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# Pertuzumab Therapy and *ERBB2 (HER2)* Genotype

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## Introduction

Pertuzumab is a monoclonal antibody used in the treatment of breast cancer. It targets a receptor in the epidermal growth factor family encoded by the *ERBB2* gene, which is commonly referred to as the *HER2* gene.

The *HER2* 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). Overall, "HER2 positive" tumors are associated with a faster rate of growth and a poorer prognosis. The use of pertuzumab in treatment regimens for breast cancer improves outcomes, but adverse effects of therapy include cardiac toxicity.

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

A guideline from ASCO/CAP states that oncologists must request HER2 testing on every primary invasive breast cancer (and on a 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 (2).

## Drug: Pertuzumab

Pertuzumab (brand name, Perjeta) is a monoclonal antibody that targets ERBB2 (a tyrosine kinase receptor, also known as HER2 or HER-2/neu). Pertuzumab is only used to treat specific tumors that overexpress ERBB2; these tumors are known as "HER2-positive" tumors.

Pertuzumab is used in the treatment of HER2-positive metastatic breast cancer to increase the chance of long-term disease-free survival. Pertuzumab is used in combination with trastuzumab (another monoclonal antibody that targets ERBB2) and docetaxel (a chemotherapy drug) (1).

Recently, HER2 targeted therapy has been approved by the FDA for use in the neoadjuvant setting. Neoadjuvant therapy is given before surgical therapy in women with early stage breast cancer. In the neoadjuvant setting, pertuzumab, along with trastuzumab and docetaxel, is used to treat HER2-positive breast cancer, which may be at an early stage, locally advanced, or inflammatory (1, 3, 4).

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Before treatment with pertuzumab begins, overexpression of the HER-2 protein or amplification of the *HER-2* gene must first be determined. In clinical studies of pertuzumab, patients with breast cancer were required to have evidence of HER-22 overexpression defined as 3+ IHC or FISH amplification ratio of 2 or greater (see Genetic Testing) (1). 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 patients with tumors that overexpress HER2. In addition, although pertuzumab is generally well tolerated, the risks of treatment include infusion reactions, and rarely pulmonary toxicity, and cardiomyopathy that can result in cardiac failure.

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, comprised of four 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 (5-8).

Another proposed mechanism is antibody-dependent cellular cytotoxicity (ADCC). 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 (9). Trastuzumab may also mediate the enhanced internalization and degradation of the HER2 receptor, inhibit angiogenesis, and inhibit HER2 shedding by preventing the cleavage of HER2 and the subsequent release of its extracellular domain (10, 11).

Unfortunately, breast cancer may start to progress again during HER2 targeted therapy. Possible 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 (12, 13).

At the time of writing, four drugs have been approved to target HER2 (pertuzumab, trastuzumab, lapatinib, and T-DM1), with more drugs in clinical trials.

## Gene: ERBB2 (HER2)

The human epidermal growth factor receptor (HER) family consists of four members: the epidermal growth factor receptor (EGFR), HER2, HER3, and HER4 (see Nomenclature). All four members are transmembrane tyrosine kinase receptors, and they regulate a number of important cellular processes, such as cell growth, survival, and differentiation (14).

*HER2*, 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 (15).

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). *HER2* is an alternate gene symbol for *ERBB2* and is more commonly used by the community in clinical care.

One unique feature of ERBB2 compared to the other receptors in the HER family is the absence of a known ligand. It is therefore thought that 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 (11). And, one unique feature of HER3 is that it has very little enzymatic activity compared to the other tyrosine kinase receptors in the HER family. It is therefore thought that an important role of HER3 is to act as a heterodimerization partner for ERBB2 (16, 17).

When a partner such as HER3 binds to ERBB2, 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 (18, 19). Impaired ERBB2 signaling is associated with the development of neurodegenerative diseases, such as multiple sclerosis and Alzheimer disease, whereas excessive ERBB2 signaling is associated with the development of cancers.

ERBB2 is overexpressed in approximately 15-20% of breast tumors, as a result of amplification of the *ERBB2* gene, and tumors with increased ERBB2 usually have a higher growth rate and more aggressive clinical behavior (2, 20-22). Although gene amplification is frequently seen in cancer and other degenerative disorders, the underlying basis for amplification remain largely unknown (23). And in the case of ERBB2, although sequence variants have been identified, it is nearly always the wildtype *ERBB2* gene that is overexpressed in tumors (24). In about 1% of breast cancers, activating mutations in *ERBB2* can be identified that are likely to drive tumorigenesis, without *ERBB2* amplification (25).

## Tumor Testing for *ERBB2 (HER2)*

There are two main methods used for HER2 testing: testing for overexpression of the HER2 protein using immunohistochemistry (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 determine the optimal assay (IHC or ISH) for the determination of HER2 status (2, 22).

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 and is an "HER2 negative" result
- IHC 1+ is also an "HER2 negative" result—there is a staining pattern with weak and incomplete staining, or weak and complete staining of very few tumor cells
- IHC 2+ is an "HER2 equivocal result"—there is a staining pattern with moderately intense staining, or intense staining of very few tumor cells
- IHC 3+ is an "HER2 positive result"—there is a staining pattern with intense membrane staining on more than 10% of tumor cells, indicating a higher than normal level of HER2

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 IHC or ISH) to confirm the results.

The ISH assay, or FISH assay (fluorescence in situ hybridization), measures *HER2* gene amplification by measuring *HER2* DNA—the actual number of copies of the *HER2* genes are counted. 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 *HER2* gene) or FISH positive (at least twice as much as normal level of *HER2* gene), but in a small number of cases the FISH result will be equivocal due to a low level of *HER2* amplification. The use of

a control helps distinguish between a negative result and a non-informative result caused by an error. Approximately 25% of patients who have an IHC 2+ result will have a FISH positive result (26).

**For the complete algorithms for evaluation of HER2 protein expression using IHC or ISH, please see the American Society of Clinical Oncology (ASCO) guidelines, located here: (27)**

## 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.**

**Statement from the US Food and Drug Administration (FDA):**

Detection of HER2 protein overexpression is necessary for selection of patients appropriate for pertuzumab therapy because these are the only patients studied and for whom benefit has been shown. Patients with breast cancer were required to have evidence of HER2 overexpression defined as 3+ IHC or FISH amplification ratio ≥ 2.0 in the clinical studies. Only limited data were available for patients whose breast cancer was positive by FISH, but did not demonstrate protein overexpression by IHC.

Assessment of HER2 status should be performed by laboratories using FDA-approved tests with demonstrated proficiency in the specific technology being utilized. 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.

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

**FDA-approved medical devices for HER2 are listed here.**

**Excerpted recommendations from the American Society of Clinical Oncology / College of American Pathologists 2013 clinical practice guideline update:**

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.

[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.

- 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.

**Please review the complete therapeutic recommendations, including Key Recommendations for Pathologists that are located here (2).**

## Nomenclature

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

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