly and were subsequently approved. First- and second-generation TKIs afatinib, dacomitinib, erlotinib, and gefitinib are recommended for the treatment NSCLC harboring EGFR exon 19 insertions, exon 19 deletions, point mutations L861Q, L858R, S768I, and codon 719 mutations, whereas most EGFR exon 20 insertions, except p.A763_Y764insFQEA, confer resistance to the same therapies[23,24,25,26]. However, in 2021, the irreversible tyrosine kinase inhibitor, mobocertinib[27]was FDA approved for the treatment of NSCLC with EGFR exon 20 insertion mutations. Additionally, in 2022, the FDA granted breakthrough therapy designation to the irreversible EGFR inhibitors, CLN-081 (TPC-064)[28] and sunvozertinib[29], for locally advanced or metastatic non-small cell lung cancer harboring EGFR exon 20 insertion mutations. In lung cancer containing EGFR exon 19 or 21 activating mutations, treatment with TKIs is eventually associated with the emergence of drug resistance[30]. The primary resistance mutation that emerges following treatment with first-generation TKI is T790M, accounting for 50-60% of resistant cases[8]. Third generation TKIs were developed to maintain sensitivity in the presence of T790M. Osimertinib[31] (2015) is an irreversible inhibitor indicated for metastatic EGFR T790M positive lung cancer and for the first-line treatment of metastatic NSCLC containing EGFR exon 19 deletions or exon 21 L858R mutations. Like first-generation TKIs, treatment with osimertinib is associated with acquired resistance. In this case, resistance is associated with the C797S mutation and occurs in 22-44% of cases[30]. The T790M and C797S mutations may be each selected following sequential treatment with a first-generation TKI followed by a third-generation TKI or vice versa[32]. T790M and C797S can occur in either cis or trans allelic orientation[32]. If C797S is observed following progression after treatment with a third-generation TKI in the first-line setting, sensitivity may be retained to first-generation TKIs[32]. If C797S co-occurs in trans with T790M following sequential treatment with first- and third-generation TKIs, patients may exhibit sensitivity to combination first- and third-generation TKIs, but resistance to third-generation TKIs alone[32,33]. However, C797S occurring in cis conformation with T790M, confers resistance to first- and third-generation TKIs[32]. Fourth-generation TKIs are in development to overcome acquired C797S and T790M resistance mutations after osimertinib treatment. EGFR targeting antibodies including cetuximab (2004), panitumumab (2006), and necitumumab (2016) are under investigation in combination with EGFR-targeting TKIs for efficacy against EGFR mutations. The bispecific antibody, amivantamab[34], targeting EGFR and MET was approved (2021) NSCLC tumors harboring EGFR exon 20 insertion mutations. The Oncoprex immunogene therapy quaratusugene ozeplasmid[35] in combination with osimertinib received a fast track designation from the FDA (2020) for NSCLC tumors harboring EGFR mutations that progressed on osimertinib alone. BDTX-189[36] was granted a fast track designation (2020) for the treatment of solid tumors harboring an EGFR exon 20 insertion mutation.

**ERBB2 (erb-b2 receptor tyrosine kinase 2)**

Background: The ERBB2 gene encodes the erb-b2 receptor tyrosine kinase 2, a member of the human epidermal growth factor receptor (HER) family. Along with ERBB2/HER2, EGFR/ERBB1/HER1, ERBB3/HER3, and ERBB4/HER4 make up the HER protein family[1]. All ERBB/HER proteins encode transmembrane receptor tyrosine kinases. However, ERBB2/HER2 is an orphan receptor with no known ligand. ERBB2 preferentially binds other ligand bound ERBB/HER family members to form hetero-dimers resulting in the activation of ERBB2 tyrosine kinase activity and subsequent activation of the PI3K/AKT/MTOR and RAS/RAF/MAPK/ERK signaling pathways which promote cell proliferation, differentiation, and survival[3]. Recurrent focal amplification of the ERBB2 gene leads to increased expression in several cancer types. ERBB2 overexpression in immortalized cell lines is oncogenic and leads to ERBB2 homo-dimerization and activation without ligand binding[37,38,39].

Alterations and prevalence: ERBB2 gene amplification occurs in 10-20% of breast, esophageal, and gastric cancers, 5-10% of bladder, cervical, pancreas, and uterine cancers, and 1-5% of colorectal, lung, and ovarian cancers[5,6,7,40,41,42,43,44]. Recurrent somatic activating mutations in ERBB2/HER2 occur at low frequencies (<1%) in diverse cancer types[7,45,46]. 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[47,48]. Trastuzumab[49] 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[50] (2012), a humanized monoclonal antibody that inhibits HER2 dimerization, and ado-trastuzumab emtansine[51] (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[52]. In addition to monoclonal antibodies, the small molecule inhibitor lapatinib[53], 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[54], 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[54] 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[55] 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[56]. The vaccine, nelipepimut-S[57], was granted fast-track designation by the FDA (2016) in patients with low to intermediate HER2 expressing

## Biomarker Descriptions (continued)

(IHC score 1+ or 2+) breast cancer. In 2018 fast-track designation was granted to the monoclonal antibody margetuximab[58] in patients with ERBB2 positive breast cancer previously treated with an anti-HER2 therapy. In 2019, fast track designation was granted to the HER2-targeting antibody drug conjugate, amcenestrant[59], for HER2-positive advanced or metastatic breast cancer after one or more prior anti-HER2 based regimens. Additionally, in 2019, the novel bispecific antibody, zanidatamab[60], received fast-track designation in combination with standard chemotherapy for patients with HER2-overexpressing gastroesophageal adenocarcinoma (GEA) and breakthrough therapy designation (2020) as a monotherapy for patients with HER2-amplified biliary tract cancer[61]. In 2020, BDTX-189[36] received fast-track designation for adult patients with solid tumors harboring an allosteric human ERBB2 mutation or exon 20 insertion, and the humanized anti-HER2 antibody drug conjugate disitamab vedotin received breakthrough designation for adult patients with HER2-positive urothelial cancer after previous platinum-chemotherapy treatment[62]. In 2021, the antibody-drug conjugate ARX788[63] received fast-track designation as a monotherapy for advanced or metastatic HER2-positive breast cancer that have progressed on one or more anti-HER2 regimens. Additionally, in 2021, fast track designation was granted to HER2 targeted chimeric antigen receptor macrophage (CAR-M), CT-0508[64], for HER2-overexpressing solid tumors. Certain activating mutations have been observed to impart sensitivity to neratinib, afatinib, lapatinib, and trastuzumab, or dacomitinib in early and ongoing clinical studies[65,66,67,68,69]. ERBB2 kinase domain mutations R896G and V659E both showed response to afatinib in two NSCLC case studies[70,71]. Additionally, acquired HER2 mutations in estrogen receptor-positive (ER+) breast cancer have been shown to confer resistance to hormone therapy[72]. However, this was shown to be overcome by neratinib in combination with therapies targeting ER[72].

**MYC (MYC proto-oncogene, bHLH transcription factor)**

Background: The MYC gene encodes the MYC proto-oncogene (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[73,74,75,76]. MYC is part of the MYC oncogene family that includes related transcription factors MYCN and MYCL that regulate transcription in 10-15% of promoter regions[77]. MYC functions as a heterodimer in complex with the transcription factor MAX[74,78].

Alterations and prevalence: Recurrent somatic alterations are observed in both solid and hematological cancers. Recurrent somatic mutations in MYC, including codon T58, are infrequent and hypothesized to increase the stability of the MYC protein[79,80]. MYC gene amplification is particularly common in diverse solid tumors. MYC amplification is observed in 30% of serous ovarian cancer, 20% of uterine serous carcinoma, 15% of esophageal and breast cancers, and is common (1-10%) in numerous other cancer types[7,81,82]. MYC is the target of the t(8;14)(q24;32) chromosomal translocation in Burkitt's lymphoma that places MYC coding sequences adjacent to immunoglobulin region regulatory sequences, which results in increased MYC expression[83,84].

Potential relevance: 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[73,85,86,87].

**PIK3CA (phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha)**

Background: The PIK3CA gene encodes the phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha of the class I phosphatidylinositol 3-kinase (PI3K) enzyme[88]. PI3K is a heterodimer that contains a p85 regulatory subunit, which couples one of four p110 catalytic subunits to activated tyrosine protein kinases[89,90]. The p110 catalytic subunits include p110α, β, δ, γ and are encoded by genes PIK3CA, PIK3CB, PIK3CD, and PIK3CG, respectively[89]. PI3K catalyzes the conversion of phosphatidylinositol (4,5)-bisphosphate (PI(4,5)P2) into phosphatidylinositol (3,4,5)-trisphosphate (PI(3,4,5)P3) while the phosphatase and tensin homolog (PTEN) catalyzes the reverse reaction[91,92]. The reversible phosphorylation of inositol lipids regulates diverse aspects of cell growth and metabolism[91,92,93,94]. Recurrent somatic alterations in PIK3CA are frequent in cancer and result in the activation of PI3K/AKT/MTOR pathway, which can influence several hallmarks of cancer including cell proliferation, apoptosis, cancer cell metabolism and invasion, and genetic instability[95,96,97].

Alterations and prevalence: Recurrent somatic activating mutations in PIK3CA are common in diverse cancers and are observed in 20-30% of breast, cervical, and uterine cancers and 10-20% of bladder, gastric, head and neck, and colorectal cancers[6,7]. Activating mutations in PIK3CA commonly cluster in two regions corresponding to the exon 9 helical (codons E542/E545) and exon 20 kinase (codon H1047) domains, each having distinct mechanisms of activation[98,99,100]. PIK3CA resides in the 3q26 cytoband, a region frequently amplified (10-30%) in diverse cancers including squamous carcinomas of the lung, cervix, head and neck, and esophagus, and in serous ovarian and uterine cancers[6,7].

Potential relevance: The PI3K inhibitor, alpelisib[101], is FDA approved (2019) in combination with fulvestrant for the treatment of patients with PIK3CA-mutated, hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative, advanced or metastatic breast cancer. Additionally, a phase Ib study of alpelisib with letrozole in patients with metastatic estrogen receptor (ER)-positive breast cancer, the clinical benefit rate, defined as lack of disease progression ≥ 6 months, was 44% (7/16) in PIK3CA-mutated tumors and 20% (2/20) in PIK3CA wild-type tumors[102]. Specifically, exon 20 H1047R mutations were associated with more durable clinical responses in comparison to exon 9 E545K mutations[102]. However, alpelisib did not improve response when administered

## Biomarker Descriptions (continued)

with letrozole in patients with ER+ early breast cancer with PIK3CA mutations[103]. Case studies with MTOR inhibitors sirolimus and temsirolimus report isolated cases of clinical response in PIK3CA mutated refractory cancers[104,105].

## Relevant Therapy Summary

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

### EGFR exon 19 deletion

| Relevant Therapy | FDA | NCCN | EMA | ESMO | Clinical Trials* |
|---|---|---|---|---|---|
| osimertinib | ● | ● | ● | ● | ● (III) |
| erlotinib + ramucirumab | ● | ● | ✖ | ● | ✖ |
| bevacizumab + erlotinib | ✖ | ● | ● | ● | ✖ |
| osimertinib + chemotherapy | ✖ | ● | ✖ | ✖ | ✖ |
| bevacizumab (Allergan) + erlotinib | ✖ | ✖ | ● | ✖ | ✖ |
| bevacizumab (Fujifilm Kyowa Kirin Biologics) + erlotinib | ✖ | ✖ | ● | ✖ | ✖ |
| bevacizumab (Mabxience) + erlotinib | ✖ | ✖ | ● | ✖ | ✖ |
| bevacizumab (Pfizer) + erlotinib | ✖ | ✖ | ● | ✖ | ✖ |
| bevacizumab (Samsung Bioepis) + erlotinib | ✖ | ✖ | ● | ✖ | ✖ |
| bevacizumab (Stada) + erlotinib | ✖ | ✖ | ● | ✖ | ✖ |
| gefitinib (Mylan) | ✖ | ✖ | ● | ✖ | ✖ |
| atezolizumab + bevacizumab + carboplatin + paclitaxel | ✖ | ✖ | ✖ | ● | ✖ |
| bevacizumab + gefitinib | ✖ | ✖ | ✖ | ● | ✖ |
| gefitinib + carboplatin + pemetrexed | ✖ | ✖ | ✖ | ● | ✖ |
| amivantamab, lazertinib, chemotherapy | ✖ | ✖ | ✖ | ✖ | ● (III) |
| osimertinib, chemotherapy | ✖ | ✖ | ✖ | ✖ | ● (III) |
| durvalumab, tremelimumab, chemotherapy | ✖ | ✖ | ✖ | ✖ | ● (II) |
| sunvozertinib | ✖ | ✖ | ✖ | ✖ | ● (I/II) |
| amivantamab, lazertinib | ✖ | ✖ | ✖ | ✖ | ● (I) |
| lazertinib, amivantamab | ✖ | ✖ | ✖ | ✖ | ● (I) |
| telisotuzumab vedotin, osimertinib | ✖ | ✖ | ✖ | ✖ | ● (I) |
| TNO-155, nazartinib | ✖ | ✖ | ✖ | ✖ | ● (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

### EGFR p.(T790M) c.2369C>T

| Relevant Therapy | FDA | NCCN | EMA | ESMO | Clinical Trials* |
|---|---|---|---|---|---|
| osimertinib | ● | ● | ● | ● | ✖ |
| osimertinib, chemotherapy | ✖ | ✖ | ✖ | ✖ | ● (III) |
| durvalumab, tremelimumab, chemotherapy | ✖ | ✖ | ✖ | ✖ | ● (II) |
| sunvozertinib | ✖ | ✖ | ✖ | ✖ | ● (I/II) |
| amivantamab | ✖ | ✖ | ✖ | ✖ | ● (I) |
| lazertinib, amivantamab, chemotherapy | ✖ | ✖ | ✖ | ✖ | ● (I) |
| telisotuzumab vedotin, osimertinib | ✖ | ✖ | ✖ | ✖ | ● (I) |

### ERBB2 amplification

| Relevant Therapy | FDA | NCCN | EMA | ESMO | Clinical Trials* |
|---|---|---|---|---|---|
| ado-trastuzumab emtansine | ○ | ○ | ○ | ○ | ✖ |
| irbinitinib + trastuzumab + capecitabine | ○ | ○ | ○ | ○ | ✖ |
| lapatinib + capecitabine | ○ | ○ | ○ | ○ | ✖ |
| neratinib | ○ | ○ | ○ | ○ | ✖ |
| pertuzumab + trastuzumab + chemotherapy | ○ | ○ | ○ | ○ | ✖ |
| pertuzumab + trastuzumab + docetaxel | ○ | ○ | ○ | ○ | ✖ |
| trastuzumab deruxtecan | ○ | ○ | ○ | ○ | ✖ |
| trastuzumab | ○ | ○ | ○ | ✖ | ✖ |
| trastuzumab + capecitabine + cisplatin | ○ | ○ | ○ | ✖ | ✖ |
| trastuzumab + carboplatin + docetaxel | ○ | ○ | ○ | ✖ | ✖ |
| trastuzumab + cisplatin + fluorouracil | ○ | ○ | ○ | ✖ | ✖ |
| trastuzumab + docetaxel | ○ | ○ | ○ | ✖ | ✖ |
| trastuzumab + paclitaxel | ○ | ○ | ○ | ✖ | ✖ |
| neratinib + capecitabine | ○ | ○ | ✖ | ✖ | ✖ |
| lapatinib + letrozole | ○ | ✖ | ○ | ✖ | ✖ |
| pertuzumab/trastuzumab/hyaluronidase-zzxf + cyclophosphamide + doxorubicin | ○ | ✖ | ○ | ✖ | ✖ |
| pertuzumab/trastuzumab/hyaluronidase-zzxf + docetaxel | ○ | ✖ | ○ | ✖ | ✖ |
| trastuzumab (Biocon) | ○ | ✖ | ○ | ✖ | ✖ |

* 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 (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 | ○ | ✖ | ○ | ✖ | ✖ |
| trastuzumab (Celltrion) + docetaxel | ○ | ✖ | ○ | ✖ | ✖ |
| trastuzumab (Celltrion) + paclitaxel | ○ | ✖ | ○ | ✖ | ✖ |
| 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 | ○ | ✖ | ○ | ✖ | ✖ |
| margetuximab + chemotherapy | ○ | ✖ | ✖ | ○ | ✖ |
| pembrolizumab + trastuzumab + chemotherapy + fluoropyrimidine | ○ | ✖ | ✖ | ✖ | ✖ |
| trastuzumab and hyaluronidase-oysk | ○ | ✖ | ✖ | ✖ | ✖ |

* 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 and hyaluronidase-oysk + carboplatin + docetaxel | ○ | ✖ | ✖ | ✖ | ✖ |
| trastuzumab and hyaluronidase-oysk + cyclophosphamide + doxorubicin + paclitaxel | ○ | ✖ | ✖ | ✖ | ✖ |
| trastuzumab and hyaluronidase-oysk + docetaxel | ○ | ✖ | ✖ | ✖ | ✖ |
| trastuzumab and hyaluronidase-oysk + paclitaxel | ○ | ✖ | ✖ | ✖ | ✖ |
| lapatinib + trastuzumab | ✖ | ○ | ○ | ○ | ✖ |
| pertuzumab + trastuzumab | ✖ | ○ | ✖ | ○ | ✖ |
| pertuzumab + trastuzumab + hormone therapy + chemotherapy | ✖ | ○ | ✖ | ○ | ✖ |
| pertuzumab + trastuzumab + paclitaxel | ✖ | ○ | ✖ | ○ | ✖ |
| tamoxifen | ✖ | ○ | ✖ | ○ | ✖ |
| trastuzumab + chemotherapy | ✖ | ○ | ✖ | ○ | ✖ |
| trastuzumab + hormone therapy + chemotherapy | ✖ | ○ | ✖ | ○ | ✖ |
| 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 | ✖ | ○ | ✖ | ✖ | ✖ |

* 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 + carboplatin + docetaxel | ✖ | ○ | ✖ | ✖ | ✖ |
| trastuzumab + aromatase inhibitor | ✖ | ○ | ✖ | ✖ | ✖ |
| trastuzumab + capecitabine | ✖ | ○ | ✖ | ✖ | ✖ |
| trastuzumab + capecitabine + oxaliplatin | ✖ | ○ | ✖ | ✖ | ✖ |
| trastuzumab + carboplatin + docetaxel + fluorouracil | ✖ | ○ | ✖ | ✖ | ✖ |
| trastuzumab + carboplatin + paclitaxel | ✖ | ○ | ✖ | ✖ | ✖ |
| trastuzumab + chemotherapy (other) | ✖ | ○ | ✖ | ✖ | ✖ |
| 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 + 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 (Biocon) + CMF + doxorubicin + paclitaxel | ✖ | ✖ | ○ | ✖ | ✖ |
| trastuzumab (Celltrion) + anastrozole | ✖ | ✖ | ○ | ✖ | ✖ |

* 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 (Celltrion) + CMF + doxorubicin + paclitaxel | ✖ | ✖ | ○ | ✖ | ✖ |
| trastuzumab (Henlius) | ✖ | ✖ | ○ | ✖ | ✖ |
| trastuzumab (Henlius) + anastrozole | ✖ | ✖ | ○ | ✖ | ✖ |
| trastuzumab (Henlius) + capecitabine + cisplatin | ✖ | ✖ | ○ | ✖ | ✖ |
| trastuzumab (Henlius) + carboplatin + docetaxel | ✖ | ✖ | ○ | ✖ | ✖ |
| trastuzumab (Henlius) + cisplatin + fluorouracil | ✖ | ✖ | ○ | ✖ | ✖ |
| trastuzumab (Henlius) + CMF + doxorubicin + paclitaxel | ✖ | ✖ | ○ | ✖ | ✖ |
| trastuzumab (Henlius) + docetaxel | ✖ | ✖ | ○ | ✖ | ✖ |
| trastuzumab (Henlius) + paclitaxel | ✖ | ✖ | ○ | ✖ | ✖ |
| trastuzumab (Pfizer) + anastrozole | ✖ | ✖ | ○ | ✖ | ✖ |
| trastuzumab (Pfizer) + CMF + doxorubicin + paclitaxel | ✖ | ✖ | ○ | ✖ | ✖ |
| trastuzumab (Samsung Bioepis) + anastrozole | ✖ | ✖ | ○ | ✖ | ✖ |
| trastuzumab (Samsung Bioepis) + CMF + doxorubicin + paclitaxel | ✖ | ✖ | ○ | ✖ | ✖ |
| trastuzumab (Synthon) | ✖ | ✖ | ○ | ✖ | ✖ |
| trastuzumab (Synthon) + anastrozole | ✖ | ✖ | ○ | ✖ | ✖ |
| trastuzumab (Synthon) + capecitabine + cisplatin | ✖ | ✖ | ○ | ✖ | ✖ |
| trastuzumab (Synthon) + carboplatin + docetaxel | ✖ | ✖ | ○ | ✖ | ✖ |
| trastuzumab (Synthon) + cisplatin + fluorouracil | ✖ | ✖ | ○ | ✖ | ✖ |
| trastuzumab (Synthon) + CMF + doxorubicin + paclitaxel | ✖ | ✖ | ○ | ✖ | ✖ |
| trastuzumab (Synthon) + docetaxel | ✖ | ✖ | ○ | ✖ | ✖ |
| trastuzumab (Synthon) + paclitaxel | ✖ | ✖ | ○ | ✖ | ✖ |
| trastuzumab + anastrozole | ✖ | ✖ | ○ | ✖ | ✖ |
| trastuzumab + CMF + doxorubicin + paclitaxel | ✖ | ✖ | ○ | ✖ | ✖ |
| aromatase inhibitor + luteinizing hormone-releasing factor | ✖ | ✖ | ✖ | ○ | ✖ |
| lapatinib + hormone therapy | ✖ | ✖ | ✖ | ○ | ✖ |
| lapatinib + trastuzumab + hormone therapy | ✖ | ✖ | ✖ | ○ | ✖ |

* 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* |
|---|---|---|---|---|---|
| margetuximab | ✖ | ✖ | ✖ | ○ | ✖ |
| neratinib + chemotherapy | ✖ | ✖ | ✖ | ○ | ✖ |
| pertuzumab + trastuzumab + hormone therapy | ✖ | ✖ | ✖ | ○ | ✖ |
| pertuzumab + trastuzumab + nab-paclitaxel | ✖ | ✖ | ✖ | ○ | ✖ |
| trastuzumab + hormone therapy | ✖ | ✖ | ✖ | ○ | ✖ |
| SAR-443216 | ✖ | ✖ | ✖ | ✖ | ● (I) |
| SHR-A1811 | ✖ | ✖ | ✖ | ✖ | ● (I) |

### PIK3CA p.(E545K) c.1633G>A

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

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

# Relevant Therapy Details

## Current FDA Information

● In this cancer type ○ In other cancer type ◑ In this cancer type and other cancer types

FDA information is current as of 2022-09-14. For the most up-to-date information, search www.fda.gov.

## EGFR exon 19 deletion

### ● erlotinib + ramucirumab

**Cancer type:** Non-Small Cell Lung Cancer **Label as of:** 2022-03-22 **Variant class:** EGFR exon 19 deletion

**Indications and usage:**

CYRAMZA® is a human vascular endothelial growth factor receptor 2 (VEGFR2) antagonist indicated:

- as a single agent or in combination with paclitaxel, for treatment of advanced or metastatic gastric or gastro-esophageal junction adenocarcinoma with disease progression on or after prior fluoropyrimidine- or platinum-containing chemotherapy.
- in combination with erlotinib, for first-line treatment of metastatic non-small cell lung cancer with epidermal growth factor receptor (EGFR) exon 19 deletions or exon 21 (L858R) mutations.
- in combination with docetaxel, for treatment of metastatic non-small cell lung cancer with disease progression on or after platinum-based chemotherapy. Patients with EGFR or ALK genomic tumor aberrations should have disease progression on FDA-approved therapy for these aberrations prior to receiving CYRAMZA®.
- in combination with FOLFIRI, for the treatment of metastatic colorectal cancer with disease progression on or after prior therapy with bevacizumab, oxaliplatin, and a fluoropyrimidine.
- as a single agent, for the treatment of hepatocellular carcinoma in patients who have an alpha fetoprotein of ≥400 ng/mL and have been treated with sorafenib.

**Reference:**

https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/125477s042lbl.pdf

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### ● osimertinib

**Cancer type:** Non-Small Cell Lung Cancer **Label as of:** 2022-01-19 **Variant class:** EGFR exon 19 deletion

**Indications and usage:**

TAGRISSO® is a kinase inhibitor indicated for:

- as adjuvant therapy after tumor resection in adult patients with non-small cell lung cancer (NSCLC) whose tumors have epidermal growth factor receptor (EGFR) exon 19 deletions or exon 21 L858R mutations, as detected by an FDA-approved test.
- the first-line treatment of adult patients with metastatic NSCLC whose tumors have EGFR exon 19 deletions or exon 21 L858R mutations, as detected by an FDA-approved test.
- the treatment of adult patients with metastatic EGFR T790M mutation positive NSCLC, as detected by an FDA-approved test, whose disease has progressed on or after EGFR TKI therapy.

**Reference:**

https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/208065s025lbl.pdf

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## EGFR p.(T790M) c.2369C>T

### osimertinib

**Cancer type:** Non-Small Cell Lung Cancer **Label as of:** 2022-01-19 **Variant class:** EGFR T790M mutation

**Indications and usage:**

TAGRISSO® is a kinase inhibitor indicated for:

- as adjuvant therapy after tumor resection in adult patients with non-small cell lung cancer (NSCLC) whose tumors have epidermal growth factor receptor (EGFR) exon 19 deletions or exon 21 L858R mutations, as detected by an FDA-approved test.
- the first-line treatment of adult patients with metastatic NSCLC whose tumors have EGFR exon 19 deletions or exon 21 L858R mutations, as detected by an FDA-approved test.
- the treatment of adult patients with metastatic EGFR T790M mutation positive NSCLC, as detected by an FDA-approved test, whose disease has progressed on or after EGFR TKI therapy.

**Reference:**

https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/208065s025lbl.pdf

## ERBB2 amplification

### ado-trastuzumab emtansine

**Cancer type:** Breast Cancer **Label as of:** 2022-02-02 **Variant class:** ERBB2 overexpression or ERBB2 amplification

**Indications and usage:**

KADCYLA® is a HER2-targeted antibody and microtubule inhibitor conjugate indicated, as a single agent, for:

- the treatment of patients with HER2-positive, metastatic breast cancer who previously received trastuzumab and a taxane, separately or in combination. Patients should have either:
  - received prior therapy for metastatic disease, or
  - developed disease recurrence during or within six months of completing adjuvant therapy.
- the adjuvant treatment of patients with HER2-positive early breast cancer who have residual invasive disease after neoadjuvant taxane and trastuzumab-based treatment.

Select patients for therapy based on an FDA-approved companion diagnostic for KADCYLA®

**Reference:**

https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/125427s111lbl.pdf

### irbinitinib + trastuzumab + capecitabine

**Cancer type:** Breast Cancer **Label as of:** 2020-04-17 **Variant class:** ERBB2 overexpression or ERBB2 amplification

**Indications and usage:**
TUKYSA™ is a kinase inhibitor indicated in combination with trastuzumab and capecitabine for treatment of adult patients with advanced unresectable or metastatic HER2-positive breast cancer, including patients with brain metastases, who have received one or more prior anti-HER2-based regimens in the metastatic setting.

**Reference:**

https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/213411s000lbl.pdf

## ERBB2 amplification (continued)

### lapatinib + capecitabine, lapatinib + letrozole

**Cancer type:** Breast Cancer **Label as of:** 2022-03-27 **Variant class:** ERBB2 overexpression

**Other criteria:** ER positive, PR positive

**Indications and usage:**

TYKERB® is a kinase inhibitor indicated in combination with:

- capecitabine for the treatment of patients with advanced or metastatic breast cancer whose tumors overexpress human epidermal growth factor receptor 2 (HER2) and who have received prior therapy including an anthracycline, a taxane, and trastuzumab.
- Limitations of Use: Patients should have disease progression on trastuzumab prior to initiation of treatment with TYKERB® in combination with capecitabine.
- letrozole for the treatment of postmenopausal women with hormone receptor-positive metastatic breast cancer that overexpresses the HER2 receptor for whom hormonal therapy is indicated.

TYKERB® in combination with an aromatase inhibitor has not been compared to a trastuzumab-containing chemotherapy regimen for the treatment of metastatic breast cancer.

**Reference:**

https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/022059s031lbl.pdf

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### margetuximab + chemotherapy

**Cancer type:** Breast Cancer **Label as of:** 2020-12-16 **Variant class:** ERBB2 overexpression or ERBB2 amplification

**Indications and usage:**
MARGENZA™ is a HER2/neu receptor antagonist indicated, in combination with chemotherapy, for the treatment of adult patients with metastatic HER2 positive breast cancer who have received two or more prior anti-HER2 regimens, at least one of which was for metastatic disease.

**Reference:**

https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/761150s000lbl.pdf

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### neratinib, neratinib + capecitabine

**Cancer type:** Breast Cancer **Label as of:** 2021-06-28 **Variant class:** ERBB2 overexpression

**Indications and usage:**

NERLYNX® is a kinase inhibitor indicated:

- As a single agent, for the extended adjuvant treatment of adult patients with early stage HER2-positive breast cancer, to follow adjuvant trastuzumab-based therapy.
- In combination with capecitabine, for the treatment of adult patients with advanced or metastatic HER2-positive breast cancer who have received two or more prior anti-HER2 based regimens in the metastatic setting.

**Reference:**

https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/208051s009lbl.pdf

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## ERBB2 amplification (continued)

### pembrolizumab + trastuzumab + chemotherapy + fluoropyrimidine

**Cancer type:** Gastric Cancer, Gastroesophageal Junction Adenocarcinoma **Label as of:** 2022-08-05 **Variant class:** ERBB2 overexpression

**Indications and usage:**

KEYTRUDA® is a programmed death receptor-1 (PD-1)-blocking antibody indicated:

Melanoma

- for the treatment of patients with unresectable or metastatic melanoma.
- for the adjuvant treatment of adult and pediatric (12 years and older) patients with Stage IIB, IIC, or III melanoma following complete resection.

Non-Small Cell Lung Cancer (NSCLC)

- in combination with pemetrexed and platinum chemotherapy, as first-line treatment of patients with metastatic nonsquamous NSCLC, with no EGFR or ALK genomic tumor aberrations.
- in combination with carboplatin and either paclitaxel or paclitaxel protein-bound, as first-line treatment of patients with metastatic squamous NSCLC.
- as a single agent for the first-line treatment of patients with NSCLC expressing PD-L1 [Tumor Proportion Score (TPS) ≥1%] as determined by an FDA-approved test, with no EGFR or ALK genomic tumor aberrations, and is:
  - stage III where patients are not candidates for surgical resection or definitive chemoradiation, or
  - metastatic.
- as a single agent for the treatment of patients with metastatic NSCLC whose tumors express PD-L1 (TPS ≥1%) as determined by an FDA-approved test, with disease progression on or after platinum-containing chemotherapy. Patients with EGFR or ALK genomic tumor aberrations should have disease progression on FDA-approved therapy for these aberrations prior to receiving KEYTRUDA®.

Head and Neck Squamous Cell Cancer (HNSCC)

- in combination with platinum and FU for the first-line treatment of patients with metastatic or with unresectable, recurrent HNSCC.
- as a single agent for the first-line treatment of patients with metastatic or with unresectable, recurrent HNSCC whose tumors express PD-L1 [Combined Positive Score (CPS) ≥1] as determined by an FDA-approved test.
- as a single agent for the treatment of patients with recurrent or metastatic HNSCC with disease progression on or after platinum-containing chemotherapy.

Classical Hodgkin Lymphoma (cHL)

- for the treatment of adult patients with relapsed or refractory cHL.
- for the treatment of pediatric patients with refractory cHL, or cHL that has relapsed after 2 or more lines of therapy.

Primary Mediastinal Large B-Cell Lymphoma (PMBCL)

- for the treatment of adult and pediatric patients with refractory PMBCL, or who have relapsed after 2 or more prior lines of therapy.
- Limitations of Use: KEYTRUDA® is not recommended for treatment of patients with PMBCL who require urgent cytoreductive therapy.

Urothelial Carcinoma

- for the treatment of patients with locally advanced or metastatic urothelial carcinoma who:
  - are not eligible for any platinum-containing chemotherapy, or
  - who have disease progression during or following platinum-containing chemotherapy or within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy
- for the treatment of patients with Bacillus Calmette-Guerin (BCG)-unresponsive, high-risk, non-muscle invasive bladder cancer (NMIBC) with carcinoma in situ (CIS) with or without papillary tumors who are ineligible for or have elected not to undergo cystectomy.

Microsatellite Instability-High or Mismatch Repair Deficient Cancer

## ERBB2 amplification (continued)

- for the treatment of adult and pediatric patients with unresectable or metastatic microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) solid tumors, as determined by an FDA-approved test, that have progressed following prior treatment and who have no satisfactory alternative treatment options.[1]
- Limitations of Use: The safety and effectiveness of KEYTRUDA® in pediatric patients with MSI-H central nervous system cancers have not been established.

Microsatellite Instability-High or Mismatch Repair Deficient Colorectal Cancer (CRC)

- for the treatment of patients with unresectable or metastatic MSI-H or dMMR colorectal cancer (CRC) as determined by an FDA-approved test.

Gastric Cancer

- in combination with trastuzumab, fluoropyrimidine- and platinum-containing chemotherapy, for the first-line treatment of patients with locally advanced unresectable or metastatic HER2-positive gastric or gastroesophageal junction (GEJ) adenocarcinoma.[1]

Esophageal Cancer

- for the treatment of patients with locally advanced or metastatic esophageal or gastroesophageal junction (GEJ) (tumors with epicenter 1 to 5 centimeters above the GEJ) carcinoma that is not amenable to surgical resection or definitive chemoradiation either:
  - in combination with platinum- and fluoropyrimidine-based chemotherapy, or
  - as a single agent after one or more prior lines of systemic therapy for patients with tumors of squamous cell histology that express PD-L1 (CPS ≥10) as determined by an FDA-approved test.

Cervical Cancer

- in combination with chemotherapy, with or without bevacizumab, for the treatment of patients with persistent, recurrent, or metastatic cervical cancer whose tumors express PD-L1 (CPS ≥1) as determined by an FDA-approved test.
- as a single agent for the treatment of patients with recurrent or metastatic cervical cancer with disease progression on or after chemotherapy whose tumors express PD-L1 (CPS ≥1) as determined by an FDA-approved test.

Hepatocellular Carcinoma (HCC)

- for the treatment of patients with HCC who have been previously treated with sorafenib.[1]

Merkel Cell Carcinoma (MCC)

- for the treatment of adult and pediatric patients with recurrent locally advanced or metastatic Merkel cell carcinoma.[1]

Renal Cell Carcinoma (RCC)

- in combination with axitinib, for the first-line treatment of adult patients with advanced RCC.
- in combination with lenvatinib, for the first-line treatment of adult patients with advanced RCC.
- for the adjuvant treatment of patients with RCC at intermediate-high or high risk of recurrence following nephrectomy, or following nephrectomy and resection of metastatic lesions.

Endometrial Carcinoma

- in combination with lenvatinib, for the treatment of patients with advanced endometrial carcinoma that is mismatch repair proficient (pMMR) as determined by an FDA-approved test or not MSI-H, who have disease progression following prior systemic therapy in any setting and are not candidates for curative surgery or radiation.
- as a single agent, for the treatment of patients with advanced endometrial carcinoma that is MSI-H or dMMR, as determined by an FDA-approved test, who have disease progression following prior systemic therapy in any setting and are not candidates for curative surgery or radiation.

Tumor Mutational Burden-High (TMB-H) Cancer

- for the treatment of adult and pediatric patients with unresectable or metastatic tumor mutational burden-high (TMB-H) [≥10 mutations/megabase (mut/Mb)] solid tumors, as determined by an FDA-approved test, that have progressed following prior treatment and who have no satisfactory alternative treatment options.[1]
- Limitations of Use: The safety and effectiveness of KEYTRUDA® in pediatric patients with TMB-H central nervous system cancers have not been established.

Cutaneous Squamous Cell Carcinoma (cSCC)

- for the treatment of patients with recurrent or metastatic cSCC or locally advanced cSCC that is not curable by surgery or radiation.

Triple-Negative Breast Cancer (TNBC)

## ERBB2 amplification (continued)

- for the treatment of patients with high-risk early-stage TNBC in combination with chemotherapy as neoadjuvant treatment, and then continued as a single agent as adjuvant treatment after surgery.
- in combination with chemotherapy, for the treatment of patients with locally recurrent unresectable or metastatic TNBC whose tumors express PD-L1 (CPS ≥10) as determined by an FDA approved test.

Adult Indications: Additional Dosing Regimen of 400 mg Every 6 Weeks

- for use at an additional recommended dosage of 400 mg every 6 weeks for all approved adult indications.[2]

[1] This indication is approved under accelerated approval based on tumor response rate and durability of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in the confirmatory trials.

[2] This indication is approved under accelerated approval based on pharmacokinetic data, the relationship of exposure to efficacy, and the relationship of exposure to safety. Continued approval for this dosing may be contingent upon verification and description of clinical benefit in the confirmatory trials.

**Reference:**

https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/125514s133lbl.pdf

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### ○ pertuzumab + trastuzumab + chemotherapy, pertuzumab + trastuzumab + docetaxel

**Cancer type:** Breast Cancer **Label as of:** 2020-01-16 **Variant class:** ERBB2 amplification or ERBB2 overexpression

**Indications and usage:**

PERJETA® is a HER2/neu receptor antagonist indicated for:

- Use in combination with trastuzumab and docetaxel for treatment of patients with HER2-positive metastatic breast cancer (MBC) who have not received prior anti-HER2 therapy or chemotherapy for metastatic disease.
- Use in combination with trastuzumab and chemotherapy as
  - neoadjuvant treatment of patients with HER2-positive, locally advanced, inflammatory, or early stage breast cancer (either greater than 2 cm in diameter or node positive) as part of a complete treatment regimen for early breast cancer.
  - adjuvant treatment of patients with HER2-positive early breast cancer at high risk of recurrence

**Reference:**

https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/125409s124lbl.pdf

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### ○ pertuzumab/trastuzumab/hyaluronidase-zzxf + cyclophosphamide + doxorubicin

**Cancer type:** Breast Cancer **Label as of:** 2020-06-29 **Variant class:** ERBB2 amplification

**Indications and usage:**

PHESGO™ is a combination of pertuzumab and trastuzumab, HER2/neu receptor antagonists, and hyaluronidase, an endoglycosidase, indicated for:

- Use in combination with chemotherapy as:
  - neoadjuvant treatment of patients with HER2-positive, locally advanced, inflammatory, or early stage breast cancer (either greater than 2 cm in diameter or node positive) as part of a complete treatment regimen for early breast cancer.
  - adjuvant treatment of patients with HER2-positive early breast cancer at high risk of recurrence
- Use in combination with docetaxel for treatment of patients with HER2 positive metastatic breast cancer (MBC) who have not received prioranti-HER2 therapy or chemotherapy for metastatic disease.

**Reference:**

https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/761170s000lbl.pdf

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## ERBB2 amplification (continued)

### pertuzumab/trastuzumab/hyaluronidase-zzxf + docetaxel, pertuzumab/trastuzumab/hyaluronidase-zzxf + cyclophosphamide + doxorubicin

**Cancer type:** Breast Cancer **Label as of:** 2020-06-29 **Variant class:** ERBB2 overexpression

**Indications and usage:**

PHESGO™ is a combination of pertuzumab and trastuzumab, HER2/neu receptor antagonists, and hyaluronidase, an endoglycosidase, indicated for:

- Use in combination with chemotherapy as:
  - neoadjuvant treatment of patients with HER2-positive, locally advanced, inflammatory, or early stage breast cancer (either greater than 2 cm in diameter or node positive) as part of a complete treatment regimen for early breast cancer.
  - adjuvant treatment of patients with HER2-positive early breast cancer at high risk of recurrence
- Use in combination with docetaxel for treatment of patients with HER2 positive metastatic breast cancer (MBC) who have not received prioranti-HER2 therapy or chemotherapy for metastatic disease.

**Reference:**

https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/761170s000lbl.pdf

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### trastuzumab (Biocon), trastuzumab (Biocon) + docetaxel, trastuzumab (Biocon) + paclitaxel, trastuzumab (Biocon) + capecitabine + cisplatin, trastuzumab (Biocon) + carboplatin + docetaxel, trastuzumab (Biocon) + cisplatin + fluorouracil

**Cancer type:** Breast Cancer, Gastric Cancer, Gastroesophageal Junction Adenocarcinoma **Label as of:** 2019-04-17 **Variant class:** ERBB2 overexpression or ERBB2 amplification

**Indications and usage:**

OGIVRI™ is a HER2/neu receptor antagonist indicated for:

- The treatment of HER2-overexpressing breast cancer.
- The treatment of HER2-overexpressing metastatic gastric or gastroesophageal junction adenocarcinoma.

Select patients for therapy based on an FDA-approved companion diagnostic for a trastuzumab product.

**Reference:**

https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/761074s004lbl.pdf

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### trastuzumab (Celltrion), trastuzumab (Celltrion) + docetaxel, trastuzumab (Celltrion) + paclitaxel, trastuzumab (Celltrion) + capecitabine + cisplatin, trastuzumab (Celltrion) + carboplatin + docetaxel, trastuzumab (Celltrion) + cisplatin + fluorouracil

**Cancer type:** Breast Cancer, Gastric Cancer, Gastroesophageal Junction Adenocarcinoma **Label as of:** 2019-05-16 **Variant class:** ERBB2 amplification or ERBB2 overexpression

**Indications and usage:**

HERZUMA® is a HER2/neu receptor antagonist indicated for:

- the treatment of HER2-overexpressing breast cancer.
- the treatment of HER2-overexpressing metastatic gastric or gastroesophageal junction adenocarcinoma.

Select patients for therapy based on an FDA-approved companion diagnostic for a trastuzumab product.

**Reference:**

https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/761091s001s002lbl.pdf

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## ERBB2 amplification (continued)

### trastuzumab (Pfizer), trastuzumab (Pfizer) + docetaxel, trastuzumab (Pfizer) + paclitaxel, trastuzumab (Pfizer) + capecitabine + cisplatin, trastuzumab (Pfizer) + carboplatin + docetaxel, trastuzumab (Pfizer) + cisplatin + fluorouracil

**Cancer type:** Breast Cancer, Gastric Cancer, Gastroesophageal Junction Adenocarcinoma

**Label as of:** 2019-03-11

**Variant class:** ERBB2 overexpression or ERBB2 amplification

**Indications and usage:**

TRAZIMERA™ is a HER2/neu receptor antagonist indicated for:

- The treatment of HER2-overexpressing breast cancer.
- The treatment of HER2-overexpressing metastatic gastric or gastroesophageal junction adenocarcinoma.

Select patients for therapy based on an FDA-approved companion diagnostic for a trastuzumab product.

**Reference:**

https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/761081s000lbl.pdf

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### trastuzumab (Samsung Bioepis), trastuzumab (Samsung Bioepis) + docetaxel, trastuzumab (Samsung Bioepis) + paclitaxel, trastuzumab (Samsung Bioepis) + capecitabine + cisplatin, trastuzumab (Samsung Bioepis) + carboplatin + docetaxel, trastuzumab (Samsung Bioepis) + cisplatin + fluorouracil

**Cancer type:** Breast Cancer, Gastric Cancer, Gastroesophageal Junction Adenocarcinoma

**Label as of:** 2019-01-18

**Variant class:** ERBB2 overexpression or ERBB2 amplification

**Indications and usage:**

Ontruzant® is a HER2/neu receptor antagonist indicated for:

- The treatment of HER2-overexpressing breast cancer.
- The treatment of HER2-overexpressing metastatic gastric or gastroesophageal junction adenocarcinoma.

Select patients for therapy based on an FDA-approved companion diagnostic for a trastuzumab product.

**Reference:**

https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/761100s000lbl.pdf

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### trastuzumab and hyaluronidase-oysk, trastuzumab and hyaluronidase-oysk + docetaxel, trastuzumab and hyaluronidase-oysk + paclitaxel, trastuzumab and hyaluronidase-oysk + carboplatin + docetaxel

**Cancer type:** Breast Cancer

**Label as of:** 2019-02-28

**Variant class:** ERBB2 amplification

**Indications and usage:**

HERCEPTIN HYLECTA™ is a combination of trastuzumab, a HER2/neu receptor antagonist, and hyaluronidase, an endoglycosidase, indicated in adults for:

- The treatment of HER2-overexpressing breast cancer.

Select patients for therapy based on an FDA-approved companion diagnostic for trastuzumab.

**Reference:**

https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/761106Orig1s000lbl.pdf

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## ERBB2 amplification (continued)

### trastuzumab and hyaluronidase-oysk, trastuzumab and hyaluronidase-oysk + docetaxel, trastuzumab and hyaluronidase-oysk + paclitaxel, trastuzumab and hyaluronidase-oysk + carboplatin + docetaxel, trastuzumab and hyaluronidase-oysk + cyclophosphamide + doxorubicin + paclitaxel

**Cancer type:** Breast Cancer **Label as of:** 2019-02-28 **Variant class:** ERBB2 overexpression

**Other criteria:** ER negative, PR negative

**Indications and usage:**

HERCEPTIN HYLECTA™ is a combination of trastuzumab, a HER2/neu receptor antagonist, and hyaluronidase, an endoglycosidase, indicated in adults for:

- The treatment of HER2-overexpressing breast cancer.

Select patients for therapy based on an FDA-approved companion diagnostic for trastuzumab.

**Reference:**

https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/761106Orig1s000lbl.pdf

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### trastuzumab deruxtecan

**Cancer type:** Breast Cancer, Gastric Cancer, Gastroesophageal Junction Adenocarcinoma **Label as of:** 2022-08-11 **Variant class:** ERBB2 overexpression

**Indications and usage:**

ENHERTU® is a HER2-directed antibody and topoisomerase inhibitor conjugate indicated for the treatment of:

- adult patients with unresectable or metastatic HER2-positive breast cancer who have received a prior anti-HER2-based regimen either:
  - in the metastatic setting, or
  - in the neoadjuvant or adjuvant setting and have developed disease recurrence during or within six months of completing therapy.
- adult patients with unresectable or metastatic HER2-low (IHC 1+ or IHC 2+/ISH-) breast cancer who have received a prior chemotherapy in the metastatic setting or developed disease recurrence during or within 6 months of completing adjuvant chemotherapy.
- adult patients with unresectable or metastatic non-small cell lung cancer (NSCLC) whose tumors have activating HER2 (ERBB2) mutations, as detected by an FDA-approved test, and who have received a prior systemic therapy.
  - This indication is approved under accelerated approval based on objective response rate and duration of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial.
- adult patients with locally advanced or metastatic HER2-positive gastric or gastroesophageal junction adenocarcinoma who have received a prior trastuzumab-based regimen.

**Reference:**

https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/761139s021lbl.pdf

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## ERBB2 amplification (continued)

### trastuzumab deruxtecan

**Cancer type:** Breast Cancer **Label as of:** 2022-08-11 **Variant class:** ERBB2 amplification

**Indications and usage:**

ENHERTU® is a HER2-directed antibody and topoisomerase inhibitor conjugate indicated for the treatment of:

- adult patients with unresectable or metastatic HER2-positive breast cancer who have received a prior anti-HER2-based regimen either:
  - in the metastatic setting, or
  - in the neoadjuvant or adjuvant setting and have developed disease recurrence during or within six months of completing therapy.
- adult patients with unresectable or metastatic HER2-low (IHC 1+ or IHC 2+/ISH-) breast cancer who have received a prior chemotherapy in the metastatic setting or developed disease recurrence during or within 6 months of completing adjuvant chemotherapy.
- adult patients with unresectable or metastatic non-small cell lung cancer (NSCLC) whose tumors have activating HER2 (ERBB2) mutations, as detected by an FDA-approved test, and who have received a prior systemic therapy.
  - This indication is approved under accelerated approval based on objective response rate and duration of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial.
- adult patients with locally advanced or metastatic HER2-positive gastric or gastroesophageal junction adenocarcinoma who have received a prior trastuzumab-based regimen.

**Reference:**

https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/761139s021lbl.pdf

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### trastuzumab, trastuzumab + docetaxel, trastuzumab + paclitaxel, trastuzumab + capecitabine + cisplatin, trastuzumab + carboplatin + docetaxel, trastuzumab + cisplatin + fluorouracil

**Cancer type:** Breast Cancer, Gastric Cancer, Gastroesophageal Junction Adenocarcinoma **Label as of:** 2018-11-29 **Variant class:** ERBB2 overexpression or ERBB2 amplification

**Indications and usage:**

HERCEPTIN® is a HER2/neu receptor antagonist indicated for:

- The treatment of HER2-overexpressing breast cancer.
- The treatment of HER2-overexpressing metastatic gastric or gastroesophageal junction adenocarcinoma.

Select patients for therapy based on an FDA-approved companion diagnostic for HERCEPTIN®.

**Reference:**

https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/103792s5345lbl.pdf

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## Current NCCN Information

● In this cancer type ○ In other cancer type ◑ In this cancer type and other cancer types

NCCN information is current as of 2022-09-01. For the most up-to-date information, search www.nccn.org.
For NCCN International Adaptations & Translations, search www.nccn.org/global/international_adaptations.aspx.

## EGFR exon 19 deletion

### ● osimertinib

**Cancer type:** Non-Small Cell Lung Cancer **Variant class:** EGFR exon 19 deletion

**NCCN Recommendation category:** 1

**Population segment (Line of therapy):**
- Adenocarcinoma, Large Cell, Squamous Cell, Not otherwise specified (NOS); Advanced, Metastatic (First-line therapy); Preferred intervention

**Reference:** NCCN Guidelines® - NCCN-Non-Small Cell Lung Cancer [Version 3.2022]

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### ● bevacizumab + erlotinib

**Cancer type:** Non-Small Cell Lung Cancer **Variant class:** EGFR exon 19 deletion

**NCCN Recommendation category:** 2A

**Population segment (Line of therapy):**
- Non-squamous Cell; Advanced, Metastatic (First-line therapy); Other recommended intervention
- Non-squamous Cell; Advanced, Metastatic (Subsequent therapy)

**Reference:** NCCN Guidelines® - NCCN-Non-Small Cell Lung Cancer [Version 3.2022]

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### ● erlotinib + ramucirumab

**Cancer type:** Non-Small Cell Lung Cancer **Variant class:** EGFR exon 19 deletion

**NCCN Recommendation category:** 2A

**Population segment (Line of therapy):**
- Adenocarcinoma, Large Cell, Squamous Cell, Not otherwise specified (NOS); Advanced, Metastatic (First-line therapy); Other recommended intervention
- Adenocarcinoma, Large Cell, Squamous Cell, Not otherwise specified (NOS); Advanced, Metastatic (Subsequent therapy)

**Reference:** NCCN Guidelines® - NCCN-Non-Small Cell Lung Cancer [Version 3.2022]

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### ● osimertinib

**Cancer type:** Non-Small Cell Lung Cancer **Variant class:** EGFR exon 19 deletion

**NCCN Recommendation category:** 2A

**Population segment (Line of therapy):**
- Brain Metastases, Leptomeningeal Metastases, Spine Metastases (Line of therapy not specified)

**Reference:** NCCN Guidelines® - NCCN-Central Nervous System Cancers [Version 1.2022]

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## EGFR exon 19 deletion (continued)

### osimertinib

**Cancer type:** Non-Small Cell Lung Cancer **Variant class:** EGFR exon 19 deletion

**NCCN Recommendation category:** 2A

**Population segment (Line of therapy):**
- Stage IB , Stage IIA, Stage IIB, Stage IIIA, Stage IIIB; Resected (Adjuvant therapy)
- Adenocarcinoma, Large Cell, Squamous Cell, Not otherwise specified (NOS); Advanced, Metastatic (Subsequent therapy); Preferred intervention
- Adenocarcinoma, Large Cell, Squamous Cell, Not otherwise specified (NOS); Leptomeningeal Metastases, Progression (Subsequent therapy); Consider

**Reference:** NCCN Guidelines® - NCCN-Non-Small Cell Lung Cancer [Version 3.2022]

### osimertinib + chemotherapy

**Cancer type:** Non-Small Cell Lung Cancer **Variant class:** EGFR exon 19 deletion

**NCCN Recommendation category:** 2A

**Population segment (Line of therapy):**
- Stage IB , Stage IIA, Stage IIB, Stage IIIA; Resected (Adjuvant therapy)

**Reference:** NCCN Guidelines® - NCCN-Non-Small Cell Lung Cancer [Version 3.2022]

## EGFR p.(T790M) c.2369C>T

### osimertinib

**Cancer type:** Non-Small Cell Lung Cancer **Variant class:** EGFR T790M mutation

**NCCN Recommendation category:** 1

**Population segment (Line of therapy):**
- Adenocarcinoma, Large Cell, Squamous Cell, Not otherwise specified (NOS); Advanced, Metastatic, Progression, Asymptomatic, Symptomatic (Subsequent therapy)

**Reference:** NCCN Guidelines® - NCCN-Non-Small Cell Lung Cancer [Version 3.2022]

### osimertinib

**Cancer type:** Non-Small Cell Lung Cancer **Variant class:** EGFR T790M mutation

**NCCN Recommendation category:** 2A

**Population segment (Line of therapy):**
- Brain Metastases, Leptomeningeal Metastases, Spine Metastases (Line of therapy not specified)

**Reference:** NCCN Guidelines® - NCCN-Central Nervous System Cancers [Version 1.2022]

## ERBB2 amplification

### irbinitinib + trastuzumab + capecitabine

**Cancer type:** Breast Cancer

**Variant class:** ERBB2 amplification or ERBB2 overexpression

**Other criteria:** Hormone receptor status

**NCCN Recommendation category:** 1

**Population segment (Line of therapy):**
- Stage IV; Invasive, Recurrent, Unresectable, Local, Regional (Third-line therapy, Subsequent therapy); Other recommended intervention

**Reference:** NCCN Guidelines® - NCCN-Breast Cancer [Version 4.2022]

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### pertuzumab + trastuzumab + docetaxel

**Cancer type:** Breast Cancer

**Variant class:** ERBB2 amplification or ERBB2 overexpression

**Other criteria:** Hormone receptor status

**NCCN Recommendation category:** 1

**Population segment (Line of therapy):**
- Stage IV; Invasive, Recurrent, Unresectable, Local, Regional (First-line therapy); Preferred intervention

**Reference:** NCCN Guidelines® - NCCN-Breast Cancer [Version 4.2022]

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### trastuzumab + capecitabine + cisplatin

**Cancer type:** Esophageal Cancer, Gastroesophageal Junction Adenocarcinoma

**Variant class:** ERBB2 amplification or ERBB2 overexpression

**NCCN Recommendation category:** 1

**Population segment (Line of therapy):**
- Adenocarcinoma; Unresectable, Locally Advanced, Recurrent, Metastatic (First-line therapy); Preferred intervention

**Reference:** NCCN Guidelines® - NCCN-Esophageal and Esophagogastric Junction Cancers [Version 3.2022]

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### trastuzumab + capecitabine + cisplatin

**Cancer type:** Gastric Cancer

**Variant class:** ERBB2 amplification or ERBB2 overexpression

**NCCN Recommendation category:** 1

**Population segment (Line of therapy):**
- Adenocarcinoma; Unresectable, Locally Advanced, Recurrent, Metastatic (First-line therapy); Preferred intervention

**Reference:** NCCN Guidelines® - NCCN-Gastric Cancer [Version 2.2022]

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## ERBB2 amplification (continued)

### trastuzumab + chemotherapy

**Cancer type:** Breast Cancer

**Variant class:** ERBB2 amplification or ERBB2 overexpression

**Other criteria:** Hormone receptor negative

**NCCN Recommendation category:** 1

**Population segment (Line of therapy):**
- Ductal, Lobular, Mixed, Micropapillary; Invasive (Adjuvant therapy)

**Reference:** NCCN Guidelines® - NCCN-Breast Cancer [Version 4.2022]

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### trastuzumab + chemotherapy

**Cancer type:** Breast Cancer

**Variant class:** ERBB2 amplification or ERBB2 overexpression

**Other criteria:** Hormone receptor positive

**NCCN Recommendation category:** 1

**Population segment (Line of therapy):**
- Ductal, Lobular, Mixed, Micropapillary; Invasive (Adjuvant therapy)

**Reference:** NCCN Guidelines® - NCCN-Breast Cancer [Version 4.2022]

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### trastuzumab + cisplatin + fluorouracil

**Cancer type:** Esophageal Cancer, Gastroesophageal Junction Adenocarcinoma

**Variant class:** ERBB2 amplification or ERBB2 overexpression

**NCCN Recommendation category:** 1

**Population segment (Line of therapy):**
- Adenocarcinoma; Unresectable, Locally Advanced, Recurrent, Metastatic (First-line therapy); Preferred intervention

**Reference:** NCCN Guidelines® - NCCN-Esophageal and Esophagogastric Junction Cancers [Version 3.2022]

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### trastuzumab + cisplatin + fluorouracil

**Cancer type:** Gastric Cancer

**Variant class:** ERBB2 amplification or ERBB2 overexpression

**NCCN Recommendation category:** 1

**Population segment (Line of therapy):**
- Adenocarcinoma; Unresectable, Locally Advanced, Recurrent, Metastatic (First-line therapy); Preferred intervention

**Reference:** NCCN Guidelines® - NCCN-Gastric Cancer [Version 2.2022]

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## ERBB2 amplification (continued)

### trastuzumab deruxtecan

**Cancer type:** Breast Cancer **Variant class:** ERBB2 amplification or ERBB2 overexpression

**Other criteria:** Hormone receptor status

**NCCN Recommendation category:** 1

**Population segment (Line of therapy):**
- Stage IV; Invasive, Recurrent, Unresectable, Local, Regional (Second-line therapy); Preferred intervention

**Reference:** NCCN Guidelines® - NCCN-Breast Cancer [Version 4.2022]

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### ado-trastuzumab emtansine

**Cancer type:** Breast Cancer **Variant class:** ERBB2 amplification or ERBB2 overexpression

**NCCN Recommendation category:** 2A

**Population segment (Line of therapy):**
- Invasive (Adjuvant therapy); Useful in certain circumstances

**Reference:** NCCN Guidelines® - NCCN-Breast Cancer [Version 4.2022]

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### ado-trastuzumab emtansine

**Cancer type:** Breast Cancer **Variant class:** ERBB2 amplification or ERBB2 overexpression

**Other criteria:** Hormone receptor status

**NCCN Recommendation category:** 2A

**Population segment (Line of therapy):**
- Stage IV; Invasive, Recurrent, Unresectable, Local, Regional (Second-line therapy); Other recommended intervention

**Reference:** NCCN Guidelines® - NCCN-Breast Cancer [Version 4.2022]

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### ado-trastuzumab emtansine

**Cancer type:** Head and Neck Cancer **Variant class:** ERBB2 amplification or ERBB2 overexpression

**NCCN Recommendation category:** 2A

**Population segment (Line of therapy):**
- Salivary Gland Neoplasm; Recurrent, Unresectable, Metastatic (Line of therapy not specified); Useful in certain circumstances

**Reference:** NCCN Guidelines® - NCCN-Head and Neck Cancers [Version 2.2022]

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## ERBB2 amplification (continued)

### aromatase inhibitor

**Cancer type:** Breast Cancer **Variant class:** ERBB2 amplification or ERBB2 overexpression

**Other criteria:** Hormone receptor positive

**NCCN Recommendation category:** 2A

**Population segment (Line of therapy):**
- Stage IV; Invasive, Recurrent, Unresectable, Local, Regional (Line of therapy not specified)

**Reference:** NCCN Guidelines® - NCCN-Breast Cancer [Version 4.2022]

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### fulvestrant

**Cancer type:** Breast Cancer **Variant class:** ERBB2 amplification or ERBB2 overexpression

**Other criteria:** Hormone receptor positive

**NCCN Recommendation category:** 2A

**Population segment (Line of therapy):**
- Stage IV; Invasive, Recurrent, Unresectable, Local, Regional (Line of therapy not specified)

**Reference:** NCCN Guidelines® - NCCN-Breast Cancer [Version 4.2022]

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### hormone therapy

**Cancer type:** Breast Cancer **Variant class:** ERBB2 amplification or ERBB2 overexpression

**Other criteria:** Hormone receptor positive

**NCCN Recommendation category:** 2A

**Population segment (Line of therapy):**
- Ductal, Lobular, Mixed, Micropapillary; Invasive (Adjuvant therapy)

**Reference:** NCCN Guidelines® - NCCN-Breast Cancer [Version 4.2022]

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### lapatinib + aromatase inhibitor

**Cancer type:** Breast Cancer **Variant class:** ERBB2 amplification or ERBB2 overexpression

**Other criteria:** Hormone receptor positive

**NCCN Recommendation category:** 2A

**Population segment (Line of therapy):**
- Stage IV; Invasive, Recurrent, Unresectable, Local, Regional (Line of therapy not specified)

**Reference:** NCCN Guidelines® - NCCN-Breast Cancer [Version 4.2022]

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## ERBB2 amplification (continued)

### lapatinib + capecitabine

**Cancer type:** Breast Cancer **Variant class:** ERBB2 amplification or ERBB2 overexpression

**Other criteria:** Hormone receptor status

**NCCN Recommendation category:** 2A

**Population segment (Line of therapy):**
- Stage IV; Invasive, Recurrent, Unresectable, Local, Regional (Third-line therapy, Subsequent therapy); Other recommended intervention

**Reference:** NCCN Guidelines® - NCCN-Breast Cancer [Version 4.2022]

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### lapatinib + capecitabine

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

**NCCN Recommendation category:** 2A

**Population segment (Line of therapy):**
- Brain Metastases (Line of therapy not specified)

**Reference:** NCCN Guidelines® - NCCN-Central Nervous System Cancers [Version 1.2022]

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### lapatinib + trastuzumab

**Cancer type:** Breast Cancer **Variant class:** ERBB2 amplification or ERBB2 overexpression

**Other criteria:** Hormone receptor status

**NCCN Recommendation category:** 2A

**Population segment (Line of therapy):**
- Stage IV; Invasive, Recurrent, Unresectable, Local, Regional (Third-line therapy, Subsequent therapy); Other recommended intervention

**Reference:** NCCN Guidelines® - NCCN-Breast Cancer [Version 4.2022]

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### lapatinib + trastuzumab

**Cancer type:** Colon Cancer **Variant class:** ERBB2 amplification or ERBB2 overexpression

**Other criteria:** BRAF wild type, RAS wild type

**NCCN Recommendation category:** 2A

**Population segment (Line of therapy):**
- Advanced, Metastatic (First-line therapy)
- Advanced, Metastatic, Progression (Subsequent therapy)

**Reference:** NCCN Guidelines® - NCCN-Colon Cancer [Version 1.2022]

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## ERBB2 amplification (continued)

### lapatinib + trastuzumab

**Cancer type:** Rectal Cancer **Variant class:** ERBB2 amplification or ERBB2 overexpression

**Other criteria:** BRAF wild type, RAS wild type

**NCCN Recommendation category:** 2A

**Population segment (Line of therapy):**
- Advanced, Metastatic (First-line therapy)
- Advanced, Metastatic, Progression (Subsequent therapy)

**Reference:** NCCN Guidelines® - NCCN-Rectal Cancer [Version 1.2022]

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### lapatinib + trastuzumab + aromatase inhibitor

**Cancer type:** Breast Cancer **Variant class:** ERBB2 amplification or ERBB2 overexpression

**Other criteria:** Hormone receptor positive

**NCCN Recommendation category:** 2A

**Population segment (Line of therapy):**
- Stage IV; Invasive, Recurrent, Unresectable, Local, Regional (Line of therapy not specified)

**Reference:** NCCN Guidelines® - NCCN-Breast Cancer [Version 4.2022]

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### margetuximab + capecitabine

**Cancer type:** Breast Cancer **Variant class:** ERBB2 amplification or ERBB2 overexpression

**Other criteria:** Hormone receptor status

**NCCN Recommendation category:** 2A

**Population segment (Line of therapy):**
- Stage IV; Invasive, Recurrent, Unresectable, Local, Regional (Third-line therapy, Subsequent therapy); Other recommended intervention

**Reference:** NCCN Guidelines® - NCCN-Breast Cancer [Version 4.2022]

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### margetuximab + eribulin

**Cancer type:** Breast Cancer **Variant class:** ERBB2 amplification or ERBB2 overexpression

**Other criteria:** Hormone receptor status

**NCCN Recommendation category:** 2A

**Population segment (Line of therapy):**
- Stage IV; Invasive, Recurrent, Unresectable, Local, Regional (Third-line therapy, Subsequent therapy); Other recommended intervention

**Reference:** NCCN Guidelines® - NCCN-Breast Cancer [Version 4.2022]

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## ERBB2 amplification (continued)

### margetuximab + gemcitabine

**Cancer type:** Breast Cancer **Variant class:** ERBB2 amplification or ERBB2 overexpression

**Other criteria:** Hormone receptor status

**NCCN Recommendation category:** 2A

**Population segment (Line of therapy):**
- Stage IV; Invasive, Recurrent, Unresectable, Local, Regional (Third-line therapy, Subsequent therapy); Other recommended intervention

**Reference:** NCCN Guidelines® - NCCN-Breast Cancer [Version 4.2022]

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### margetuximab + vinorelbine

**Cancer type:** Breast Cancer **Variant class:** ERBB2 amplification or ERBB2 overexpression

**Other criteria:** Hormone receptor status

**NCCN Recommendation category:** 2A

**Population segment (Line of therapy):**
- Stage IV; Invasive, Recurrent, Unresectable, Local, Regional (Third-line therapy, Subsequent therapy); Other recommended intervention

**Reference:** NCCN Guidelines® - NCCN-Breast Cancer [Version 4.2022]

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### neratinib

**Cancer type:** Breast Cancer **Variant class:** ERBB2 amplification or ERBB2 overexpression

**Other criteria:** Hormone receptor positive

**NCCN Recommendation category:** 2A

**Population segment (Line of therapy):**
- Ductal, Lobular, Mixed, Micropapillary; Invasive (Adjuvant therapy); Consider

**Reference:** NCCN Guidelines® - NCCN-Breast Cancer [Version 4.2022]

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### neratinib

**Cancer type:** Breast Cancer **Variant class:** ERBB2 amplification or ERBB2 overexpression

**NCCN Recommendation category:** 2A

**Population segment (Line of therapy):**
- Invasive (Adjuvant therapy); Useful in certain circumstances

**Reference:** NCCN Guidelines® - NCCN-Breast Cancer [Version 4.2022]

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## ERBB2 amplification (continued)

### neratinib + capecitabine

**Cancer type:** Breast Cancer

**Variant class:** ERBB2 amplification or ERBB2 overexpression

**Other criteria:** Hormone receptor status

**NCCN Recommendation category:** 2A

**Population segment (Line of therapy):**
- Stage IV; Invasive, Recurrent, Unresectable, Local, Regional (Third-line therapy, Subsequent therapy); Other recommended intervention

**Reference:** NCCN Guidelines® - NCCN-Breast Cancer [Version 4.2022]

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### neratinib + capecitabine

**Cancer type:** Breast Cancer

**Variant class:** ERBB2 amplification or ERBB2 overexpression

**NCCN Recommendation category:** 2A

**Population segment (Line of therapy):**
- Brain Metastases (Line of therapy not specified)

**Reference:** NCCN Guidelines® - NCCN-Central Nervous System Cancers [Version 1.2022]

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### pembrolizumab + trastuzumab + capecitabine + cisplatin

**Cancer type:** Esophageal Cancer, Gastroesophageal Junction Adenocarcinoma

**Variant class:** ERBB2 amplification or ERBB2 overexpression

**NCCN Recommendation category:** 2A

**Population segment (Line of therapy):**
- Adenocarcinoma; Unresectable, Locally Advanced, Recurrent, Metastatic (First-line therapy); Other recommended intervention

**Reference:** NCCN Guidelines® - NCCN-Esophageal and Esophagogastric Junction Cancers [Version 3.2022]

---

### pembrolizumab + trastuzumab + capecitabine + cisplatin

**Cancer type:** Gastric Cancer

**Variant class:** ERBB2 amplification or ERBB2 overexpression

**NCCN Recommendation category:** 2A

**Population segment (Line of therapy):**
- Adenocarcinoma; Unresectable, Locally Advanced, Recurrent, Metastatic (First-line therapy); Other recommended intervention

**Reference:** NCCN Guidelines® - NCCN-Gastric Cancer [Version 2.2022]

---

## ERBB2 amplification (continued)

### pembrolizumab + trastuzumab + capecitabine + oxaliplatin

**Cancer type:** Esophageal Cancer, Gastroesophageal Junction Adenocarcinoma

**Variant class:** ERBB2 amplification or ERBB2 overexpression

**NCCN Recommendation category:** 2A

**Population segment (Line of therapy):**
- Adenocarcinoma; Unresectable, Locally Advanced, Recurrent, Metastatic (First-line therapy); Other recommended intervention

**Reference:** NCCN Guidelines® - NCCN-Esophageal and Esophagogastric Junction Cancers [Version 3.2022]

---

### pembrolizumab + trastuzumab + capecitabine + oxaliplatin

**Cancer type:** Gastric Cancer

**Variant class:** ERBB2 amplification or ERBB2 overexpression

**NCCN Recommendation category:** 2A

**Population segment (Line of therapy):**
- Adenocarcinoma; Unresectable, Locally Advanced, Recurrent, Metastatic (First-line therapy); Other recommended intervention

**Reference:** NCCN Guidelines® - NCCN-Gastric Cancer [Version 2.2022]

---

### pembrolizumab + trastuzumab + cisplatin + fluorouracil

**Cancer type:** Esophageal Cancer, Gastroesophageal Junction Adenocarcinoma

**Variant class:** ERBB2 amplification or ERBB2 overexpression

**NCCN Recommendation category:** 2A

**Population segment (Line of therapy):**
- Adenocarcinoma; Unresectable, Locally Advanced, Recurrent, Metastatic (First-line therapy); Other recommended intervention

**Reference:** NCCN Guidelines® - NCCN-Esophageal and Esophagogastric Junction Cancers [Version 3.2022]

---

### pembrolizumab + trastuzumab + cisplatin + fluorouracil

**Cancer type:** Gastric Cancer

**Variant class:** ERBB2 amplification or ERBB2 overexpression

**NCCN Recommendation category:** 2A

**Population segment (Line of therapy):**
- Adenocarcinoma; Unresectable, Locally Advanced, Recurrent, Metastatic (First-line therapy); Other recommended intervention

**Reference:** NCCN Guidelines® - NCCN-Gastric Cancer [Version 2.2022]

---

## ERBB2 amplification (continued)

### pembrolizumab + trastuzumab + fluorouracil + oxaliplatin

**Cancer type:** Esophageal Cancer, Gastroesophageal Junction Adenocarcinoma

**Variant class:** ERBB2 amplification or ERBB2 overexpression

**NCCN Recommendation category:** 2A

**Population segment (Line of therapy):**
- Adenocarcinoma; Unresectable, Locally Advanced, Recurrent, Metastatic (First-line therapy); Other recommended intervention

**Reference:** NCCN Guidelines® - NCCN-Esophageal and Esophagogastric Junction Cancers [Version 3.2022]

---

### pembrolizumab + trastuzumab + fluorouracil + oxaliplatin

**Cancer type:** Gastric Cancer

**Variant class:** ERBB2 amplification or ERBB2 overexpression

**NCCN Recommendation category:** 2A

**Population segment (Line of therapy):**
- Adenocarcinoma; Unresectable, Locally Advanced, Recurrent, Metastatic (First-line therapy); Other recommended intervention

**Reference:** NCCN Guidelines® - NCCN-Gastric Cancer [Version 2.2022]

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### pertuzumab + trastuzumab

**Cancer type:** Colon Cancer

**Variant class:** ERBB2 amplification or ERBB2 overexpression

**Other criteria:** BRAF wild type, RAS wild type

**NCCN Recommendation category:** 2A

**Population segment (Line of therapy):**
- Advanced, Metastatic (First-line therapy)
- Advanced, Metastatic, Progression (Subsequent therapy)

**Reference:** NCCN Guidelines® - NCCN-Colon Cancer [Version 1.2022]

---

### pertuzumab + trastuzumab

**Cancer type:** Head and Neck Cancer

**Variant class:** ERBB2 amplification or ERBB2 overexpression

**NCCN Recommendation category:** 2A

**Population segment (Line of therapy):**
- Salivary Gland Neoplasm; Recurrent, Unresectable, Metastatic (Line of therapy not specified); Useful in certain circumstances

**Reference:** NCCN Guidelines® - NCCN-Head and Neck Cancers [Version 2.2022]

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## ERBB2 amplification (continued)

### pertuzumab + trastuzumab

**Cancer type:** Extrahepatic Cholangiocarcinoma, Gallbladder Carcinoma, Intrahepatic Cholangiocarcinoma

**Variant class:** ERBB2 amplification

**NCCN Recommendation category:** 2A

**Population segment (Line of therapy):**
- Unresectable, Metastatic, Progression (Subsequent therapy); Useful in certain circumstances

**Reference:** NCCN Guidelines® - NCCN-Hepatobiliary Cancers [Version 2.2022]

---

### pertuzumab + trastuzumab

**Cancer type:** Rectal Cancer

**Variant class:** ERBB2 amplification or ERBB2 overexpression

**Other criteria:** BRAF wild type, RAS wild type

**NCCN Recommendation category:** 2A

**Population segment (Line of therapy):**
- Advanced, Metastatic (First-line therapy)
- Advanced, Metastatic, Progression (Subsequent therapy)

**Reference:** NCCN Guidelines® - NCCN-Rectal Cancer [Version 1.2022]

---

### pertuzumab + trastuzumab + carboplatin + docetaxel

**Cancer type:** Breast Cancer

**Variant class:** ERBB2 amplification or ERBB2 overexpression

**NCCN Recommendation category:** 2A

**Population segment (Line of therapy):**
- Stage IV; Recurrent, Invasive (Adjuvant therapy); Preferred intervention

**Reference:** NCCN Guidelines® - NCCN-Breast Cancer [Version 4.2022]

---

### pertuzumab + trastuzumab + chemotherapy

**Cancer type:** Breast Cancer

**Variant class:** ERBB2 amplification or ERBB2 overexpression

**Other criteria:** Hormone receptor negative

**NCCN Recommendation category:** 2A

**Population segment (Line of therapy):**
- Ductal, Lobular, Mixed, Micropapillary; Invasive (Adjuvant therapy)

**Reference:** NCCN Guidelines® - NCCN-Breast Cancer [Version 4.2022]

---

## ERBB2 amplification (continued)

### pertuzumab + trastuzumab + hormone therapy + chemotherapy

**Cancer type:** Breast Cancer **Variant class:** ERBB2 amplification or ERBB2 overexpression

**Other criteria:** Hormone receptor positive

**NCCN Recommendation category:** 2A

**Population segment (Line of therapy):**
- Ductal, Lobular, Mixed, Micropapillary; Invasive (Adjuvant therapy)

**Reference:** NCCN Guidelines® - NCCN-Breast Cancer [Version 4.2022]

---

### pertuzumab + trastuzumab + paclitaxel

**Cancer type:** Breast Cancer **Variant class:** ERBB2 amplification or ERBB2 overexpression

**NCCN Recommendation category:** 2A

**Population segment (Line of therapy):**
- Invasive (Adjuvant therapy); Useful in certain circumstances

**Reference:** NCCN Guidelines® - NCCN-Breast Cancer [Version 4.2022]

---

### pertuzumab + trastuzumab + paclitaxel

**Cancer type:** Breast Cancer **Variant class:** ERBB2 amplification or ERBB2 overexpression

**Other criteria:** Hormone receptor status

**NCCN Recommendation category:** 2A

**Population segment (Line of therapy):**
- Stage IV; Invasive, Recurrent, Unresectable, Local, Regional (First-line therapy); Preferred intervention

**Reference:** NCCN Guidelines® - NCCN-Breast Cancer [Version 4.2022]

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### tamoxifen

**Cancer type:** Breast Cancer **Variant class:** ERBB2 amplification or ERBB2 overexpression

**Other criteria:** Hormone receptor positive

**NCCN Recommendation category:** 2A

**Population segment (Line of therapy):**
- Stage IV; Invasive, Recurrent, Unresectable, Local, Regional (Line of therapy not specified)

**Reference:** NCCN Guidelines® - NCCN-Breast Cancer [Version 4.2022]

---

## ERBB2 amplification (continued)

### trastuzumab

**Cancer type:** Head and Neck Cancer

**Variant class:** ERBB2 amplification or ERBB2 overexpression

**NCCN Recommendation category:** 2A

**Population segment (Line of therapy):**
- Salivary Gland Neoplasm; Recurrent, Unresectable, Metastatic (Line of therapy not specified); Useful in certain circumstances

**Reference:** NCCN Guidelines® - NCCN-Head and Neck Cancers [Version 2.2022]

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### trastuzumab + aromatase inhibitor

**Cancer type:** Breast Cancer

**Variant class:** ERBB2 amplification or ERBB2 overexpression

**Other criteria:** Hormone receptor positive

**NCCN Recommendation category:** 2A

**Population segment (Line of therapy):**
- Stage IV; Invasive, Recurrent, Unresectable, Local, Regional (Line of therapy not specified)

**Reference:** NCCN Guidelines® - NCCN-Breast Cancer [Version 4.2022]

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### trastuzumab + capecitabine

**Cancer type:** Breast Cancer

**Variant class:** ERBB2 amplification or ERBB2 overexpression

**Other criteria:** Hormone receptor status

**NCCN Recommendation category:** 2A

**Population segment (Line of therapy):**
- Stage IV; Invasive, Recurrent, Unresectable, Local, Regional (Third-line therapy, Subsequent therapy); Other recommended intervention

**Reference:** NCCN Guidelines® - NCCN-Breast Cancer [Version 4.2022]

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### trastuzumab + capecitabine

**Cancer type:** Esophageal Cancer, Gastroesophageal Junction Adenocarcinoma

**Variant class:** ERBB2 amplification or ERBB2 overexpression

**NCCN Recommendation category:** 2A

**Population segment (Line of therapy):**
- Adenocarcinoma; Unresectable, Locally Advanced, Recurrent, Metastatic (First-line therapy); Other recommended intervention

**Reference:** NCCN Guidelines® - NCCN-Esophageal and Esophagogastric Junction Cancers [Version 3.2022]

---

## ERBB2 amplification (continued)

### trastuzumab + capecitabine

**Cancer type:** Gastric Cancer

**Variant class:** ERBB2 amplification or ERBB2 overexpression

**NCCN Recommendation category:** 2A

**Population segment (Line of therapy):**
- Adenocarcinoma; Unresectable, Locally Advanced, Recurrent, Metastatic (First-line therapy); Other recommended intervention

**Reference:** NCCN Guidelines® - NCCN-Gastric Cancer [Version 2.2022]

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### trastuzumab + capecitabine + oxaliplatin

**Cancer type:** Esophageal Cancer, Gastroesophageal Junction Adenocarcinoma

**Variant class:** ERBB2 amplification or ERBB2 overexpression

**NCCN Recommendation category:** 2A

**Population segment (Line of therapy):**
- Adenocarcinoma; Unresectable, Locally Advanced, Recurrent, Metastatic (First-line therapy); Preferred intervention

**Reference:** NCCN Guidelines® - NCCN-Esophageal and Esophagogastric Junction Cancers [Version 3.2022]

---

### trastuzumab + capecitabine + oxaliplatin

**Cancer type:** Gastric Cancer

**Variant class:** ERBB2 amplification or ERBB2 overexpression

**NCCN Recommendation category:** 2A

**Population segment (Line of therapy):**
- Adenocarcinoma; Unresectable, Locally Advanced, Recurrent, Metastatic (First-line therapy); Preferred intervention

**Reference:** NCCN Guidelines® - NCCN-Gastric Cancer [Version 2.2022]

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### trastuzumab + carboplatin + docetaxel

**Cancer type:** Breast Cancer

**Variant class:** ERBB2 amplification or ERBB2 overexpression

**NCCN Recommendation category:** 2A

**Population segment (Line of therapy):**
- Stage IV; Recurrent, Invasive (Adjuvant therapy); Preferred intervention

**Reference:** NCCN Guidelines® - NCCN-Breast Cancer [Version 4.2022]

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## ERBB2 amplification (continued)

### trastuzumab + carboplatin + paclitaxel

**Cancer type:** Breast Cancer **Variant class:** ERBB2 amplification or ERBB2 overexpression

**Other criteria:** Hormone receptor status

**NCCN Recommendation category:** 2A

**Population segment (Line of therapy):**
- Stage IV; Invasive, Recurrent, Unresectable, Local, Regional (Third-line therapy, Subsequent therapy); Other recommended intervention

**Reference:** NCCN Guidelines® - NCCN-Breast Cancer [Version 4.2022]

---

### trastuzumab + carboplatin + paclitaxel

**Cancer type:** Esophageal Cancer, Gastroesophageal Junction Adenocarcinoma **Variant class:** ERBB2 amplification or ERBB2 overexpression

**NCCN Recommendation category:** 2A

**Population segment (Line of therapy):**
- Adenocarcinoma; Unresectable, Locally Advanced, Recurrent, Metastatic (First-line therapy); Other recommended intervention

**Reference:** NCCN Guidelines® - NCCN-Esophageal and Esophagogastric Junction Cancers [Version 3.2022]

---

### trastuzumab + carboplatin + paclitaxel

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

**NCCN Recommendation category:** 2A

**Population segment (Line of therapy):**
- Adenocarcinoma; Unresectable, Locally Advanced, Recurrent, Metastatic (First-line therapy); Other recommended intervention

**Reference:** NCCN Guidelines® - NCCN-Gastric Cancer [Version 2.2022]

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### trastuzumab + carboplatin + paclitaxel

**Cancer type:** Endometrial Serous Adenocarcinoma **Variant class:** ERBB2 overexpression

**NCCN Recommendation category:** 2A

**Population segment (Line of therapy):**
- Stage III/IV; Recurrent (Line of therapy not specified); Preferred intervention

**Reference:** NCCN Guidelines® - NCCN-Uterine Neoplasms [Version 1.2022]

---

## ERBB2 amplification (continued)

### trastuzumab + chemotherapy

**Cancer type:** Breast Cancer

**Variant class:** ERBB2 amplification or ERBB2 overexpression

**Other criteria:** Hormone receptor negative

**NCCN Recommendation category:** 2A

**Population segment (Line of therapy):**
- Ductal, Lobular, Mixed, Micropapillary; Invasive (Adjuvant therapy); Consider

**Reference:** NCCN Guidelines® - NCCN-Breast Cancer [Version 4.2022]

---

### trastuzumab + chemotherapy (other)

**Cancer type:** Breast Cancer

**Variant class:** ERBB2 amplification or ERBB2 overexpression

**Other criteria:** Hormone receptor status

**NCCN Recommendation category:** 2A

**Population segment (Line of therapy):**
- Stage IV; Invasive, Recurrent, Unresectable, Local, Regional (Third-line therapy, Subsequent therapy); Other recommended intervention

**Reference:** NCCN Guidelines® - NCCN-Breast Cancer [Version 4.2022]

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### trastuzumab + cisplatin + docetaxel

**Cancer type:** Esophageal Cancer, Gastroesophageal Junction Adenocarcinoma

**Variant class:** ERBB2 amplification or ERBB2 overexpression

**NCCN Recommendation category:** 2A

**Population segment (Line of therapy):**
- Adenocarcinoma; Unresectable, Locally Advanced, Recurrent, Metastatic (First-line therapy); Other recommended intervention

**Reference:** NCCN Guidelines® - NCCN-Esophageal and Esophagogastric Junction Cancers [Version 3.2022]

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### trastuzumab + cisplatin + docetaxel

**Cancer type:** Gastric Cancer

**Variant class:** ERBB2 amplification or ERBB2 overexpression

**NCCN Recommendation category:** 2A

**Population segment (Line of therapy):**
- Adenocarcinoma; Unresectable, Locally Advanced, Recurrent, Metastatic (First-line therapy); Other recommended intervention

**Reference:** NCCN Guidelines® - NCCN-Gastric Cancer [Version 2.2022]

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## ERBB2 amplification (continued)

### trastuzumab + cisplatin + docetaxel + fluorouracil

**Cancer type:** Esophageal Cancer, Gastroesophageal Junction Adenocarcinoma

**Variant class:** ERBB2 amplification or ERBB2 overexpression

**NCCN Recommendation category:** 2A

**Population segment (Line of therapy):**
- Adenocarcinoma; Unresectable, Locally Advanced, Recurrent, Metastatic (First-line therapy); Other recommended intervention

**Reference:** NCCN Guidelines® - NCCN-Esophageal and Esophagogastric Junction Cancers [Version 3.2022]

---

### trastuzumab + cisplatin + docetaxel + fluorouracil

**Cancer type:** Gastric Cancer

**Variant class:** ERBB2 amplification or ERBB2 overexpression

**NCCN Recommendation category:** 2A

**Population segment (Line of therapy):**
- Adenocarcinoma; Unresectable, Locally Advanced, Recurrent, Metastatic (First-line therapy); Other recommended intervention

**Reference:** NCCN Guidelines® - NCCN-Gastric Cancer [Version 2.2022]

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### trastuzumab + cisplatin + paclitaxel

**Cancer type:** Esophageal Cancer, Gastroesophageal Junction Adenocarcinoma

**Variant class:** ERBB2 amplification or ERBB2 overexpression

**NCCN Recommendation category:** 2A

**Population segment (Line of therapy):**
- Adenocarcinoma; Unresectable, Locally Advanced, Recurrent, Metastatic (First-line therapy); Other recommended intervention

**Reference:** NCCN Guidelines® - NCCN-Esophageal and Esophagogastric Junction Cancers [Version 3.2022]

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### trastuzumab + cisplatin + paclitaxel

**Cancer type:** Gastric Cancer

**Variant class:** ERBB2 amplification or ERBB2 overexpression

**NCCN Recommendation category:** 2A

**Population segment (Line of therapy):**
- Adenocarcinoma; Unresectable, Locally Advanced, Recurrent, Metastatic (First-line therapy); Other recommended intervention

**Reference:** NCCN Guidelines® - NCCN-Gastric Cancer [Version 2.2022]

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## ERBB2 amplification (continued)

### trastuzumab + cyclophosphamide + docetaxel

**Cancer type:** Breast Cancer

**Variant class:** ERBB2 amplification or ERBB2 overexpression

**NCCN Recommendation category:** 2A

**Population segment (Line of therapy):**
- Stage IV; Recurrent, Invasive (Adjuvant therapy); Useful in certain circumstances

**Reference:** NCCN Guidelines® - NCCN-Breast Cancer [Version 4.2022]

---

### trastuzumab + docetaxel

**Cancer type:** Breast Cancer

**Variant class:** ERBB2 amplification or ERBB2 overexpression

**Other criteria:** Hormone receptor status

**NCCN Recommendation category:** 2A

**Population segment (Line of therapy):**
- Stage IV; Invasive, Recurrent, Unresectable, Local, Regional (Third-line therapy, Subsequent therapy); Other recommended intervention

**Reference:** NCCN Guidelines® - NCCN-Breast Cancer [Version 4.2022]

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### trastuzumab + docetaxel

**Cancer type:** Esophageal Cancer, Gastroesophageal Junction Adenocarcinoma

**Variant class:** ERBB2 amplification or ERBB2 overexpression

**NCCN Recommendation category:** 2A

**Population segment (Line of therapy):**
- Adenocarcinoma; Unresectable, Locally Advanced, Recurrent, Metastatic (First-line therapy); Other recommended intervention

**Reference:** NCCN Guidelines® - NCCN-Esophageal and Esophagogastric Junction Cancers [Version 3.2022]

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### trastuzumab + docetaxel

**Cancer type:** Gastric Cancer

**Variant class:** ERBB2 amplification or ERBB2 overexpression

**NCCN Recommendation category:** 2A

**Population segment (Line of therapy):**
- Adenocarcinoma; Unresectable, Locally Advanced, Recurrent, Metastatic (First-line therapy); Other recommended intervention

**Reference:** NCCN Guidelines® - NCCN-Gastric Cancer [Version 2.2022]

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## ERBB2 amplification (continued)

### trastuzumab + docetaxel

**Cancer type:** Head and Neck Cancer

**Variant class:** ERBB2 amplification or ERBB2 overexpression

**NCCN Recommendation category:** 2A

**Population segment (Line of therapy):**
- Salivary Gland Neoplasm; Recurrent, Unresectable, Metastatic (Line of therapy not specified); Useful in certain circumstances

**Reference:** NCCN Guidelines® - NCCN-Head and Neck Cancers [Version 2.2022]

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### trastuzumab + docetaxel + fluorouracil + oxaliplatin

**Cancer type:** Esophageal Cancer, Gastroesophageal Junction Adenocarcinoma

**Variant class:** ERBB2 amplification or ERBB2 overexpression

**NCCN Recommendation category:** 2A

**Population segment (Line of therapy):**
- Adenocarcinoma; Unresectable, Locally Advanced, Recurrent, Metastatic (First-line therapy); Other recommended intervention

**Reference:** NCCN Guidelines® - NCCN-Esophageal and Esophagogastric Junction Cancers [Version 3.2022]

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### trastuzumab + docetaxel + fluorouracil + oxaliplatin

**Cancer type:** Gastric Cancer

**Variant class:** ERBB2 amplification or ERBB2 overexpression

**NCCN Recommendation category:** 2A

**Population segment (Line of therapy):**
- Adenocarcinoma; Unresectable, Locally Advanced, Recurrent, Metastatic (First-line therapy); Other recommended intervention

**Reference:** NCCN Guidelines® - NCCN-Gastric Cancer [Version 2.2022]

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### trastuzumab + fluorouracil

**Cancer type:** Esophageal Cancer, Gastroesophageal Junction Adenocarcinoma

**Variant class:** ERBB2 amplification or ERBB2 overexpression

**NCCN Recommendation category:** 2A

**Population segment (Line of therapy):**
- Adenocarcinoma; Unresectable, Locally Advanced, Recurrent, Metastatic (First-line therapy); Other recommended intervention

**Reference:** NCCN Guidelines® - NCCN-Esophageal and Esophagogastric Junction Cancers [Version 3.2022]

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## ERBB2 amplification (continued)

### trastuzumab + fluorouracil

**Cancer type:** Gastric Cancer

**Variant class:** ERBB2 amplification or ERBB2 overexpression

**NCCN Recommendation category:** 2A

**Population segment (Line of therapy):**
- Adenocarcinoma; Unresectable, Locally Advanced, Recurrent, Metastatic (First-line therapy); Other recommended intervention

**Reference:** NCCN Guidelines® - NCCN-Gastric Cancer [Version 2.2022]

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### trastuzumab + fluorouracil + irinotecan

**Cancer type:** Esophageal Cancer, Gastroesophageal Junction Adenocarcinoma

**Variant class:** ERBB2 amplification or ERBB2 overexpression

**NCCN Recommendation category:** 2A

**Population segment (Line of therapy):**
- Adenocarcinoma; Unresectable, Locally Advanced, Recurrent, Metastatic (First-line therapy); Other recommended intervention

**Reference:** NCCN Guidelines® - NCCN-Esophageal and Esophagogastric Junction Cancers [Version 3.2022]

---

### trastuzumab + fluorouracil + irinotecan

**Cancer type:** Gastric Cancer

**Variant class:** ERBB2 amplification or ERBB2 overexpression

**NCCN Recommendation category:** 2A

**Population segment (Line of therapy):**
- Adenocarcinoma; Unresectable, Locally Advanced, Recurrent, Metastatic (First-line therapy); Other recommended intervention

**Reference:** NCCN Guidelines® - NCCN-Gastric Cancer [Version 2.2022]

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### trastuzumab + fluorouracil + oxaliplatin

**Cancer type:** Esophageal Cancer, Gastroesophageal Junction Adenocarcinoma

**Variant class:** ERBB2 amplification or ERBB2 overexpression

**NCCN Recommendation category:** 2A

**Population segment (Line of therapy):**
- Adenocarcinoma; Unresectable, Locally Advanced, Recurrent, Metastatic (First-line therapy); Preferred intervention

**Reference:** NCCN Guidelines® - NCCN-Esophageal and Esophagogastric Junction Cancers [Version 3.2022]

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## ERBB2 amplification (continued)

### trastuzumab + fluorouracil + oxaliplatin

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

**NCCN Recommendation category:** 2A

**Population segment (Line of therapy):**
- Adenocarcinoma; Unresectable, Locally Advanced, Recurrent, Metastatic (First-line therapy); Preferred intervention

**Reference:** NCCN Guidelines® - NCCN-Gastric Cancer [Version 2.2022]

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### trastuzumab + fulvestrant

**Cancer type:** Breast Cancer **Variant class:** ERBB2 amplification or ERBB2 overexpression

**Other criteria:** Hormone receptor positive

**NCCN Recommendation category:** 2A

**Population segment (Line of therapy):**
- Stage IV; Invasive, Recurrent, Unresectable, Local, Regional (Line of therapy not specified)

**Reference:** NCCN Guidelines® - NCCN-Breast Cancer [Version 4.2022]

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### trastuzumab + hormone therapy + chemotherapy

**Cancer type:** Breast Cancer **Variant class:** ERBB2 amplification or ERBB2 overexpression

**Other criteria:** Hormone receptor positive

**NCCN Recommendation category:** 2A

**Population segment (Line of therapy):**
- Ductal, Lobular, Mixed, Micropapillary; Invasive (Adjuvant therapy)

**Reference:** NCCN Guidelines® - NCCN-Breast Cancer [Version 4.2022]

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### trastuzumab + paclitaxel

**Cancer type:** Breast Cancer **Variant class:** ERBB2 amplification or ERBB2 overexpression

**NCCN Recommendation category:** 2A

**Population segment (Line of therapy):**
- Invasive (Adjuvant therapy); Consider

**Reference:** NCCN Guidelines® - NCCN-Breast Cancer [Version 4.2022]

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## ERBB2 amplification (continued)

### trastuzumab + paclitaxel

**Cancer type:** Breast Cancer

**Variant class:** ERBB2 amplification or ERBB2 overexpression

**Other criteria:** Hormone receptor status

**NCCN Recommendation category:** 2A

**Population segment (Line of therapy):**
- Stage IV; Invasive, Recurrent, Unresectable, Local, Regional (Third-line therapy, Subsequent therapy); Other recommended intervention

**Reference:** NCCN Guidelines® - NCCN-Breast Cancer [Version 4.2022]

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### trastuzumab + paclitaxel

**Cancer type:** Breast Cancer

**Variant class:** ERBB2 amplification or ERBB2 overexpression

**NCCN Recommendation category:** 2A

**Population segment (Line of therapy):**
- Stage IV; Recurrent, Invasive (Adjuvant therapy); Preferred intervention

**Reference:** NCCN Guidelines® - NCCN-Breast Cancer [Version 4.2022]

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### trastuzumab + paclitaxel

**Cancer type:** Esophageal Cancer, Gastroesophageal Junction Adenocarcinoma

**Variant class:** ERBB2 amplification or ERBB2 overexpression

**NCCN Recommendation category:** 2A

**Population segment (Line of therapy):**
- Adenocarcinoma; Unresectable, Locally Advanced, Recurrent, Metastatic (First-line therapy); Other recommended intervention

**Reference:** NCCN Guidelines® - NCCN-Esophageal and Esophagogastric Junction Cancers [Version 3.2022]

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### trastuzumab + paclitaxel

**Cancer type:** Gastric Cancer

**Variant class:** ERBB2 amplification or ERBB2 overexpression

**NCCN Recommendation category:** 2A

**Population segment (Line of therapy):**
- Adenocarcinoma; Unresectable, Locally Advanced, Recurrent, Metastatic (First-line therapy); Other recommended intervention

**Reference:** NCCN Guidelines® - NCCN-Gastric Cancer [Version 2.2022]

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## ERBB2 amplification (continued)

### trastuzumab + tamoxifen

**Cancer type:** Breast Cancer

**Variant class:** ERBB2 amplification or ERBB2 overexpression

**Other criteria:** Hormone receptor positive

**NCCN Recommendation category:** 2A

**Population segment (Line of therapy):**
- Stage IV; Invasive, Recurrent, Unresectable, Local, Regional (Line of therapy not specified)

**Reference:** NCCN Guidelines® - NCCN-Breast Cancer [Version 4.2022]

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### trastuzumab + vinorelbine

**Cancer type:** Breast Cancer

**Variant class:** ERBB2 amplification or ERBB2 overexpression

**Other criteria:** Hormone receptor status

**NCCN Recommendation category:** 2A

**Population segment (Line of therapy):**
- Stage IV; Invasive, Recurrent, Unresectable, Local, Regional (Third-line therapy, Subsequent therapy); Other recommended intervention

**Reference:** NCCN Guidelines® - NCCN-Breast Cancer [Version 4.2022]

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### trastuzumab deruxtecan

**Cancer type:** Colon Cancer

**Variant class:** ERBB2 amplification or ERBB2 overexpression

**Other criteria:** BRAF wild type, RAS wild type

**NCCN Recommendation category:** 2A

**Population segment (Line of therapy):**
- Advanced, Metastatic, Progression (Subsequent therapy)

**Reference:** NCCN Guidelines® - NCCN-Colon Cancer [Version 1.2022]

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### trastuzumab deruxtecan

**Cancer type:** Esophageal Cancer, Gastroesophageal Junction Adenocarcinoma

**Variant class:** ERBB2 amplification or ERBB2 overexpression

**NCCN Recommendation category:** 2A

**Population segment (Line of therapy):**
- Adenocarcinoma; Unresectable, Locally Advanced, Recurrent, Metastatic (Second-line therapy, Subsequent therapy); Preferred intervention

**Reference:** NCCN Guidelines® - NCCN-Esophageal and Esophagogastric Junction Cancers [Version 3.2022]

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## ERBB2 amplification (continued)

### trastuzumab deruxtecan

**Cancer type:** Gastric Cancer

**Variant class:** ERBB2 amplification or ERBB2 overexpression

**NCCN Recommendation category:** 2A

**Population segment (Line of therapy):**
- Adenocarcinoma; Unresectable, Locally Advanced, Recurrent, Metastatic (Second-line therapy, Subsequent therapy); Preferred intervention

**Reference:** NCCN Guidelines® - NCCN-Gastric Cancer [Version 2.2022]

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### trastuzumab deruxtecan

**Cancer type:** Rectal Cancer

**Variant class:** ERBB2 amplification or ERBB2 overexpression

**Other criteria:** BRAF wild type, RAS wild type

**NCCN Recommendation category:** 2A

**Population segment (Line of therapy):**
- Advanced, Metastatic, Progression (Subsequent therapy)

**Reference:** NCCN Guidelines® - NCCN-Rectal Cancer [Version 1.2022]

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### hormone therapy

**Cancer type:** Breast Cancer

**Variant class:** ERBB2 amplification or ERBB2 overexpression

**Other criteria:** Hormone receptor positive

**NCCN Recommendation category:** 2B

**Population segment (Line of therapy):**
- Ductal, Lobular, Mixed, Micropapillary; Invasive (Adjuvant therapy); Consider

**Reference:** NCCN Guidelines® - NCCN-Breast Cancer [Version 4.2022]

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### trastuzumab + carboplatin + docetaxel + fluorouracil

**Cancer type:** Esophageal Cancer, Gastroesophageal Junction Adenocarcinoma

**Variant class:** ERBB2 amplification or ERBB2 overexpression

**NCCN Recommendation category:** 2B

**Population segment (Line of therapy):**
- Adenocarcinoma; Unresectable, Locally Advanced, Recurrent, Metastatic (First-line therapy); Other recommended intervention

**Reference:** NCCN Guidelines® - NCCN-Esophageal and Esophagogastric Junction Cancers [Version 3.2022]

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## ERBB2 amplification (continued)

### trastuzumab + carboplatin + docetaxel + fluorouracil

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

**NCCN Recommendation category:** 2B

**Population segment (Line of therapy):**
- Adenocarcinoma; Unresectable, Locally Advanced, Recurrent, Metastatic (First-line therapy); Other recommended intervention

**Reference:** NCCN Guidelines® - NCCN-Gastric Cancer [Version 2.2022]

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### trastuzumab + chemotherapy

**Cancer type:** Breast Cancer **Variant class:** ERBB2 amplification or ERBB2 overexpression

**Other criteria:** Hormone receptor negative

**NCCN Recommendation category:** 2B

**Population segment (Line of therapy):**
- Ductal, Lobular, Mixed, Micropapillary; Invasive (Adjuvant therapy); Consider

**Reference:** NCCN Guidelines® - NCCN-Breast Cancer [Version 4.2022]

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### trastuzumab + hormone therapy + chemotherapy

**Cancer type:** Breast Cancer **Variant class:** ERBB2 amplification or ERBB2 overexpression

**Other criteria:** Hormone receptor positive

**NCCN Recommendation category:** 2B

**Population segment (Line of therapy):**
- Ductal, Lobular, Mixed, Micropapillary; Invasive (Adjuvant therapy); Consider

**Reference:** NCCN Guidelines® - NCCN-Breast Cancer [Version 4.2022]

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### trastuzumab deruxtecan

**Cancer type:** Head and Neck Cancer **Variant class:** ERBB2 amplification or ERBB2 overexpression

**NCCN Recommendation category:** 2B

**Population segment (Line of therapy):**
- Salivary Gland Neoplasm; Recurrent, Unresectable, Metastatic (Line of therapy not specified); Useful in certain circumstances

**Reference:** NCCN Guidelines® - NCCN-Head and Neck Cancers [Version 2.2022]

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## ERBB2 amplification (continued)

### irbinitinib + trastuzumab + capecitabine

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

**NCCN Recommendation category:** 1

**Population segment (Line of therapy):**
- Brain Metastases (Subsequent therapy)

**Reference:** NCCN Guidelines® - NCCN-Central Nervous System Cancers [Version 1.2022]

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### pertuzumab + trastuzumab

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

**NCCN Recommendation category:** 2A

**Population segment (Line of therapy):**
- Brain Metastases (Line of therapy not specified)

**Reference:** NCCN Guidelines® - NCCN-Central Nervous System Cancers [Version 1.2022]

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### trastuzumab + chemotherapy

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

**NCCN Recommendation category:** 2A

**Population segment (Line of therapy):**
- Leptomeningeal Metastases, Spine Metastases (Line of therapy not specified)

**Reference:** NCCN Guidelines® - NCCN-Central Nervous System Cancers [Version 1.2022]

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### trastuzumab deruxtecan

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

**NCCN Recommendation category:** 2A

**Population segment (Line of therapy):**
- Brain Metastases (Line of therapy not specified)

**Reference:** NCCN Guidelines® - NCCN-Central Nervous System Cancers [Version 1.2022]

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### neratinib + paclitaxel

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

**NCCN Recommendation category:** 2B

**Population segment (Line of therapy):**
- Brain Metastases (Line of therapy not specified)

**Reference:** NCCN Guidelines® - NCCN-Central Nervous System Cancers [Version 1.2022]

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## Current EMA Information

● In this cancer type ○ In other cancer type ◑ In this cancer type and other cancer types

EMA information is current as of 2022-09-14. For the most up-to-date information, search www.ema.europa.eu/ema.

## EGFR exon 19 deletion

### ● bevacizumab (Allergan) + erlotinib

**Cancer type:** Non-Small Cell Lung Cancer **Label as of:** 2022-07-14 **Variant class:** EGFR exon 19 deletion

**Reference:**

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

### ● bevacizumab (Fujifilm Kyowa Kirin Biologics) + erlotinib

**Cancer type:** Non-Small Cell Lung Cancer **Label as of:** 2021-06-23 **Variant class:** EGFR exon 19 deletion

**Reference:**

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

### ● bevacizumab (Mabxience) + erlotinib

**Cancer type:** Non-Small Cell Lung Cancer **Label as of:** 2022-07-06 **Variant class:** EGFR exon 19 deletion

**Reference:**

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

### ● bevacizumab (Pfizer) + erlotinib

**Cancer type:** Non-Small Cell Lung Cancer **Label as of:** 2022-07-26 **Variant class:** EGFR exon 19 deletion

**Reference:**

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

### ● bevacizumab (Samsung Bioepis) + erlotinib

**Cancer type:** Non-Small Cell Lung Cancer **Label as of:** 2022-07-21 **Variant class:** EGFR exon 19 deletion

**Reference:**

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

### ● bevacizumab (Samsung Bioepis) + erlotinib

**Cancer type:** Non-Small Cell Lung Cancer **Label as of:** 2022-07-21 **Variant class:** EGFR exon 19 deletion

**Reference:**

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

## EGFR exon 19 deletion (continued)

### bevacizumab (Stada) + erlotinib

**Cancer type:** Non-Small Cell Lung Cancer **Label as of:** 2022-07-05 **Variant class:** EGFR exon 19 deletion

**Reference:**

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

### bevacizumab + erlotinib

**Cancer type:** Non-Small Cell Lung Cancer **Label as of:** 2022-08-25 **Variant class:** EGFR exon 19 deletion

**Reference:**

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

### bevacizumab + erlotinib

**Cancer type:** Non-Small Cell Lung Cancer **Label as of:** 2022-07-01 **Variant class:** EGFR exon 19 deletion

**Reference:**

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

### gefitinib (Mylan)

**Cancer type:** Non-Small Cell Lung Cancer **Label as of:** 2022-06-16 **Variant class:** EGFR exon 19 deletion

**Reference:**

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

### osimertinib

**Cancer type:** Non-Small Cell Lung Cancer **Label as of:** 2022-04-07 **Variant class:** EGFR exon 19 deletion

**Reference:**

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

## EGFR p.(T790M) c.2369C>T

### osimertinib

**Cancer type:** Non-Small Cell Lung Cancer **Label as of:** 2022-04-07 **Variant class:** EGFR T790M mutation

**Reference:**

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

## ERBB2 amplification

### ado-trastuzumab emtansine

**Cancer type:** Breast Cancer **Label as of:** 2022-02-14 **Variant class:** ERBB2 overexpression or ERBB2 amplification

**Reference:**

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

### irbinitinib + trastuzumab + capecitabine

**Cancer type:** Breast Cancer **Label as of:** 2022-02-14 **Variant class:** ERBB2 amplification or ERBB2 overexpression

**Reference:**

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

### lapatinib + capecitabine, lapatinib + letrozole, lapatinib + trastuzumab

**Cancer type:** Breast Cancer **Label as of:** 2022-03-07 **Variant class:** ERBB2 amplification or ERBB2 overexpression

**Other criteria:** ER positive, PR positive or Hormone receptor negative

**Reference:**

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

### neratinib

**Cancer type:** Breast Cancer **Label as of:** 2022-05-06 **Variant class:** ERBB2 amplification or ERBB2 overexpression

**Other criteria:** Hormone receptor positive

**Reference:**

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

### pertuzumab + trastuzumab + chemotherapy, pertuzumab + trastuzumab + docetaxel

**Cancer type:** Breast Cancer **Label as of:** 2021-12-09 **Variant class:** ERBB2 amplification or ERBB2 overexpression

**Reference:**

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

## ERBB2 amplification (continued)

### pertuzumab/trastuzumab/hyaluronidase-zzxf + docetaxel, pertuzumab/trastuzumab/hyaluronidase-zzxf + paclitaxel, pertuzumab/trastuzumab/hyaluronidase-zzxf + carboplatin + docetaxel, pertuzumab/trastuzumab/hyaluronidase-zzxf + cyclophosphamide + doxorubicin, pertuzumab/trastuzumab/hyaluronidase-zzxf + cyclophosphamide + epirubicin, pertuzumab/trastuzumab/hyaluronidase-zzxf + cyclophosphamide + doxorubicin + fluorouracil

**Cancer type:** Breast Cancer **Label as of:** 2022-03-02 **Variant class:** ERBB2 overexpression or ERBB2 amplification

**Reference:**

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

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### trastuzumab (Biocon), trastuzumab (Biocon) + anastrozole, trastuzumab (Biocon) + docetaxel, trastuzumab (Biocon) + paclitaxel, trastuzumab (Biocon) + capecitabine + cisplatin, trastuzumab (Biocon) + carboplatin + docetaxel, trastuzumab (Biocon) + cisplatin + fluorouracil, trastuzumab (Biocon) + CMF + doxorubicin + paclitaxel

**Cancer type:** Breast Cancer, Gastric Cancer, Gastroesophageal Junction Adenocarcinoma **Label as of:** 2022-01-12 **Variant class:** ERBB2 overexpression

**Other criteria:** ER positive, PR positive

**Reference:**

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

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### trastuzumab (Biocon), trastuzumab (Biocon) + anastrozole, trastuzumab (Biocon) + docetaxel, trastuzumab (Biocon) + paclitaxel, trastuzumab (Biocon) + carboplatin + docetaxel, trastuzumab (Biocon) + CMF + doxorubicin + paclitaxel

**Cancer type:** Breast Cancer **Label as of:** 2022-01-12 **Variant class:** ERBB2 amplification

**Other criteria:** ER positive, PR positive

**Reference:**

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

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### trastuzumab (Celltrion), trastuzumab (Celltrion) + anastrozole, trastuzumab (Celltrion) + docetaxel, trastuzumab (Celltrion) + paclitaxel, trastuzumab (Celltrion) + capecitabine + cisplatin, trastuzumab (Celltrion) + carboplatin + docetaxel, trastuzumab (Celltrion) + cisplatin + fluorouracil, trastuzumab (Celltrion) + CMF + doxorubicin + paclitaxel

**Cancer type:** Breast Cancer, Gastric Cancer, Gastroesophageal Junction Adenocarcinoma **Label as of:** 2022-04-06 **Variant class:** ERBB2 overexpression

**Other criteria:** ER positive, PR positive

**Reference:**

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

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## ERBB2 amplification (continued)

### trastuzumab (Celltrion), trastuzumab (Celltrion) + anastrozole, trastuzumab (Celltrion) + docetaxel, trastuzumab (Celltrion) + paclitaxel, trastuzumab (Celltrion) + carboplatin + docetaxel, trastuzumab (Celltrion) + CMF + doxorubicin + paclitaxel

**Cancer type:** Breast Cancer **Label as of:** 2022-04-06 **Variant class:** ERBB2 amplification

**Other criteria:** ER positive, PR positive

**Reference:**

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

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### trastuzumab (Henlius), trastuzumab (Henlius) + anastrozole, trastuzumab (Henlius) + docetaxel, trastuzumab (Henlius) + paclitaxel, trastuzumab (Henlius) + capecitabine + cisplatin, trastuzumab (Henlius) + carboplatin + docetaxel, trastuzumab (Henlius) + cisplatin + fluorouracil, trastuzumab (Henlius) + CMF + doxorubicin + paclitaxel

**Cancer type:** Breast Cancer, Gastric Cancer, Gastroesophageal Junction Adenocarcinoma **Label as of:** 2022-02-09 **Variant class:** ERBB2 overexpression

**Other criteria:** ER positive, PR positive

**Reference:**

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

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### trastuzumab (Henlius), trastuzumab (Henlius) + anastrozole, trastuzumab (Henlius) + docetaxel, trastuzumab (Henlius) + paclitaxel, trastuzumab (Henlius) + carboplatin + docetaxel, trastuzumab (Henlius) + CMF + doxorubicin + paclitaxel

**Cancer type:** Breast Cancer **Label as of:** 2022-02-09 **Variant class:** ERBB2 amplification

**Other criteria:** ER positive, PR positive

**Reference:**

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

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### trastuzumab (Pfizer), trastuzumab (Pfizer) + anastrozole, trastuzumab (Pfizer) + docetaxel, trastuzumab (Pfizer) + paclitaxel, trastuzumab (Pfizer) + capecitabine + cisplatin, trastuzumab (Pfizer) + carboplatin + docetaxel, trastuzumab (Pfizer) + cisplatin + fluorouracil, trastuzumab (Pfizer) + CMF + doxorubicin + paclitaxel

**Cancer type:** Breast Cancer, Gastric Cancer, Gastroesophageal Junction Adenocarcinoma **Label as of:** 2022-01-28 **Variant class:** ERBB2 overexpression

**Other criteria:** ER positive, PR positive

**Reference:**

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

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## ERBB2 amplification (continued)

### trastuzumab (Pfizer), trastuzumab (Pfizer) + anastrozole, trastuzumab (Pfizer) + docetaxel, trastuzumab (Pfizer) + paclitaxel, trastuzumab (Pfizer) + carboplatin + docetaxel, trastuzumab (Pfizer) + CMF + doxorubicin + paclitaxel

**Cancer type:** Breast Cancer **Label as of:** 2022-01-28 **Variant class:** ERBB2 amplification

**Other criteria:** ER positive, PR positive

**Reference:**

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

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### trastuzumab (Samsung Bioepis), trastuzumab (Samsung Bioepis) + anastrozole, trastuzumab (Samsung Bioepis) + docetaxel, trastuzumab (Samsung Bioepis) + paclitaxel, trastuzumab (Samsung Bioepis) + capecitabine + cisplatin, trastuzumab (Samsung Bioepis) + carboplatin + docetaxel, trastuzumab (Samsung Bioepis) + cisplatin + fluorouracil, trastuzumab (Samsung Bioepis) + CMF + doxorubicin + paclitaxel

**Cancer type:** Breast Cancer, Gastric Cancer, Gastroesophageal Junction Adenocarcinoma **Label as of:** 2022-07-26 **Variant class:** ERBB2 overexpression

**Other criteria:** ER positive, PR positive

**Reference:**

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

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### trastuzumab (Samsung Bioepis), trastuzumab (Samsung Bioepis) + anastrozole, trastuzumab (Samsung Bioepis) + docetaxel, trastuzumab (Samsung Bioepis) + paclitaxel, trastuzumab (Samsung Bioepis) + carboplatin + docetaxel, trastuzumab (Samsung Bioepis) + CMF + doxorubicin + paclitaxel

**Cancer type:** Breast Cancer **Label as of:** 2022-07-26 **Variant class:** ERBB2 amplification

**Other criteria:** ER positive, PR positive

**Reference:**

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

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### trastuzumab (Synthon), trastuzumab (Synthon) + anastrozole, trastuzumab (Synthon) + docetaxel, trastuzumab (Synthon) + paclitaxel, trastuzumab (Synthon) + capecitabine + cisplatin, trastuzumab (Synthon) + carboplatin + docetaxel, trastuzumab (Synthon) + cisplatin + fluorouracil, trastuzumab (Synthon) + CMF + doxorubicin + paclitaxel

**Cancer type:** Breast Cancer, Gastric Cancer, Gastroesophageal Junction Adenocarcinoma **Label as of:** 2022-01-21 **Variant class:** ERBB2 overexpression

**Other criteria:** ER positive, PR positive

**Reference:**

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

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## ERBB2 amplification (continued)

### trastuzumab (Synthon), trastuzumab (Synthon) + anastrozole, trastuzumab (Synthon) + docetaxel, trastuzumab (Synthon) + paclitaxel, trastuzumab (Synthon) + carboplatin + docetaxel, trastuzumab (Synthon) + CMF + doxorubicin + paclitaxel

**Cancer type:** Breast Cancer **Label as of:** 2022-01-21 **Variant class:** ERBB2 amplification

**Other criteria:** ER positive, PR positive

**Reference:**

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

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### trastuzumab deruxtecan

**Cancer type:** Breast Cancer **Label as of:** 2022-08-01 **Variant class:** ERBB2 overexpression or ERBB2 amplification

**Reference:**

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

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### trastuzumab, trastuzumab + anastrozole, trastuzumab + docetaxel, trastuzumab + paclitaxel, trastuzumab + capecitabine + cisplatin, trastuzumab + carboplatin + docetaxel, trastuzumab + cisplatin + fluorouracil, trastuzumab + CMF + doxorubicin + paclitaxel

**Cancer type:** Breast Cancer, Gastric Cancer, Gastroesophageal Junction Adenocarcinoma **Label as of:** 2021-09-10 **Variant class:** ERBB2 overexpression

**Other criteria:** ER positive, PR positive

**Reference:**

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

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### trastuzumab, trastuzumab + anastrozole, trastuzumab + docetaxel, trastuzumab + paclitaxel, trastuzumab + carboplatin + docetaxel, trastuzumab + CMF + doxorubicin + paclitaxel

**Cancer type:** Breast Cancer **Label as of:** 2021-09-10 **Variant class:** ERBB2 amplification

**Other criteria:** ER positive, PR positive

**Reference:**

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

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## Current ESMO Information

● In this cancer type ○ In other cancer type ◑ In this cancer type and other cancer types

ESMO information is current as of 2022-09-01. For the most up-to-date information, search www.esmo.org.

## EGFR exon 19 deletion

### ● bevacizumab + erlotinib

**Cancer type:** Non-Small Cell Lung Cancer **Variant class:** EGFR exon 19 deletion

**ESMO Level of Evidence/Grade of Recommendation:** I / A

**Population segment (Line of therapy):**
- Stage IV (First-line therapy)

**Reference:** ESMO Clinical Practice Guidelines - ESMO-Metastatic Non-Small-Cell Lung Cancer [Online Guideline (15SEP2020 - https://www.esmo.org/guidelines/lung-and-chest-tumours/clinical-practice-living-guidelines-metastatic-non-small-cell-lung-cancer); Ann Oncol (2018) 29 (suppl 4): iv192–iv237.]

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### ● bevacizumab + gefitinib

**Cancer type:** Non-Small Cell Lung Cancer **Variant class:** EGFR exon 19 deletion

**ESMO Level of Evidence/Grade of Recommendation:** I / A

**Population segment (Line of therapy):**
- Stage IV (First-line therapy)

**Reference:** ESMO Clinical Practice Guidelines - ESMO-Metastatic Non-Small-Cell Lung Cancer [Online Guideline (15SEP2020 - https://www.esmo.org/guidelines/lung-and-chest-tumours/clinical-practice-living-guidelines-metastatic-non-small-cell-lung-cancer); Ann Oncol (2018) 29 (suppl 4): iv192–iv237.]

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### ● erlotinib + ramucirumab

**Cancer type:** Non-Small Cell Lung Cancer **Variant class:** EGFR exon 19 deletion

**ESMO Level of Evidence/Grade of Recommendation:** I / A

**Population segment (Line of therapy):**
- Stage IV (First-line therapy)

**Reference:** ESMO Clinical Practice Guidelines - ESMO-Metastatic Non-Small-Cell Lung Cancer [Online Guideline (15SEP2020 - https://www.esmo.org/guidelines/lung-and-chest-tumours/clinical-practice-living-guidelines-metastatic-non-small-cell-lung-cancer); Ann Oncol (2018) 29 (suppl 4): iv192–iv237.]

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### ● gefitinib + carboplatin + pemetrexed

**Cancer type:** Non-Small Cell Lung Cancer **Variant class:** EGFR exon 19 deletion

**ESMO Level of Evidence/Grade of Recommendation:** I / A

**Population segment (Line of therapy):**
- Stage IV (First-line therapy)

**Reference:** ESMO Clinical Practice Guidelines - ESMO-Metastatic Non-Small-Cell Lung Cancer [Online Guideline (15SEP2020 - https://www.esmo.org/guidelines/lung-and-chest-tumours/clinical-practice-living-guidelines-metastatic-non-small-cell-lung-cancer); Ann Oncol (2018) 29 (suppl 4): iv192–iv237.]

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## EGFR exon 19 deletion (continued)

### osimertinib

**Cancer type:** Non-Small Cell Lung Cancer **Variant class:** EGFR exon 19 deletion

**ESMO Level of Evidence/Grade of Recommendation:** I / A

**Population segment (Line of therapy):**
- Stage IB , Stage IIA, Stage IIB, Stage IIIA; Resected (Adjuvant therapy); ESMO-MCBS v1.1 score: A

**Reference:** ESMO Clinical Practice Guidelines - ESMO-Early-Stage and Locally Advanced (non-metastatic) Non-Small-Cell Lung Cancer [Ann Oncol (2017) 28 (suppl 4): iv1–iv21. (eUpdate: 01 September 2021, 04 May 2020)]

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### bevacizumab + erlotinib

**Cancer type:** Non-Small Cell Lung Cancer **Variant class:** EGFR exon 19 deletion

**ESMO Level of Evidence/Grade of Recommendation:** I / B

**Population segment (Line of therapy):**
- Stage IV (First-line therapy); ESMO-MCBS v1.1 score: 3

**Reference:** ESMO Clinical Practice Guidelines - ESMO-Metastatic Non-Small-Cell Lung Cancer [Online Guideline (15SEP2020 - https://www.esmo.org/guidelines/lung-and-chest-tumours/clinical-practice-living-guidelines-metastatic-non-small-cell-lung-cancer); Ann Oncol (2018) 29 (suppl 4): iv192–iv237.]

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### bevacizumab + gefitinib

**Cancer type:** Non-Small Cell Lung Cancer **Variant class:** EGFR exon 19 deletion

**ESMO Level of Evidence/Grade of Recommendation:** I / B

**Population segment (Line of therapy):**
- Stage IV (First-line therapy); ESMO-MCBS v1.1 score: 3

**Reference:** ESMO Clinical Practice Guidelines - ESMO-Metastatic Non-Small-Cell Lung Cancer [Online Guideline (15SEP2020 - https://www.esmo.org/guidelines/lung-and-chest-tumours/clinical-practice-living-guidelines-metastatic-non-small-cell-lung-cancer); Ann Oncol (2018) 29 (suppl 4): iv192–iv237.]

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### erlotinib + ramucirumab

**Cancer type:** Non-Small Cell Lung Cancer **Variant class:** EGFR exon 19 deletion

**ESMO Level of Evidence/Grade of Recommendation:** I / B

**Population segment (Line of therapy):**
- Stage IV (First-line therapy); ESMO-MCBS v1.1 score: 3

**Reference:** ESMO Clinical Practice Guidelines - ESMO-Metastatic Non-Small-Cell Lung Cancer [Online Guideline (15SEP2020 - https://www.esmo.org/guidelines/lung-and-chest-tumours/clinical-practice-living-guidelines-metastatic-non-small-cell-lung-cancer); Ann Oncol (2018) 29 (suppl 4): iv192–iv237.]

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## EGFR exon 19 deletion (continued)

### gefitinib + carboplatin + pemetrexed

**Cancer type:** Non-Small Cell Lung Cancer **Variant class:** EGFR exon 19 deletion

**ESMO Level of Evidence/Grade of Recommendation:** I / B

**Population segment (Line of therapy):**
- Advanced (First-line therapy)

**Reference:** ESMO Clinical Practice Guidelines - ESMO-Metastatic Non-Small-Cell Lung Cancer [Online Guideline (15SEP2020 - https://www.esmo.org/guidelines/lung-and-chest-tumours/clinical-practice-living-guidelines-metastatic-non-small-cell-lung-cancer); Ann Oncol (2018) 29 (suppl 4): iv192–iv237.]

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### atezolizumab + bevacizumab + carboplatin + paclitaxel

**Cancer type:** Non-Small Cell Lung Cancer **Variant class:** EGFR exon 19 deletion

**ESMO Level of Evidence/Grade of Recommendation:** III / A

**Population segment (Line of therapy):**
- Non-squamous Cell; Metastatic (First-line therapy); ESMO-MCBS v1.1 score: 3
- Metastatic (Second-line therapy)

**Reference:** ESMO Clinical Practice Guidelines - ESMO-Metastatic Non-Small-Cell Lung Cancer [Online Guideline (15SEP2020 - https://www.esmo.org/guidelines/lung-and-chest-tumours/clinical-practice-living-guidelines-metastatic-non-small-cell-lung-cancer); Ann Oncol (2018) 29 (suppl 4): iv192–iv237.]

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### bevacizumab + erlotinib

**Cancer type:** Non-Small Cell Lung Cancer **Variant class:** EGFR exon 19 deletion

**ESMO Level of Evidence/Grade of Recommendation:** III / A

**Population segment (Line of therapy):**
- Stage IV (First-line therapy)

**Reference:** ESMO Clinical Practice Guidelines - ESMO-Metastatic Non-Small-Cell Lung Cancer [Online Guideline (15SEP2020 - https://www.esmo.org/guidelines/lung-and-chest-tumours/clinical-practice-living-guidelines-metastatic-non-small-cell-lung-cancer); Ann Oncol (2018) 29 (suppl 4): iv192–iv237.]

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### bevacizumab + gefitinib

**Cancer type:** Non-Small Cell Lung Cancer **Variant class:** EGFR exon 19 deletion

**ESMO Level of Evidence/Grade of Recommendation:** III / A

**Population segment (Line of therapy):**
- Stage IV (First-line therapy)

**Reference:** ESMO Clinical Practice Guidelines - ESMO-Metastatic Non-Small-Cell Lung Cancer [Online Guideline (15SEP2020 - https://www.esmo.org/guidelines/lung-and-chest-tumours/clinical-practice-living-guidelines-metastatic-non-small-cell-lung-cancer); Ann Oncol (2018) 29 (suppl 4): iv192–iv237.]

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## EGFR exon 19 deletion (continued)

### erlotinib + ramucirumab

**Cancer type:** Non-Small Cell Lung Cancer **Variant class:** EGFR exon 19 deletion

**ESMO Level of Evidence/Grade of Recommendation:** III / A

**Population segment (Line of therapy):**
- Stage IV (First-line therapy)

**Reference:** ESMO Clinical Practice Guidelines - ESMO-Metastatic Non-Small-Cell Lung Cancer [Online Guideline (15SEP2020 - https://www.esmo.org/guidelines/lung-and-chest-tumours/clinical-practice-living-guidelines-metastatic-non-small-cell-lung-cancer); Ann Oncol (2018) 29 (suppl 4): iv192–iv237.]

### gefitinib + carboplatin + pemetrexed

**Cancer type:** Non-Small Cell Lung Cancer **Variant class:** EGFR exon 19 deletion

**ESMO Level of Evidence/Grade of Recommendation:** III / A

**Population segment (Line of therapy):**
- Stage IV (First-line therapy)

**Reference:** ESMO Clinical Practice Guidelines - ESMO-Metastatic Non-Small-Cell Lung Cancer [Online Guideline (15SEP2020 - https://www.esmo.org/guidelines/lung-and-chest-tumours/clinical-practice-living-guidelines-metastatic-non-small-cell-lung-cancer); Ann Oncol (2018) 29 (suppl 4): iv192–iv237.]

### osimertinib

**Cancer type:** Non-Small Cell Lung Cancer **Variant class:** EGFRi sensitizing mutation

**ESMO Level of Evidence/Grade of Recommendation:** I / A

**Population segment (Line of therapy):**
- Advanced (First-line therapy); ESMO-MCBS v1.1 score: 4

**Reference:** ESMO Clinical Practice Guidelines - ESMO-Metastatic Non-Small-Cell Lung Cancer [Online Guideline (15SEP2020 - https://www.esmo.org/guidelines/lung-and-chest-tumours/clinical-practice-living-guidelines-metastatic-non-small-cell-lung-cancer); Ann Oncol (2018) 29 (suppl 4): iv192–iv237.]

## EGFR p.(T790M) c.2369C>T

### osimertinib

**Cancer type:** Non-Small Cell Lung Cancer **Variant class:** EGFR T790M mutation

**ESMO Level of Evidence/Grade of Recommendation:** I / A

**Population segment (Line of therapy):**
- Stage IV (Second-line therapy); ESMO-MCBS v1.1 score: 4

**Reference:** ESMO Clinical Practice Guidelines - ESMO-Metastatic Non-Small-Cell Lung Cancer [Online Guideline (15SEP2020 - https://www.esmo.org/guidelines/lung-and-chest-tumours/clinical-practice-living-guidelines-metastatic-non-small-cell-lung-cancer); Ann Oncol (2018) 29 (suppl 4): iv192–iv237.]

## ERBB2 amplification

### ado-trastuzumab emtansine

**Cancer type:** Breast Cancer **Variant class:** ERBB2 amplification or ERBB2 overexpression

**ESMO Level of Evidence/Grade of Recommendation:** I / A

**Population segment (Line of therapy):**
- Residual, Invasive, Local (Line of therapy not specified)

**Reference:** ESMO Clinical Practice Guidelines - ESMO-Early Breast Cancer [Ann Oncol (2019); 30: 1194-1220.]

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### pertuzumab + trastuzumab + chemotherapy

**Cancer type:** Breast Cancer **Variant class:** ERBB2 amplification or ERBB2 overexpression

**Other criteria:** ER negative, PR negative

**ESMO Level of Evidence/Grade of Recommendation:** I / A

**Population segment (Line of therapy):**
- Local (Line of therapy not specified)

**Reference:** ESMO Clinical Practice Guidelines - ESMO-Early Breast Cancer [Ann Oncol (2019); 30: 1194-1220.]

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### pertuzumab + trastuzumab + hormone therapy + chemotherapy

**Cancer type:** Breast Cancer **Variant class:** ERBB2 amplification or ERBB2 overexpression

**Other criteria:** ER positive, PR status

**ESMO Level of Evidence/Grade of Recommendation:** I / A

**Population segment (Line of therapy):**
- Luminal B; Local (Line of therapy not specified)

**Reference:** ESMO Clinical Practice Guidelines - ESMO-Early Breast Cancer [Ann Oncol (2019); 30: 1194-1220.]

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### trastuzumab + chemotherapy

**Cancer type:** Breast Cancer **Variant class:** ERBB2 amplification or ERBB2 overexpression

**Other criteria:** ER negative, PR negative

**ESMO Level of Evidence/Grade of Recommendation:** I / A

**Population segment (Line of therapy):**
- Local (Line of therapy not specified)

**Reference:** ESMO Clinical Practice Guidelines - ESMO-Early Breast Cancer [Ann Oncol (2019); 30: 1194-1220.]

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## ERBB2 amplification (continued)

### trastuzumab + chemotherapy

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

**ESMO Level of Evidence/Grade of Recommendation:** I / A

**Population segment (Line of therapy):**
- Advanced, Metastatic, Unresectable (First-line therapy); ESMO-MCBS v1.1 score: 3

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

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### trastuzumab + hormone therapy + chemotherapy

**Cancer type:** Breast Cancer **Variant class:** ERBB2 amplification or ERBB2 overexpression

**Other criteria:** ER positive, PR status

**ESMO Level of Evidence/Grade of Recommendation:** I / A

**Population segment (Line of therapy):**
- Luminal B; Local (Line of therapy not specified)

**Reference:** ESMO Clinical Practice Guidelines - ESMO-Early Breast Cancer [Ann Oncol (2019); 30: 1194-1220.]

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### pertuzumab + trastuzumab + chemotherapy

**Cancer type:** Breast Cancer **Variant class:** ERBB2 amplification or ERBB2 overexpression

**ESMO Level of Evidence/Grade of Recommendation:** II / B

**Population segment (Line of therapy):**
- Local (First-line therapy)

**Reference:** ESMO Clinical Practice Guidelines - ESMO-Early Breast Cancer [Ann Oncol (2019); 30: 1194-1220.]

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### trastuzumab deruxtecan

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

**ESMO Level of Evidence/Grade of Recommendation:** II / B

**Population segment (Line of therapy):**
- Advanced, Metastatic (Second-line therapy, Subsequent therapy); ESMO-MCBS v1.1 score: 4

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

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## ERBB2 amplification (continued)

### pertuzumab + trastuzumab + hormone therapy

**Cancer type:** Breast Cancer **Variant class:** ERBB2 amplification or ERBB2 overexpression

**Other criteria:** ER positive, PR status

**ESMO Level of Evidence/Grade of Recommendation:** III / B

**Population segment (Line of therapy):**
- Luminal B; Local (Line of therapy not specified)

**Reference:** ESMO Clinical Practice Guidelines - ESMO-Early Breast Cancer [Ann Oncol (2019); 30: 1194-1220.]

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### trastuzumab + hormone therapy

**Cancer type:** Breast Cancer **Variant class:** ERBB2 amplification or ERBB2 overexpression

**Other criteria:** ER positive, PR status

**ESMO Level of Evidence/Grade of Recommendation:** III / B

**Population segment (Line of therapy):**
- Luminal B; Local (Line of therapy not specified)

**Reference:** ESMO Clinical Practice Guidelines - ESMO-Early Breast Cancer [Ann Oncol (2019); 30: 1194-1220.]

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### tamoxifen

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

**Other criteria:** ER positive, PR status

**ESMO Level of Evidence/Grade of Recommendation:** IV / A

**Population segment (Line of therapy):**
- Luminal-like, Ductal, Male Breast Cancer; Invasive (Adjuvant therapy)

**Reference:** ESMO Clinical Practice Guidelines - ESMO-Early Breast Cancer [Ann Oncol (2019); 30: 1194-1220.]

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### tamoxifen

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

**Other criteria:** ER positive, PR status

**ESMO Level of Evidence/Grade of Recommendation:** IV / A

**Population segment (Line of therapy):**
- Luminal A, Luminal B, Ductal; Invasive, Local (Adjuvant therapy)

**Reference:** ESMO Clinical Practice Guidelines - ESMO-Early Breast Cancer [Ann Oncol (2019); 30: 1194-1220.]

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## ERBB2 amplification (continued)

### aromatase inhibitor + luteinizing hormone-releasing factor

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

**Other criteria:** ER positive, PR status

**ESMO Level of Evidence/Grade of Recommendation:** IV / B

**Population segment (Line of therapy):**
- Luminal A, Luminal B, Ductal, Male Breast Cancer; Local, Invasive (Line of therapy not specified)

**Reference:** ESMO Clinical Practice Guidelines - ESMO-Early Breast Cancer [Ann Oncol (2019); 30: 1194-1220.]

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### aromatase inhibitor + luteinizing hormone-releasing factor

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

**Other criteria:** ER positive, PR status

**ESMO Level of Evidence/Grade of Recommendation:** IV / B

**Population segment (Line of therapy):**
- Luminal A, Luminal B, Ductal; Invasive, Local (Line of therapy not specified)

**Reference:** ESMO Clinical Practice Guidelines - ESMO-Early Breast Cancer [Ann Oncol (2019); 30: 1194-1220.]

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### trastuzumab + hormone therapy

**Cancer type:** Breast Cancer **Variant class:** ERBB2 amplification or ERBB2 overexpression

**Other criteria:** ER positive

**ESMO Level of Evidence/Grade of Recommendation:** V / A

**Population segment (Line of therapy):**
- Luminal B; Local (Line of therapy not specified)

**Reference:** ESMO Clinical Practice Guidelines - ESMO-Early Breast Cancer [Ann Oncol (2019); 30: 1194-1220.]

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### ado-trastuzumab emtansine

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

**ESMO Level of Evidence/Grade of Recommendation:** I / A

**Population segment (Line of therapy):**
- Advanced, Metastatic, Progression (Second-line therapy); ESMO-MCBS v1.1 score: 4
- Advanced, Metastatic (Third-line therapy); ESMO-MCBS v1.1 score: 4

**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]

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## ERBB2 amplification (continued)

### irbinitinib + trastuzumab + capecitabine

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

**ESMO Level of Evidence/Grade of Recommendation:** I / A

**Population segment (Line of therapy):**
- Advanced, Metastatic (Third-line therapy); ESMO-MCBS v1.1 score: 3

**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]

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### pertuzumab + trastuzumab + docetaxel

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

**ESMO Level of Evidence/Grade of Recommendation:** I / A

**Population segment (Line of therapy):**
- Advanced, Metastatic (First-line therapy); ESMO-MCBS v1.1 score: 4

**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]

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### trastuzumab deruxtecan

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

**ESMO Level of Evidence/Grade of Recommendation:** I / A

**Population segment (Line of therapy):**
- Advanced, Metastatic, Progression (Second-line therapy)

**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]

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### lapatinib + trastuzumab

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

**ESMO Level of Evidence/Grade of Recommendation:** I / B

**Population segment (Line of therapy):**
- Advanced, Metastatic (Subsequent therapy); ESMO-MCBS v1.1 score: 4

**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]

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## ERBB2 amplification (continued)

### margetuximab

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

**ESMO Level of Evidence/Grade of Recommendation:** I / B

**Population segment (Line of therapy):**
- Advanced, Metastatic (Subsequent therapy); ESMO-MCBS v1.1 score: 2

**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]

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### margetuximab + chemotherapy

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

**ESMO Level of Evidence/Grade of Recommendation:** I / B

**Population segment (Line of therapy):**
- Advanced, Metastatic (Subsequent therapy); ESMO-MCBS v1.1 score: 2

**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]

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### lapatinib + capecitabine

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

**ESMO Level of Evidence/Grade of Recommendation:** I / C

**Population segment (Line of therapy):**
- Advanced, Metastatic (Subsequent therapy)

**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]

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### lapatinib + hormone therapy

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

**ESMO Level of Evidence/Grade of Recommendation:** I / C

**Population segment (Line of therapy):**
- Advanced, Metastatic (Subsequent therapy)

**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]

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## ERBB2 amplification (continued)

### lapatinib + trastuzumab

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

**ESMO Level of Evidence/Grade of Recommendation:** I / C

**Population segment (Line of therapy):**
- Advanced, Metastatic (Subsequent therapy)

**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]

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### neratinib

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

**ESMO Level of Evidence/Grade of Recommendation:** I / C

**Population segment (Line of therapy):**
- Advanced, Metastatic (Subsequent therapy); ESMO-MCBS v1.1 score: 1

**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]

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### neratinib + chemotherapy

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

**ESMO Level of Evidence/Grade of Recommendation:** I / C

**Population segment (Line of therapy):**
- Advanced, Metastatic (Subsequent therapy); ESMO-MCBS v1.1 score: 1

**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]

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### irbinitinib + trastuzumab + capecitabine

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

**ESMO Level of Evidence/Grade of Recommendation:** II / A

**Population segment (Line of therapy):**
- Advanced, Brain Metastases (Second-line therapy, Third-line therapy); ESMO-MCBS v1.1 score: 3

**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]

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## ERBB2 amplification (continued)

### pertuzumab + trastuzumab + hormone therapy

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

**Other criteria:** Hormone receptor positive

**ESMO Level of Evidence/Grade of Recommendation:** II / A

**Population segment (Line of therapy):**
- Advanced, Metastatic (Maintenance therapy)

**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]

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### pertuzumab + trastuzumab + nab-paclitaxel

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

**ESMO Level of Evidence/Grade of Recommendation:** II / A

**Population segment (Line of therapy):**
- Advanced, Metastatic (First-line therapy)

**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]

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### pertuzumab + trastuzumab + paclitaxel

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

**ESMO Level of Evidence/Grade of Recommendation:** II / A

**Population segment (Line of therapy):**
- Advanced, Metastatic (First-line therapy)

**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]

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### trastuzumab deruxtecan

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

**ESMO Level of Evidence/Grade of Recommendation:** II / A

**Population segment (Line of therapy):**
- Advanced, Brain Metastases (Second-line therapy)
- Advanced, Brain Metastases (Subsequent therapy); ESMO-MCBS v1.1 score: 2

**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]

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## ERBB2 amplification (continued)

### lapatinib + hormone therapy

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

**Other criteria:** Hormone receptor positive

**ESMO Level of Evidence/Grade of Recommendation:** II / B

**Population segment (Line of therapy):**
- Advanced, Metastatic (First-line therapy)

**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]

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### lapatinib + trastuzumab + hormone therapy

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

**Other criteria:** Hormone receptor positive

**ESMO Level of Evidence/Grade of Recommendation:** II / B

**Population segment (Line of therapy):**
- Advanced, Metastatic (First-line therapy)

**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]

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### pertuzumab + trastuzumab

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

**Other criteria:** Hormone receptor negative

**ESMO Level of Evidence/Grade of Recommendation:** II / B

**Population segment (Line of therapy):**
- Advanced, Metastatic (First-line therapy)

**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]

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### pertuzumab + trastuzumab + hormone therapy

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

**Other criteria:** Hormone receptor positive

**ESMO Level of Evidence/Grade of Recommendation:** II / B

**Population segment (Line of therapy):**
- Advanced, Metastatic (First-line therapy)

**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]

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## ERBB2 amplification (continued)

### trastuzumab + hormone therapy

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

**Other criteria:** Hormone receptor positive

**ESMO Level of Evidence/Grade of Recommendation:** II / B

**Population segment (Line of therapy):**
- Advanced, Metastatic (First-line therapy)

**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]

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### trastuzumab + chemotherapy

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

**ESMO Level of Evidence/Grade of Recommendation:** III / A

**Population segment (Line of therapy):**
- Advanced, Metastatic, Progression (Subsequent therapy)

**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]

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### trastuzumab deruxtecan

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

**ESMO Level of Evidence/Grade of Recommendation:** III / A

**Population segment (Line of therapy):**
- Advanced, Metastatic (Third-line therapy); ESMO-MCBS v1.1 score: 2

**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]

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# Clinical Trials in Taiwan region:

## Clinical Trials Summary

### EGFR exon 19 deletion + EGFR p.(T790M) c.2369C>T

| NCT ID | Title | Phase |
|---|---|---|
| NCT04351555 | A Phase III, Randomised, Controlled, Multi-center, 3-Arm Study of Neoadjuvant Osimertinib as Monotherapy or in Combination With Chemotherapy Versus Standard of Care Chemotherapy Alone for the Treatment of Patients With Epidermal Growth Factor Receptor Mutation Positive, Resectable Non-small Cell Lung Cancer | III |
| NCT03994393 | A Phase II Trial of Durvalumab (MEDI4736) and Tremelimumab With Chemotherapy in Metastatic EGFR Mutant Non-squamous Non-small Cell Lung Cancer (NSCLC) Following Progression on EGFR Tyrosine Kinase Inhibitors (TKIs) | II |
| NCT02099058 | A Multicenter, Phase I/Ib, Open-Label, Dose-Escalation Study of ABBV-399, an Antibody Drug Conjugate, in Subjects With Advanced Solid Tumors | I |

### EGFR exon 19 deletion

| NCT ID | Title | Phase |
|---|---|---|
| NCT04988295 | A Phase III, Open-Label, Randomized Study of Amivantamab and Lazertinib in Combination With Platinum-Based Chemotherapy Compared With Platinum-Based Chemotherapy in Patients With EGFR-Mutated Locally Advanced or Metastatic Non-Small Cell Lung Cancer After Osimertinib Failure | III |
| NCT05120349 | A Phase III, Double-blind, Randomised, Placebo-Controlled, International Study to Assess the Efficacy and Safety of Adjuvant Osimertinib Versus Placebo in Participants With EGFR Mutation-positive Stage IA2-IA3 Non-small Cell Lung Cancer, Following Complete Tumour Resection | III |
| NCT02609776 | A Phase I, First-in-Human, Open-Label, Dose Escalation Study of JNJ-61186372, a Human Bispecific EGFR and cMet Antibody, in Subjects With Advanced Non-Small Cell Lung Cancer. | I |
| NCT04077463 | An Open-label Phase I/Ib Study to Evaluate the Safety and Pharmacokinetics of JNJ-73841937 (Lazertinib), a Third Generation EGFR-TKI, as Monotherapy or in Combinations With JNJ-61186372, a Human Bispecific EGFR and cMet Antibody in Participants With Advanced Non-Small Cell Lung Cancer | I |
| NCT03114319 | An Open-label, Multi-center, Phase I, Dose Finding Study of Oral TNO155 in Adult Patients With Advanced Solid Tumors. | I |
| NCT03974022 | A Phase I/II, Open-Label, Multicenter Study to Assess the Safety, Tolerability, Pharmacokinetics and Anti-tumor Efficacy of DZD9008 in Patients With Advanced Non-Small Cell Lung Cancer (NSCLC) with EGFR or HER2 Mutation | I/II |

### EGFR p.(T790M) c.2369C>T

| NCT ID | Title | Phase |
|---|---|---|
| NCT02609776 | A Phase I, First-in-Human, Open-Label, Dose Escalation Study of JNJ-61186372, a Human Bispecific EGFR and cMet Antibody, in Subjects With Advanced Non-Small Cell Lung Cancer. | I |
| NCT03974022 | A Phase I/II, Open-Label, Multicenter Study to Assess the Safety, Tolerability, Pharmacokinetics and Anti-tumor Efficacy of DZD9008 in Patients With Advanced Non-Small Cell Lung Cancer (NSCLC) with EGFR or HER2 Mutation | I/II |
| NCT04077463 | An Open-label Phase I/Ib Study to Evaluate the Safety and Pharmacokinetics of JNJ-73841937 (Lazertinib), a Third Generation EGFR-TKI, as Monotherapy or in Combinations With JNJ-61186372, a Human Bispecific EGFR and cMet Antibody in Participants With Advanced Non-Small Cell Lung Cancer | I |

# Clinical Trials Summary (continued)

## ERBB2 amplification

| NCT ID | Title | Phase |
|---|---|---|
| NCT05013554 | A Phase I/Ib Open-label, First-in-human, Single Agent, Dose Escalation and Expansion Study for the Evaluation of Safety, Pharmacokinetics, Pharmacodynamics, and Anti-tumor Activity of SAR443216 in Participants with Relapsed/Refractory HER2 Expressing Solid Tumors. | I |
| NCT04446260 | A Phase I Multi-Country, Multi-Center, Open-Label Study to Evaluate the Safety, Tolerability, Pharmacokinetics and Efficacy of SHR-A1811 in HER2 Expressing or Mutated Advanced Malignant Solid Tumor Subjects | I |

## PIK3CA p.(E545K) c.1633G>A

| NCT ID | Title | Phase |
|---|---|---|
| NCT04589845 | Tumor-Agnostic Precision Immunooncology and Somatic Targeting Rational for You (TAPISTRY) Phase II Platform Trial | II |

# Alerts Informed By Public Data Sources

## Current FDA Information

Contraindicated  Not recommended  Resistance  Breakthrough  Fast Track

FDA information is current as of 2022-09-14. For the most up-to-date information, search www.fda.gov.

## EGFR exon 19 deletion

### patritumab deruxtecan

**Cancer type:** Non-Small Cell Lung Cancer

**Variant class:** EGFR exon 19 deletion

**Supporting Statement:**
The FDA has granted Breakthrough Therapy Designation to a potential first-in-class HER3 directed antibody-drug conjugate, patritumab deruxtecan, for metastatic or locally advanced, EGFR-mutant non-small cell lung cancer.

**Reference:**

https://www.cancernetwork.com/view/fda-grants-breakthrough-therapy-status-to-patritumab-deruxtecan-for-egfr-metastatic-nsclc

### osimertinib + quaratusugene ozeplasmid

**Cancer type:** Non-Small Cell Lung Cancer

**Variant class:** EGFR mutation

**Supporting Statement:**
The FDA has granted Fast Track Designation to the immunogene therapy, quaratusugene ozeplasmid, in combination with EGFR inhibitor osimertinib for the treatment of non-small cell lung cancer (NSCLC) with EFGR mutations that progressed after treatment with osimertinib alone.

**Reference:**

https://www.genprex.com/news/genprex-receives-u-s-fda-fast-track-designation-for-gene-therapy-that-targets-lung-cancer/

## EGFR p.(T790M) c.2369C>T

### osimertinib + quaratusugene ozeplasmid

**Cancer type:** Non-Small Cell Lung Cancer **Variant class:** EGFR mutation

**Supporting Statement:**
The FDA has granted Fast Track Designation to the immunogene therapy, quaratusugene ozeplasmid, in combination with EGFR inhibitor osimertinib for the treatment of non-small cell lung cancer (NSCLC) with EFGR mutations that progressed after treatment with osimertinib alone.

**Reference:**

https://www.genprex.com/news/genprex-receives-u-s-fda-fast-track-designation-for-gene-therapy-that-targets-lung-cancer/

## ERBB2 amplification

### zanidatamab

**Cancer type:** Biliary Tract Carcinoma **Variant class:** ERBB2 amplification

**Supporting Statement:**
The FDA has granted Breakthrough Therapy Designation to the HER2 targeted bispecific antibody, zanidatamab, for previously-treated HER2 gene-amplified biliary tract cancer (BTC).

**Reference:**

https://www.targetedonc.com/view/fda-grants-breakthrough-designation-to-zanidatamab-for-her2-amplified-biliary-tract-cancer

### disitamab vedotinaide

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

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

**Reference:**

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

### CT-0508

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

**Supporting Statement:**

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

**Reference:**

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

## ERBB2 amplification (continued)

### 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

### evorpacept

**Cancer type:** Gastric Cancer, Gastroesophageal Junction Adenocarcinoma

**Variant class:** ERBB2 positive

**Supporting Statement:**
The FDA has granted Fast Track Designation to ALX148, a CD47 checkpoint inhibitor, 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

### Current NCCN Information

Contraindicated | Not recommended | Resistance | Breakthrough | Fast Track

NCCN information is current as of 2022-09-01. For the most up-to-date information, search www.nccn.org.
For NCCN International Adaptations & Translations, search www.nccn.org/global/international_adaptations.aspx.

## EGFR exon 19 deletion

### atezolizumab

**Cancer type:** Non-Small Cell Lung Cancer

**Variant class:** EGFR mutation

**Summary:**

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

- "subsequent therapy with pembrolizumab, nivolumab, or atezolizumab is not recommended in patients with EGFR mutations or ALK rearrangements."

**Reference:** NCCN Guidelines® - NCCN-Non-Small Cell Lung Cancer [Version 3.2022]

## EGFR exon 19 deletion (continued)

### nivolumab

**Cancer type:** Non-Small Cell Lung Cancer **Variant class:** EGFR mutation

**Summary:**

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

- "subsequent therapy with pembrolizumab, nivolumab, or atezolizumab is not recommended in patients with EGFR mutations or ALK rearrangements."

**Reference:** NCCN Guidelines® - NCCN-Non-Small Cell Lung Cancer [Version 3.2022]

### pembrolizumab

**Cancer type:** Non-Small Cell Lung Cancer **Variant class:** EGFR mutation

**Summary:**

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

- "subsequent therapy with pembrolizumab, nivolumab, or atezolizumab is not recommended in patients with EGFR mutations or ALK rearrangements."

**Reference:** NCCN Guidelines® - NCCN-Non-Small Cell Lung Cancer [Version 3.2022]

## EGFR p.(T790M) c.2369C>T

### atezolizumab

**Cancer type:** Non-Small Cell Lung Cancer **Variant class:** EGFR mutation

**Summary:**

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

- "subsequent therapy with pembrolizumab, nivolumab, or atezolizumab is not recommended in patients with EGFR mutations or ALK rearrangements."

**Reference:** NCCN Guidelines® - NCCN-Non-Small Cell Lung Cancer [Version 3.2022]

### nivolumab

**Cancer type:** Non-Small Cell Lung Cancer **Variant class:** EGFR mutation

**Summary:**

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

- "subsequent therapy with pembrolizumab, nivolumab, or atezolizumab is not recommended in patients with EGFR mutations or ALK rearrangements."

**Reference:** NCCN Guidelines® - NCCN-Non-Small Cell Lung Cancer [Version 3.2022]

## EGFR p.(T790M) c.2369C>T (continued)

### pembrolizumab

**Cancer type:** Non-Small Cell Lung Cancer **Variant class:** EGFR mutation

**Summary:**

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

- "subsequent therapy with pembrolizumab, nivolumab, or atezolizumab is not recommended in patients with EGFR mutations or ALK rearrangements."

**Reference:** NCCN Guidelines® - NCCN-Non-Small Cell Lung Cancer [Version 3.2022]

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### afatinib

**Cancer type:** Non-Small Cell Lung Cancer **Variant class:** EGFR T790M mutation

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

- "The most common known mechanism is the acquisition of T790M (which is a secondary mutation in EGFR), which renders the kinase resistant to erlotinib, gefitinib, dacomitinib, or afatinib."

**Reference:** NCCN Guidelines® - NCCN-Non-Small Cell Lung Cancer [Version 3.2022]

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### dacomitinib

**Cancer type:** Non-Small Cell Lung Cancer **Variant class:** EGFR T790M mutation

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

- "The most common known mechanism is the acquisition of T790M (which is a secondary mutation in EGFR), which renders the kinase resistant to erlotinib, gefitinib, dacomitinib, or afatinib."

**Reference:** NCCN Guidelines® - NCCN-Non-Small Cell Lung Cancer [Version 3.2022]

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### erlotinib

**Cancer type:** Non-Small Cell Lung Cancer **Variant class:** EGFR T790M mutation

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

- "The most common known mechanism is the acquisition of T790M (which is a secondary mutation in EGFR), which renders the kinase resistant to erlotinib, gefitinib, dacomitinib, or afatinib."

**Reference:** NCCN Guidelines® - NCCN-Non-Small Cell Lung Cancer [Version 3.2022]

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### gefitinib

**Cancer type:** Non-Small Cell Lung Cancer **Variant class:** EGFR T790M mutation

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

- "The most common known mechanism is the acquisition of T790M (which is a secondary mutation in EGFR), which renders the kinase resistant to erlotinib, gefitinib, dacomitinib, or afatinib."

**Reference:** NCCN Guidelines® - NCCN-Non-Small Cell Lung Cancer [Version 3.2022]

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## Current EMA Information

Contraindicated Not recommended Resistance Breakthrough Fast Track

EMA information is current as of 2022-09-14. For the most up-to-date information, search www.ema.europa.eu/ema.

## EGFR p.(T790M) c.2369C>T

### gefitinib

**Cancer type:** Non-Small Cell Lung Cancer **Label as of:** 2022-07-05 **Variant class:** EGFR T790M mutation

**Reference:**

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

### gefitinib (Mylan)

**Cancer type:** Non-Small Cell Lung Cancer **Label as of:** 2022-06-16 **Variant class:** EGFR T790M mutation

**Reference:**

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

## Current ESMO Information

Contraindicated Not recommended Resistance Breakthrough Fast Track

ESMO information is current as of 2022-09-01. For the most up-to-date information, search www.esmo.org.

## ERBB2 amplification

### lapatinib + trastuzumab + chemotherapy

**Cancer type:** Breast Cancer **Variant class:** ERBB2 amplification or ERBB2 overexpression

**ESMO Level of Evidence/Grade of Recommendation:** I / E

**Summary:**

ESMO Clinical Practice Guidelines include the following supporting statement(s):

- "Dual blockade with trastuzumab/lapatinib has not led to improved long-term outcomes and cannot therefore be recommended [I, E]."

**Reference:** ESMO Clinical Practice Guidelines - ESMO-Early Breast Cancer [Ann Oncol (2019); 30: 1194-1220.]

## ERBB2 amplification (continued)

### aromatase inhibitor

**Cancer type:** Breast Cancer **Variant class:** ERBB2 amplification or ERBB2 overexpression

**Other criteria:** ER positive, PR status

**ESMO Level of Evidence/Grade of Recommendation:** IV / E

**Summary:**

ESMO Clinical Practice Guidelines include the following supporting statement(s):

- "An AI alone should not be used as adjuvant ET in male breast cancer patients [IV, E]."

**Reference:** ESMO Clinical Practice Guidelines - ESMO-Early Breast Cancer [Ann Oncol (2019); 30: 1194-1220.]

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### trastuzumab + anthracycline

**Cancer type:** Breast Cancer **Variant class:** ERBB2 amplification or ERBB2 overexpression

**ESMO Level of Evidence/Grade of Recommendation:** I / D

**Summary:**

ESMO Clinical Practice Guidelines include the following supporting statement(s):

- "Trastuzumab should usually not be given concomitantly with anthracycline-based ChT [I, D]".

**Reference:** ESMO Clinical Practice Guidelines - ESMO-Early Breast Cancer [Ann Oncol (2019); 30: 1194-1220.]

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### 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 [Annals of Oncology (2022), doi: https://doi.org/10.1016/j.annonc.2022.07.004.]

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### 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]

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## Signatures

**Testing Personnel:**

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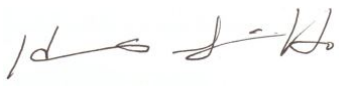
**Laboratory Supervisor:**



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**Pathologist:**

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## References


1. King et al. Amplification of a novel v-erbB-related gene in a human mammary carcinoma. Science. 1985 Sep 6;229(4717):974-6. PMID: 2992089
2. Zhixiang. ErbB Receptors and Cancer. Methods Mol. Biol. 2017;1652:3-35. PMID: 28791631
3. Gutierrez et al. HER2: biology, detection, and clinical implications. Arch. Pathol. Lab. Med. 2011 Jan;135(1):55-62. PMID: 21204711
4. Pines et al. Oncogenic mutant forms of EGFR: lessons in signal transduction and targets for cancer therapy. FEBS Lett. 2010 Jun 18;584(12):2699-706. PMID: 20388509
5. Cancer Genome Atlas Research Network. Comprehensive molecular profiling of lung adenocarcinoma. Nature. 2014 Jul 31;511(7511):543-50. doi: 10.1038/nature13385. Epub 2014 Jul 9. PMID: 25079552
6. Weinstein et al. The Cancer Genome Atlas Pan-Cancer analysis project. Nat. Genet. 2013 Oct;45(10):1113-20. PMID: 24071849
7. Cerami et al. The cBio cancer genomics portal: an open platform for exploring multidimensional cancer genomics data. Cancer Discov. 2012 May;2(5):401-4. PMID: 22588877
8. da et al. EGFR mutations and lung cancer. Annu Rev Pathol. 2011;6:49-69. doi: 10.1146/annurev-pathol-011110-130206. PMID: 20887192
9. Arcila et al. EGFR exon 20 insertion mutations in lung adenocarcinomas: prevalence, molecular heterogeneity, and clinicopathologic characteristics. Mol. Cancer Ther. 2013 Feb;12(2):220-9. PMID: 23371856
10. Kobayashi et al. EGFR Exon 18 Mutations in Lung Cancer: Molecular Predictors of Augmented Sensitivity to Afatinib or Neratinib as Compared with First- or Third-Generation TKIs. Clin Cancer Res. 2015 Dec 1;21(23):5305-13. doi: 10.1158/1078-0432.CCR-15-1046. Epub 2015 Jul 23. PMID: 26206867
11. Yasuda et al. Structural, biochemical, and clinical characterization of epidermal growth factor receptor (EGFR) exon 20 insertion mutations in lung cancer. Sci Transl Med. 2013 Dec 18;5(216):216ra177. PMID: 24353160
12. Chiu et al. Epidermal Growth Factor Receptor Tyrosine Kinase Inhibitor Treatment Response in Advanced Lung Adenocarcinomas with G719X/L861Q/S768I Mutations. J Thorac Oncol. 2015 May;10(5):793-9. PMID: 25668120
13. Karachaliou et al. KRAS mutations in lung cancer. Clin Lung Cancer. 2013 May;14(3):205-14. PMID: 23122493
14. Brennan et al. The somatic genomic landscape of glioblastoma. Cell. 2013 Oct 10;155(2):462-77. PMID: 24120142
15. Cancer Genome Atlas Network. Comprehensive genomic characterization of head and neck squamous cell carcinomas. Nature. 2015 Jan 29;517(7536):576-82. PMID: 25631445
16. Mitsudomi et al. Epidermal growth factor receptor in relation to tumor development: EGFR gene and cancer. FEBS J. 2010 Jan;277(2):301-8. PMID: 19922469
17. Gazdar. Activating and resistance mutations of EGFR in non-small-cell lung cancer: role in clinical response to EGFR tyrosine kinase inhibitors. Oncogene. 2009 Aug;28 Suppl 1:S24-31. PMID: 19680293
18. Gan et al. The EGFRvIII variant in glioblastoma multiforme. J Clin Neurosci. 2009 Jun;16(6):748-54. PMID: 19324552
19. https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/021743s025lbl.pdf
20. https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/206995s004lbl.pdf
21. https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/201292s017lbl.pdf
22. https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/211288s003lbl.pdf
23. NCCN Guidelines® - NCCN-Non-Small Cell Lung Cancer [Version 3.2022]
24. Naidoo et al. Epidermal growth factor receptor exon 20 insertions in advanced lung adenocarcinomas: Clinical outcomes and response to erlotinib. Cancer. 2015 Sep 15;121(18):3212-3220. PMID: 26096453
25. Vyse et al. Targeting EGFR exon 20 insertion mutations in non-small cell lung cancer. Signal Transduct Target Ther. 2019;4:5. PMID: 30854234
26. Yi et al. A comparison of epidermal growth factor receptor mutation testing methods in different tissue types in non-small cell lung cancer. Int J Mol Med. 2014 Aug;34(2):464-74. PMID: 24891042
27. https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/215310s000lbl.pdf
28. https://investors.cullinanoncology.com/news-releases/news-release-details/fda-grants-breakthrough-therapy-designation-cullinan-oncologys
29. https://www.prnewswire.com/news-releases/fda-grants-breakthrough-therapy-designation-for-dizal-pharmaceuticals-dzd9008-in-patients-with-locally-advanced-or-metastatic-non-small-cell-lung-cancer-harboring-egfr-exon20-insertion-301469692.html
30. Madic et al. EGFR C797S, EGFR T790M and EGFR sensitizing mutations in non-small cell lung cancer revealed by six-color crystal digital PCR. Oncotarget. 2018 Dec 21;9(100):37393-37406. PMID: 30647840

## References (continued)


31. https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/208065s025lbl.pdf
32. Niederst et al. The Allelic Context of the C797S Mutation Acquired upon Treatment with Third-Generation EGFR Inhibitors Impacts Sensitivity to Subsequent Treatment Strategies. Clin. Cancer Res. 2015 Sep 1;21(17):3924-33. PMID: 25964297
33. Wang et al. Lung Adenocarcinoma Harboring EGFR T790M and In Trans C797S Responds to Combination Therapy of First- and Third-Generation EGFR TKIs and Shifts Allelic Configuration at Resistance. J Thorac Oncol. 2017 Nov;12(11):1723-1727. PMID: 28662863
34. https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/761210s001lbl.pdf
35. https://www.genprex.com/news/genprex-receives-u-s-fda-fast-track-designation-for-gene-therapy-that-targets-lung-cancer/
36. https://investors.blackdiamondtherapeutics.com/news-releases/news-release-details/black-diamond-therapeutics-granted-fast-track-designation-fda
37. Di et al. erbB-2 is a potent oncogene when overexpressed in NIH/3T3 cells. Science. 1987 Jul 10;237(4811):178-82. PMID: 2885917
38. Hudziak et al. Increased expression of the putative growth factor receptor p185HER2 causes transformation and tumorigenesis of NIH 3T3 cells. Proc. Natl. Acad. Sci. U.S.A. 1987 Oct;84(20):7159-63. PMID: 2890160
39. Lonardo et al. The normal erbB-2 product is an atypical receptor-like tyrosine kinase with constitutive activity in the absence of ligand. New Biol. 1990 Nov;2(11):992-1003. PMID: 1983208
40. Ciriello et al. Comprehensive Molecular Portraits of Invasive Lobular Breast Cancer. Cell. 2015 Oct 8;163(2):506-19. PMID: 26451490
41. Cancer Genome Atlas Research Network. Comprehensive molecular characterization of gastric adenocarcinoma. Nature. 2014 Sep 11;513(7517):202-9. doi: 10.1038/nature13480. Epub 2014 Jul 23. PMID: 25079317
42. Cancer Genome Atlas Research Network. Comprehensive molecular characterization of urothelial bladder carcinoma. Nature. 2014 Mar 20;507(7492):315-22. doi: 10.1038/nature12965. Epub 2014 Jan 29. PMID: 24476821
43. Donna et al. Comprehensive molecular characterization of human colon and rectal cancer. Nature. 2012 Jul 18;487(7407):330-7. PMID: 22810696
44. Cancer Genome Atlas Research Network. Integrated genomic analyses of ovarian carcinoma. Nature. 2011 Jun 29;474(7353):609-15. PMID: 21720365
45. Petrelli et al. Clinical and pathological characterization of HER2 mutations in human breast cancer: a systematic review of the literature. Breast Cancer Res. Treat. 2017 Nov;166(2):339-349. PMID: 28762010
46. Bose et al. Activating HER2 mutations in HER2 gene amplification negative breast cancer. Cancer Discov. 2013 Feb;3(2):224-37. doi: 10.1158/2159-8290.CD-12-0349. Epub 2012 Dec 7. PMID: 23220880
47. Hudis. Trastuzumab--mechanism of action and use in clinical practice. N. Engl. J. Med. 2007 Jul 5;357(1):39-51. PMID: 17611206
48. Slamon et al. Human breast cancer: correlation of relapse and survival with amplification of the HER-2/neu oncogene. Science. 1987 Jan 9;235(4785):177-82. PMID: 3798106
49. https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/103792s5345lbl.pdf
50. https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/125409s124lbl.pdf
51. https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/125427s111lbl.pdf
52. NCCN Guidelines® - NCCN-Breast Cancer [Version 4.2022]
53. https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/022059s031lbl.pdf
54. https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/208051s009lbl.pdf
55. https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/213411s000lbl.pdf
56. https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/125514s133lbl.pdf
57. https://www.globenewswire.com/news-release/2016/06/01/845166/0/en/Galena-Biopharma-Receives-Fast-Track-Designation-for-NeuVax-nelipepimut-S-PRESENT-Clinical-Trial.html
58. https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/761150s000lbl.pdf
59. https://www.prnewswire.com/news-releases/fda-grants-arx788-fast-track-designation-for-her2-positive-metastatic-breast-cancer-301199951.html
60. https://www.targetedonc.com/view/her2targeted-antibody-zw25-earns-fda-fast-track-designation-in-gea
61. https://www.targetedonc.com/view/fda-grants-breakthrough-designation-to-zanidatamab-for-her2-amplified-biliary-tract-cancer

## References (continued)


62. https://www.prnewswire.com/news-releases/remegen-announces-us-fda-has-granted-breakthrough-therapy-designation-for-disitamab-vedotin-rc48-in-urothelial-cancer-301138315.html
63. http://ambrx.com/fda-grants-arx788-fast-track-designation-for-her2-positive-metastatic-breast-cancer
64. https://www.prnewswire.com/news-releases/carisma-therapeutics-announces-us-food-and-drug-administration-grants-fast-track-designation-to-ct-0508-for-the-treatment-of-patients-with-solid-tumors-301381843.html
65. Ma et al. Neratinib Efficacy and Circulating Tumor DNA Detection of HER2 Mutations in HER2 Nonamplified Metastatic Breast Cancer. Clin. Cancer Res. 2017 Oct 1;23(19):5687-5695. PMID: 28679771
66. De et al. Clinical activity of afatinib (BIBW 2992) in patients with lung adenocarcinoma with mutations in the kinase domain of HER2/neu. Lung Cancer. 2012 Apr;76(1):123-7. PMID: 22325357
67. Kris et al. Targeting HER2 aberrations as actionable drivers in lung cancers: phase II trial of the pan-HER tyrosine kinase inhibitor dacomitinib in patients with HER2-mutant or amplified tumors. Ann. Oncol. 2015 Jul;26(7):1421-7. PMID: 25899785
68. Falchook et al. Non-small-cell lung cancer with HER2 exon 20 mutation: regression with dual HER2 inhibition and anti-VEGF combination treatment. J Thorac Oncol. 2013 Feb;8(2):e19-20. PMID: 23328556
69. David et al. Neratinib in HER2- or HER3-mutant solid tumors: SUMMIT, a global, multi-histology, open-label, phase 2 'basket' study. AACR 2017. Abstract CT001
70. Lin et al. Response to Afatinib in a Patient with Non-Small Cell Lung Cancer Harboring HER2 R896G Mutation: A Case Report. Onco Targets Ther. 2019;12:10897-10902. PMID: 31849493
71. Chang et al. Sustained Partial Response to Afatinib in a Patient With Lung Adenocarcinoma Harboring HER2V659E Mutation. JCO Precis Oncol. 2020 Aug; 912-915. DOI: 10.1200/PO.20.00114
72. Nayar et al. Acquired HER2 mutations in ER+ metastatic breast cancer confer resistance to estrogen receptor-directed therapies. Nat. Genet. 2019 Feb;51(2):207-216. PMID: 30531871
73. Chen et al. Targeting oncogenic Myc as a strategy for cancer treatment. Signal Transduct Target Ther. 2018 Feb 23;3:5. doi: 10.1038/s41392-018-0008-7. eCollection 2018. PMID: 29527331
74. Dang. MYC on the path to cancer. Cell. 2012 Mar 30;149(1):22-35. PMID: 22464321
75. Dominguez-Sola et al. Non-transcriptional control of DNA replication by c-Myc. Nature. 2007 Jul 26;448(7152):445-51. PMID: 17597761
76. Wahlström et al. Impact of MYC in regulation of tumor cell metabolism. Biochim. Biophys. Acta. 2015 May;1849(5):563-9. PMID: 25038584
77. Dang et al. The c-Myc target gene network. Semin. Cancer Biol. 2006 Aug;16(4):253-64. PMID: 16904903
78. Blackwood et al. Myc and Max function as a nucleoprotein complex. Curr. Opin. Genet. Dev. 1992 Apr;2(2):227-35. PMID: 1638116
79. Chakraborty et al. A common functional consequence of tumor-derived mutations within c-MYC. Oncogene. 2015 Apr 30;34(18):2406-9. PMID: 24998853
80. Xu-Monette et al. Clinical and Biologic Significance of MYC Genetic Mutations in De Novo Diffuse Large B-cell Lymphoma. Clin. Cancer Res. 2016 Jul 15;22(14):3593-605. PMID: 26927665
81. Kalkat et al. MYC Deregulation in Primary Human Cancers. Genes (Basel). 2017 May 25;8(6). PMID: 28587062
82. Beroukhim et al. The landscape of somatic copy-number alteration across human cancers. Nature. 2010 Feb 18;463(7283):899-905. doi: 10.1038/nature08822. PMID: 20164920
83. Taub et al. Translocation of the c-myc gene into the immunoglobulin heavy chain locus in human Burkitt lymphoma and murine plasmacytoma cells. Proc Natl Acad Sci U S A. 1982 Dec;79(24):7837-41. PMID: 6818551
84. Ott et al. Understanding MYC-driven aggressive B-cell lymphomas: pathogenesis and classification. Hematology Am Soc Hematol Educ Program. 2013;2013:575-83. PMID: 24319234
85. Posternak et al. Strategically targeting MYC in cancer. F1000Res. 2016;5. PMID: 27081479
86. Carabet et al. Therapeutic Inhibition of Myc in Cancer. Structural Bases and Computer-Aided Drug Discovery Approaches. Int J Mol Sci. 2018 Dec 29;20(1). PMID: 30597997
87. Shahbazi et al. The Bromodomain Inhibitor JQ1 and the Histone Deacetylase Inhibitor Panobinostat Synergistically Reduce N-Myc Expression and Induce Anticancer Effects. Clin. Cancer Res. 2016 May 15;22(10):2534-44. PMID: 26733615
88. Volinia et al. Molecular cloning, cDNA sequence, and chromosomal localization of the human phosphatidylinositol 3-kinase p110 alpha (PIK3CA) gene. Genomics. 1994 Dec;24(3):472-7. PMID: 7713498
89. Whale et al. Functional characterization of a novel somatic oncogenic mutation of PIK3CB. Signal Transduct Target Ther. 2017;2:17063. PMID: 29279775

## References (continued)


90. Osaki et al. PI3K-Akt pathway: its functions and alterations in human cancer. Apoptosis. 2004 Nov;9(6):667-76. PMID: 15505410
91. Cantley. The phosphoinositide 3-kinase pathway. Science. 2002 May 31;296(5573):1655-7. PMID: 12040186
92. Fruman et al. The PI3K Pathway in Human Disease. Cell. 2017 Aug 10;170(4):605-635. PMID: 28802037
93. Engelman et al. The evolution of phosphatidylinositol 3-kinases as regulators of growth and metabolism. Nat. Rev. Genet. 2006 Aug;7(8):606-19. PMID: 16847462
94. Vanhaesebroeck et al. PI3K signalling: the path to discovery and understanding. Nat. Rev. Mol. Cell Biol. 2012 Feb 23;13(3):195-203. PMID: 22358332
95. Yuan et al. PI3K pathway alterations in cancer: variations on a theme. Oncogene. 2008 Sep 18;27(41):5497-510. PMID: 18794884
96. Liu et al. Targeting the phosphoinositide 3-kinase pathway in cancer. Nat Rev Drug Discov. 2009 Aug;8(8):627-44. PMID: 19644473
97. Hanahan et al. Hallmarks of cancer: the next generation. Cell. 2011 Mar 4;144(5):646-74. PMID: 21376230
98. Miled et al. Mechanism of two classes of cancer mutations in the phosphoinositide 3-kinase catalytic subunit. Science. 2007 Jul 13;317(5835):239-42. PMID: 17626883
99. Burke et al. Synergy in activating class I PI3Ks. Trends Biochem. Sci. 2015 Feb;40(2):88-100. PMID: 25573003
100. Burke et al. Oncogenic mutations mimic and enhance dynamic events in the natural activation of phosphoinositide 3-kinase p110α (PIK3CA). Proc. Natl. Acad. Sci. U.S.A. 2012 Sep 18;109(38):15259-64. PMID: 22949682
101. https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/212526s006lbl.pdf
102. Mayer et al. A Phase Ib Study of Alpelisib (BYL719), a PI3Kα-Specific Inhibitor, with Letrozole in ER+/HER2- Metastatic Breast Cancer. Clin. Cancer Res. 2017 Jan 1;23(1):26-34. PMID: 27126994
103. Mayer et al. A Phase II Randomized Study of Neoadjuvant Letrozole Plus Alpelisib for Hormone Receptor-Positive, Human Epidermal Growth Factor Receptor 2-Negative Breast Cancer (NEO-ORB). Clin. Cancer Res. 2019 Feb 5. PMID: 30723140
104. Jung et al. Pilot study of sirolimus in patients with PIK3CA mutant/amplified refractory solid cancer. Mol Clin Oncol. 2017 Jul;7(1):27-31. PMID: 28685070
105. Janku et al. PIK3CA mutations in patients with advanced cancers treated with PI3K/AKT/mTOR axis inhibitors. Mol. Cancer Ther. 2011 Mar;10(3):558-65. PMID: 21216929