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Pertuzumab Therapy and *ERBB2* Genotype

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Introduction

Pertuzumab (brand name, Perjeta) is a monoclonal antibody used in the treatment of breast cancer. Pertuzumab was designed to target an epidermal growth factor receptor encoded by the *ERBB2* gene, commonly referred to as the *HER2* gene.

The *ERBB2* gene is overexpressed in 15–20% of breast cancers and is also overexpressed in some cases of other cancer types (gastric, colon, head, and neck). Historically, "HER2-positive" tumors are associated with a faster rate of growth and a poorer prognosis than other breast cancer subtypes. The use of pertuzumab in treatment regimens improves outcomes, with limited adverse effects that include cardiac toxicity.

Pertuzumab is used with other drugs as an advanced breast cancer treatment, a neoadjuvant treatment, and an adjuvant treatment for HER2-positive breast cancer. In the advanced/metastatic setting, pertuzumab added to trastuzumab and a taxane is used to increase long-term progression-free and overall survival when administered in the first line setting. As neoadjuvant treatment, pertuzumab is given with trastuzumab and chemotherapy before surgery in individuals with early breast cancer to increase pathologic complete response rates. And as an adjuvant treatment, pertuzumab is given with trastuzumab and chemotherapy to reduce the risk of cancer reoccurrence in individuals with early breast cancer (Table 1).

The 2020 FDA-approved drug label states that pertuzumab should only be used to treat individuals with tumors that have either HER2 protein overexpression or *ERBB2* gene amplification, as determined by an accurate and validated FDA-approved assay. This is because these are the only individuals studied for whom benefit has been shown (1).

The most recent update (2018) American Society of Clinical Oncology (ASCO) / College of American Pathologists (CAP) guidelines continue to state that all newly diagnosed individuals with breast cancer must have an HER2 test performed. Individuals who then develop metastatic disease must have an HER2 test performed in a metastatic site, if a tissue sample is available (2).

Table 1. The FDA Indications and Usage of Pertuzumab in HER2-positive Breast Cancer (2020)

Individual selection*	Metastatic breast cancer (treatment)	Breast cancer (neoadjuvant treatment)	Early breast cancer (adjuvant treatment)
Tumor HER2 status	HER2-positive	HER2-positive	HER2-positive

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Table 1. continued from previous page.

Individual selection*	Metastatic breast cancer (treatment)	Breast cancer (neoadjuvant treatment)	Early breast cancer (adjuvant treatment)
Usage	Use pertuzumab with trastuzumab and docetaxel	Use pertuzumab with trastuzumab and chemotherapy	
Indications	Indicated for individuals with metastatic breast cancer who have not received before anti-HER2 therapy or chemotherapy for metastatic disease	Indicated for individuals with locally advanced, inflammatory, or early-stage breast cancer (either greater than 2 cm in diameter or node positive) as part of a treatment regime for early breast cancer	Indicated for individuals with early breast cancer at high risk of recurrence

* Select individuals based on HER2 protein overexpression or *HER2* gene amplification in tumor specimens. Assessment of HER2 protein overexpression and *ERBB2* gene amplification should be performed using FDA-approved tests specific for breast cancer by laboratories with demonstrated proficiency. Information on the FDA-approved tests for the detection of HER2 protein overexpression and *ERBB2* gene amplification is available at: http://www.fda.gov/CompanionDiagnostics.
Improper assay performance, including use of sub optimally fixed tissue, failure to utilize specified reagents, deviation from specific assay instructions, and failure to include appropriate controls for assay validation, can lead to unreliable results.
This FDA table was created from (1).

Drug Class: HER2 Inhibitors

Human epidermal growth factor receptor 2 (commonly referred to as HER2 or HER-2/neu) is encoded by the gene *ERBB2,* which is a transmembrane receptor tyrosine kinase. Overexpression of *ERBB2* leads to rapid cell growth in multiple types of solid tumors. The HER2 can be inactivated by a class of chemicals known as tyrosine kinase inhibitors or via targeted monoclonal antibodies. An increasing number of HER2-targeted therapies have been approved to treat HER2-positive breast cancer, including:

- Pertuzumab –– monoclonal antibody (brand name Perjeta)
- Trastuzumab –– monoclonal antibody (brand name Herceptin)
- Ado-trastuzumab emtansine –– antibody-drug-conjugate (monoclonal antibody attached to a chemotherapy drug (brand name Kadcyla, also called TDM-1)
- Fam-trastuzumab deruxtecan –– antibody-drug-conjugate (brand name Enhertu)
- Neratinib –– a kinase inhibitor (brand name Nerlynx)
- Lapatinib –– a kinase inhibitor (brand name Tykerb)
- Tucatinib –– a kinase inhibitor (brand name Tukysa)
- Dacomitinib –– a kinase inhibitor (brand name Vizimpro)

There are more anti-HER2 drugs progressing through clinical trials, and some trials are looking at whether HER2-targeted therapies could be used to treat other tumors that overexpress HER2, such as colorectal and non-small-cell lung cancer. However, early results are not replicating the success of HER2-targeted therapies in breast and gastric cancer (3, 4, 5). One exception is the use of trastuzumab, which has been approved for use in HER2-positive metastatic gastric cancer (6).

Drug: Pertuzumab

Pertuzumab is a monoclonal antibody that targets HER2 (a tyrosine kinase receptor, encoded by the *ERBB2* gene). Pertuzumab is only used to treat specific tumors that overexpress or are amplified for *ERBB2*, which are known as "HER2-positive" tumors.

In 2012, the FDA approved the use of pertuzumab in the treatment of HER2-positive metastatic breast cancer to increase the chance of long-term disease-free survival. Pertuzumab is used with trastuzumab (another

monoclonal antibody that targets *ERBB2*) and docetaxel (a chemotherapy drug) to treat individuals who have not previously had anti-HER2 therapy or chemotherapy for HER2-positive metastatic breast cancer.

In 2013, the FDA granted an accelerated approval to pertuzumab, again with trastuzumab and docetaxel, as a neoadjuvant treatment of HER2-positive breast cancer. In the neoadjuvant setting, pertuzumab is given before surgical therapy in women with HER2-positive breast cancer that is locally advanced, inflammatory, or at an early stage (either greater than 2 cm in diameter or lymph node positive) (1, 7, 8, 9). In 2017, the FDA approved pertuzumab for use with trastuzumab and chemotherapy as an adjuvant treatment for individuals with HER2-positive early breast cancer with a high risk of recurrence, to reduce the risk of recurrence (10, 11).

Before treatment with pertuzumab begins, overexpression of the HER-2 protein or amplification of the *ERBB2* gene must first be determined. In clinical studies of pertuzumab, individuals with breast cancer were required to have evidence of HER2 overexpression defined as 3+ immunohistochemistry (IHC) or fluorescence *in situ* hybridization (FISH) amplification ratio of 2 or greater (see Tumor Testing for *ERBB2* (HER2)).

The FDA recommends that testing be performed using an FDA-approved test, in a laboratory with demonstrated proficiency with the technology being used. This is because the benefits of pertuzumab have only been proven in individuals with HER2 positive tumors (12).

In addition, although pertuzumab is well tolerated, the risks of treatment include infusion reactions, diarrhea, and cardiomyopathy that can result in cardiac failure. The mechanism of how anti-HER2 drugs such as pertuzumab can cause cardiotoxicity is not known, but evidence from mouse models suggests HER2 signaling plays a key role in heart development and cardiomyocyte survival during stress (reviewed by (13). Additional evidence suggests that using cardiac drugs, such as beta blockers and ace inhibitors, may help prevent subsequent cardiomyopathy. Data on the safety of anti-HER2 drugs in older individuals, who are most likely to take these drugs, are lacking, having been mostly derived from subgroup analysis of larger trials (14, 15, 16).

The pregnancy status of women of child-bearing age should be checked, and women should be warned that exposure to pertuzumab during pregnancy, or within 7 months before conception, can result in fetal harm and potentially, fetal death. Therefore, women should use effective contraception for 7 months following their last dose of pertuzumab (1).

Pertuzumab targets the HER2 receptor by binding to a specific region in its extracellular domain. The HER2 receptor is an epidermal growth factor receptor, consisting of an intracellular tyrosine kinase domain, a single transmembrane spanning region, and an extracellular domain, made up of 4 subdomains (I–IV). Pertuzumab binds to subdomain II and trastuzumab binds to subdomain IV. This binding limits the receptor's ability to activate its intrinsic kinase, which in turn, limits the activation of numerous signaling pathways that can promote cell growth.

A number of proposed mechanisms may underlie the anti-tumor effects of pertuzumab and trastuzumab. One such mechanism is that these drugs block the HER3 receptor from binding to HER2. The HER2-HER3 dimerized receptor is thought to be highly active, triggering many signaling cascades in the absence of a "true" ligand (17, 18, 19, 20).

Another proposed mechanism is antibody-dependent cellular cytotoxicity. Once pertuzumab or trastuzumab have bound to a cancer cell, immune cells (typically activated natural killer cells) bind to the drug and initiate lysis of the cancer cell (21).

Unfortunately, breast cancer may start to progress again during HER2 targeted therapy. Mechanisms that may facilitate drug resistance and disease progression during treatment include increased signaling from the HER family of receptors, an upregulation of downstream signaling pathways, and an increased level of insulin growth factor-1 receptor (22, 23). In the instance of metastatic disease, ASCO practice guidelines suggest obtaining a tissue sample from the metastatic site to confirm HER2-status in case of relapse after curative treatment (24).

As a new drug, there is not enough data on the risk of developing resistance to pertuzumab therapy. However, there is a lower response rate to pertuzumab among individuals previously treated with trastuzumab. Resistance is particularly problematic because pertuzumab is now being used earlier, to treat of early-stage disease (25, 26).

Gene: *ERBB2* (*HER2*)

The human epidermal growth factor receptor (HER) protein family consists of 4 members: the epidermal growth factor receptor (EGFR), *ERBB2* (HER2), *ERBB3* (HER3), and *ERBB4* (HER4) (see Nomenclature for Selected Genes). All 4 members are transmembrane tyrosine kinase receptors, and they regulate a number of important cellular processes, such as cell growth, survival, and differentiation (27).

The *ERBB2* gene, along with *EGFR*, are proto-oncogenes. Proto-oncogenes are a group of genes that, when mutated or expressed at abnormally high levels, can contribute to abnormal cell growth. The mutated version of the proto-oncogene is called an oncogene. Proto-oncogenes typically encode proteins that stimulate cell division, inhibit cell differentiation, and halt cell death. All these are important biological processes. However, the increased production of these proteins, caused by oncogenes, can lead to the proliferation of poorly differentiated cancer cells (28).

The official gene symbol for HER2 is *ERBB2*, which is derived from a viral oncogene with which the receptor shares homology; "v-erb-b2 avian erythroblastic leukemia viral oncogene homolog 2." However, clinicians commonly refer to the *ERBB2* gene as "*HER2*" (Human Epidermal growth factor Receptor 2) or "*HER2/neu*" (neu was the name given to the gene that caused cancer derived from a rodent neuro/glioblastoma). It is the legacy gene symbol for *ERBB2* and may be more commonly used by the community in clinical care, it is also commonly used to describe the protein encoded by the *ERBB2* gene.

One unique feature of HER2 compared with the other receptors in the HER family is the absence of a known ligand. This receptor may permanently be in an activated state, or it may become activated during heterodimerization with one of the other members of the HER family (29). Additionally, one unique feature of HER3 is that it has little enzymatic activity compared with the other tyrosine kinase receptors in the HER family. An important role of HER3 is to act as a heterodimerization partner for HER2 (30, 31).

When a partner such as HER3 binds to HER2, the heterodimer undergoes activation, which stimulates the intrinsic tyrosine kinase activity of the receptor. Autophosphorylation of several key residues of the receptor triggers the downstream activation of many commonly used growth factor signaling pathways, such as the PI3K/AKT/mTOR pathway and the RAS/RAF/MEK/ERK pathway (17, 32). Impaired HER2 signaling is associated with the development of neurodegenerative diseases, such as multiple sclerosis and Alzheimer disease, while excessive HER2 signaling is associated with the development of cancers.

The *ERBB2* gene is overexpressed in approximately 15–20% of breast tumors, as a result of amplification of the *ERBB2* gene, and tumors with increased HER2 typically have a higher growth rate and more aggressive clinical behavior (33, 34, 35, 36). Although gene amplification is frequently seen in cancer and other degenerative disorders, the underlying basis for amplification remains largely unknown (37). In the case of *ERBB2*, although sequence variants have been identified, it is most commonly a wildtype *ERBB2* gene copy that is overexpressed in tumors (23). In approximately 1% of breast cancers, activating variants in *ERBB2* can be identified that are likely to drive tumorigenesis, without *ERBB2* amplification (38).

Genes: *ESR1* and *PR*

The *ESR1* gene encodes the estrogen receptor, and the *PR* gene encodes the progesterone receptor. Breast cancer cells may have:

- a receptor for estrogen (ER-positive)

- a receptor for progesterone (PR-positive)
- receptors for both estrogen and progesterone (hormone receptor positive)
- nether receptor (hormone receptor negative)
- or receptors for both hormones and HER2 overexpression (triple positive).

Endocrine (hormone) therapy is typically indicated for hormone receptor positive tumors. Some evidence suggests that HER2 status influences the response of hormone receptor positive tumors to endocrine therapy. In one study, individuals with ER-positive tumors and low-level *ERBB2* amplification (as defined by quantitative FISH) had significantly less benefit from adjuvant anti-HER2 therapy after chemotherapy (39). However, ASCO guidelines clearly state that HER2 status should not be used to withhold endocrine therapy for an individual with a hormone receptor-positive breast cancer, nor to select one specific type of endocrine therapy over another (40).

The drug label discuses 2 trials that included analyses of how hormone receptor status influenced the response of HER2-positive tumors to pertuzumab. The NeoSphere clinical trial (NCT00545688) reported that individuals with hormone receptor-positive tumors responded less well to pertuzumab therapy compared with individuals with hormone receptor-negative tumors. The CLEOPATRA clinical trial (NCT00567190) reported that individuals with hormone receptor–positive disease had a higher hazard ratio than individuals with hormone receptor-negative disease. (1, 41, 42) Furthermore, in the interim overall survival analysis of the APHINITY clinical trial (NCT01358877), a treatment benefit of pertuzumab was seen in the node positive, hormone receptor positive cohort (invasive disease-free survival hazard ratio for HR positive is 0.73 [95% confidence interval 0.59–0.92]). Subgroup analysis of the APHINITY trial further suggests that ER-negative individuals benefit more from dual blockade with trastuzumab and pertuzumab. (43) Early results from another study (NCT02564900) suggest that trastuzumab deruxtecan may be effective as an anti-HER2 therapy in HER2-low expressing (HER2 "negative" scores of 1+ or 2+ by standard IHC testing) tumors (44).

Linking Gene Overexpression with Treatment Response

The HER2 overexpression or amplification is strongly linked to a beneficial treatment response to pertuzumab. This is to be expected, given that pertuzumab was developed to target HER2. Consequently, current guidelines for breast cancer treatment limit the use of HER2-blocking agents to tumors with HER2 gene amplification (2, 35, 36).

Genetic Testing

The NIH Genetic Testing Registry (GTR) displays genetic tests that are available for the *ERBB2* gene and the pertuzumab drug response.

Tumor Testing for *ERBB2* (HER2) Gene and Protein

There are 2 main methods used for *ERBB2*/HER2 testing: testing for overexpression of the HER2 protein using IHC or testing for gene amplification using *in situ* hybridization (ISH). Each assay type has diagnostic pitfalls that must be avoided, and so the pathologist who reviews the histologic findings should decide the optimal assay (IHC or ISH) for the determination of HER2 status (35, 36).

In an IHC assay, a slice of tumor tissue is stained, along with a control sample that contains high levels of HER2. The tumor sample is then examined by light microscopy to assess the intensity of membrane staining—the amount of staining correlates with the quantity of HER2 protein and is typically graded from 0 to 3+:

- IHC 0 means no visible staining or membrane staining that is incomplete and is faint/barely perceptible and in ≤10% of tumor cells

- IHC 1+ is also an "HER2 negative" result—there is a staining pattern of incomplete membrane staining that is faint/barely perceptible and in >10% of tumor cells
- IHC 2+ is an "HER2 equivocal result"— invasive breast cancer with "weak to moderate complete membrane staining observed in >10% of tumor cells."
- IHC 3+ is an "HER2 positive result"—there is a staining pattern with circumferential membrane staining that is complete, intense and in >10% of tumor cells. This should be readily appreciated using a low-power objective and observed within a homogenous and continuous invasive cell population.

For an equivocal (IHC 2+) result, either a reflex test must be ordered (same specimen using ISH), or a new test must be ordered (using a new specimen, if available, using ISH or FISH) to confirm the results.

The ISH assay, or FISH/CISH assay (fluorescence or chromogenic *in situ* hybridization), measures *ERBB2* gene amplification by measuring *ERBB2* DNA—the actual number of copies of the *ERBB2* genes are counted. Using the FISH assay, under the microscope, the genes appear as red signals or dots, in a blue-stained cancer cell nucleus. The result is usually either FISH negative (normal level of *ERBB2* gene) or FISH positive (at least twice as much as the normal level of *ERBB2* gene), but in a small number of cases the FISH result will be equivocal due to a low level of *ERBB2* amplification. The use of a control helps distinguish between a negative result and a non-informative result caused by an error. Approximately 25% of individuals who have an IHC 2+ result will have a FISH positive result (45).

For the complete algorithms for evaluation of HER2 protein expression using IHC or ISH, please see the ASCO guidelines, located here: (2).

Therapeutic Recommendations based on Genotype

This section contains excerpted[1] information on gene-based dosing recommendations. Neither this section nor other parts of this review contain the complete recommendations from the sources.

2020 Statement from the US Food and Drug Administration (FDA)

Pertuzumab 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.

[…]

Select patients based on HER2 protein overexpression or *HER2* gene amplification in tumor specimens. Assessment of HER2 protein overexpression and *HER2* gene amplification should be performed using FDA-approved tests specific for breast cancer by laboratories with demonstrated proficiency. Information on the FDA-approved tests for the detection of HER2 protein overexpression and *HER2* gene amplification is available at: http://www.fda.gov/CompanionDiagnostics.

[1] The FDA labels specific drug formulations. We have substituted the generic names for any drug labels in this excerpt. The FDA may not have labeled all formulations containing the generic drug. Certain terms, genes and genetic variants may be corrected in accordance with nomenclature standards, where necessary. We have given the full name of abbreviations, shown in square brackets, where necessary.

Improper assay performance, including use of suboptimally fixed tissue, failure to utilize specified reagents, deviation from specific assay instructions, and failure to include appropriate controls for assay validation, can lead to unreliable results.

Please review the complete therapeutic recommendations that are located here: (1).

2018 Update: American Society of Clinical Oncology (ASCO) /College of American Pathologists (CAP) Recommendations

First released in 2007 and updated in 2013 and 2018, the recommendations by the American Society of Clinical Oncology (ASCO)/College of American Pathologists (CAP) human epidermal growth factor receptor 2 (HER2) testing Expert Panel are aimed at improving the analytic validity of HER2 testing and the clinical utility of HER2 as a predictive biomarker for potential responsiveness to therapies targeting the HER2 protein.

2013: ASCO/CAP Key Recommendations for Oncologists

- Must request HER2 testing on every primary invasive breast cancer (and on metastatic site, if stage IV and if specimen available) from a patient with breast cancer to guide decision to pursue HER2-targeted therapy. This should be especially considered for a patient who previously tested HER2 negative in a primary tumor and presents with disease recurrence with clinical behavior suggestive of HER2-positive or triple-negative disease.
- Should recommend HER2-targeted therapy if HER2 test result is positive, if there is no apparent histopathologic discordance with HER2 testing and if clinically appropriate.
- Must delay decision to recommend HER2-targeted therapy if initial HER2 test result is equivocal. Reflex testing should be performed on the same specimen using the alternative test if initial HER2 test result is equivocal or on an alternative specimen.
- Must not recommend HER2-targeted therapy if HER2 test result is negative and if there is no apparent histopathologic discordance with HER2 testing.
- Should delay decision to recommend HER2-targeted therapy if HER2 status cannot be confirmed as positive or negative after separate HER2 tests (HER2 test result or results equivocal). The oncologist should confer with the pathologist regarding the need for additional HER2 testing on the same or another tumor specimen.
- If the HER2 test result is ultimately deemed to be equivocal, even after reflex testing with an alternative assay (i.e., if neither test is unequivocally positive), the oncologist may consider HER2-targeted therapy. The oncologist should also consider the feasibility of testing another tumor specimen to attempt to definitely establish the tumor HER2 status and guide therapeutic decisions. A clinical decision to ultimately consider HER2-targeted therapy in such cases should be individualized on the basis of patient status (comorbidities, prognosis, and so on) and patient preferences after discussing available clinical evidence.

2018: ASCO/CAP Updated Key Recommendations for HER2 testing

[…]

Two recommendations addressed via correspondence in 2015 are included. First, immunohistochemistry (IHC) 2+ is defined as invasive breast cancer with weak to moderate complete membrane staining observed in >10% of tumor cells. Second, if the initial HER2 test result in a core needle biopsy specimen of a primary breast cancer is negative, a new HER2 test may (not "must") be ordered on the excision specimen based on specific clinical criteria.

Please review the complete ASCO/CAP recommendations in the 2013 update (20) and 2018 update (2).

Nomenclature for Selected Genes Associated with Pertuzumab Response

Common gene symbols	Alternative gene symbols
EGFR	*ERBB1* *ERBB* *HER1*
ERBB2	*HER2* *HER-2* *HER-2/neu* *NEU*
ERBB3	*HER3*
ERBB4	*HER4*

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