



## Trastuzumab Therapy and *ERBB2* Genotype

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### Introduction

Trastuzumab (brand name, Herceptin) is a monoclonal antibody used in the treatment of breast and gastric/gastroesophageal cancer. It targets an epidermal growth factor receptor encoded by the *ERBB2* gene, which is commonly referred to as the *HER2* gene. Multiple biosimilar products to Herceptin are now available: Kanjinti, Trazimera, Ontruzant, Herzuma and Ogivri.

The *ERBB2* gene is overexpressed in 15–20% of breast cancers and 15–20% of gastric and esophageal cancers. Overall, “HER2 positive” tumors are associated with a faster rate of growth and—in some cases—a poorer prognosis in absence of anti-HER2 therapy. The use of trastuzumab in treatment regimens improves outcomes, with limited adverse effects that include cardiac toxicity.

The FDA-approved drug label states that trastuzumab 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, specific for the type of tumor tested (breast or gastric) (Table 1)(1). The FDA-approved drug label for all trastuzumab biosimilars describes only the use of trastuzumab in adjuvant treatment of breast cancer, though its efficacy in neoadjuvant care for breast cancer (reviewed in part by (2)) and esophageal adenocarcinoma (3) has also been documented.

The most recent update (2018) of the American Society of Clinical Oncology (ASCO)/College of American Pathologists (CAP) guidelines continues 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 tissue sample is available (4).

**Table 1.** The FDA Indications and Usage of Trastuzumab (2020)

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

Table 1. continued from previous page.

Individual selection*	Breast cancer (adjuvant treatment)	Metastatic breast cancer	Metastatic gastric cancer
Indications and usage	Indicated for adjuvant treatment of HER2 overexpressing node positive or node negative breast cancer. -As part of a treatment regimen consisting of doxorubicin, cyclophosphamide, and either paclitaxel or docetaxel # -As part of a treatment regimen with docetaxel and carboplatin # -As a single agent following multi-modality anthracycline based therapy #	Indicated in combination with paclitaxel for first-line treatment of HER2-overexpressing metastatic breast cancer, or as a single agent for treatment of HER2-overexpressing breast cancer	Indicated for the treatment of individuals with HER2-overexpressing metastatic gastric or gastroesophageal junction adenocarcinoma who have not received prior treatment for metastatic disease. (in combination with cisplatin and capecitabine or 5-fluorouracil)#

\* Select individuals based on HER2 protein overexpression or *ERBB2* gene amplification in tumor specimens.

# Combination therapy administration notes are specific to FDA labels for Trazimera and Ogivri (5, 6)

This FDA table was adapted 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 Tykysa)
- Dacomitinib--a kinase inhibitor (brand name Vizimpro)

There are several 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 (7, 8, 9).

## Drug: Trastuzumab

Trastuzumab (brand name, Herceptin) is a monoclonal antibody that targets HER2 (a tyrosine kinase receptor, encoded by the gene *ERBB2*). Multiple biosimilar products to trastuzumab are now available under the brand names Kanjinti, Trazimera, Ontruzant, Herzuma and Ogivri. Trastuzumab is only used to treat specific tumors that overexpress *ERBB2*, which are known as “HER2-positive” tumors.

Trastuzumab is the first molecular targeted agent approved as standard therapy for gastric cancer, and is the only HER2 targeted therapy approved for the treatment of advanced gastric cancer. The 2015 NCCN guidelines recommend the first-line treatment of trastuzumab combined with chemotherapy in individuals overexpressing HER2 (10).

Trastuzumab was also the first targeted anti-HER2 therapy available for metastatic HER2-positive breast cancer, and led to significant improvement in prognosis over the previous standard of care chemotherapy regimens, and was the first monoclonal antibody to be approved for non-metastatic HER2-positive breast cancer (11).

Trastuzumab is typically used with chemotherapy as neoadjuvant or adjuvant treatment of early-stage HER2-positive breast cancer. Neoadjuvant therapy is given before primary therapy to shrink a tumor to an operable size, help make decisions for further therapy after surgery, allow for breast-conserving surgery, and increase the chance of long-term, disease-free survival. Adjuvant therapies are used after surgery to increase the chance of long-term disease-free survival. Trastuzumab can be used with chemotherapy with or without another HER2 targeted agent pertuzumab (12). Trastuzumab is also used in the treatment of HER2-positive metastatic breast cancer and HER2-positive metastatic gastric cancer (1, 13).

Pertuzumab, another targeted anti-HER2 therapy, can also be added to multiple treatment regimens, including trastuzumab/chemotherapy combination therapy, in the neoadjuvant, adjuvant, or metastatic setting (14, 15, 16, 17, 18). Regardless of whether initial treatment was given before or after surgery, adjuvant trastuzumab should be continued to complete one year of therapy.

Recently, another HER2-targeted therapy ado-trastuzumab emtansine (Kadcyla) has been approved by the FDA for adjuvant treatment of HER2-positive early breast cancer (EBC) in individuals who have residual invasive disease after receiving taxane and trastuzumab-based treatment.

Before treatment with trastuzumab begins, overexpression of the *ERBB2* protein or amplification of the *ERBB2* gene must first be determined. The FDA recommends that testing be performed using an FDA-approved test for the specific tumor type (breast or gastric tumor), in a laboratory with demonstrated proficiency with the technology being used. This is because the benefits of trastuzumab have only been proven in individuals with tumors that overexpress *ERBB2*. In addition, although trastuzumab is generally well tolerated, the risks of treatment include infusion reactions, pulmonary toxicity, and cardiomyopathy that can result in cardiac failure (1, 19).

Trastuzumab targets the *ERBB2* receptor protein by binding to the juxtamembrane portion of the extracellular domain. This binding limits the receptor's ability to activate its intrinsic tyrosine kinase, which in turn, limits the activation of numerous signaling pathways that can promote the growth of cancerous cells.

A number of proposed mechanisms may underlie the anti-tumor effects of trastuzumab. Of note, when HER2 is overexpressed, HER2 receptors exist on the cell surface as homodimers and heterodimers with other HER family receptors. It has been suggested that trastuzumab has preferential activity against breast cancers driven by HER2 homodimers (20). Additionally, it has been proposed that trastuzumab disrupts signaling activation by the ligand-independent HER2/HER3 complex (21). The HER2-HER3 dimerized receptor is thought to be highly active, triggering many signaling cascades in the absence of a "true" ligand (22).

Another proposed mechanism is antibody-dependent cellular cytotoxicity (ADCC). Once trastuzumab has bound to a cancer cell, immune cells (typically activated natural killer cells) bind to trastuzumab and initiate lysis of the cancer cell (23). 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 (24, 25).

Unfortunately, cancer is a complex disease involving many different genes and pathways. Breast cancer or gastric cancer may start to progress again during trastuzumab therapy. Possible mechanisms that may facilitate 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 (26, 27, 28, 29, 30, 31).

## Gene: **ERBB2 (HER2)**

The 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 below). All 4 members are transmembrane tyrosine kinase receptors, and they regulate a number of important cellular processes, such as cell growth, survival, and differentiation (32).

The genes *ERBB2* and *EGFR* are proto-oncogenes. Proto-oncogenes are a group of genes that, when mutated or expressed at abnormally high levels, can contribute to normal cells becoming cancerous cells. The mutated version of the proto-oncogene is called an oncogene. Proto-oncogenes typically encode proteins that stimulate cell division, regulate 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 (33).

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*” or “*HER2/neu*” (*neu* was the name given to the gene that caused cancer derived from a rodent neuro/glioblastoma). The *HER2* is the legacy gene symbol for *ERBB2* and may be more commonly used by the community; *HER2* 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. 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 (25, 30). One unique feature of HER3 is that it has very little enzymatic activity compared with 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 HER2 (34, 35) and other HER family members.

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 (36, 37). Impaired *ERBB2* signaling is associated with the development of neurodegenerative diseases (38), such as Alzheimer disease (39), whereas excessive *ERBB2* signaling is associated with the development of cancers (40).

The *ERBB2* 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, with the exception of esophagogastric adenocarcinoma (41, 42, 43, 44, 45). Although gene amplification is frequently seen in cancer and other degenerative disorders, the underlying basis for amplification remains largely unknown (46). And 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 (47). In approximately 1% of breast cancers, activating mutations in *ERBB2* can be identified that are likely to drive tumorigenesis without *ERBB2* amplification (48). Importantly, it has recently been shown that these variants are further acquired in estrogen receptor-positive metastatic breast cancer, conferring resistance to endocrine therapy (49). Early results from one 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 (50).

## Linking Gene Overexpression with Treatment Response

Overexpression of HER2 is strongly linked to a beneficial treatment response to trastuzumab. As a consequence, current guidelines for breast cancer treatment limit the use of HER2-blocking agents to tumors with HER2 gene amplification or with HER2 protein overexpression (namely, IHC 3+) (4, 43, 44).

### Genetic Testing

The NIH Genetic Testing Registry (GTR) displays tests that are available for the *ERBB2* gene and the trastuzumab drug response. Increased awareness of *ERBB2* testing and trastuzumab administration may improve quality of care and individual outcomes (51). In addition, because HER2 expression can change over time in breast cancer, retesting the HER2 status upon change in disease status is helpful in determining the appropriate treatment. Somatic alterations in *ERBB2* have been observed in multiple solid tumor types, though the frequency of variants and the specific variants are highly variable (9). Testing of the tumor tissue itself for *ERBB2* overexpression is recommended before initiating anti-HER2 therapies.

### 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 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 (43, 44).

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+ in breast tumor biopsies (4):

- IHC 0 means no visible staining or membrane staining that is incomplete and is faint/barely perceptible and in  $\leq 10\%$  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 gastroesophageal adenocarcinoma, a similar scoring metric is used for HER2 testing (52):

- IHC 0 is a negative result, Surgical specimens have no reactivity or membranous activity in  $<10\%$  of tumor cells; biopsy specimens have no reactivity in any tumor cell
- IHC 1+ is also negative. Surgical specimens have faint/barely perceptible membranous reactivity in  $\geq 10\%$  of tumor cells, cells are reactive in only part of their membrane; biopsy specimens show that tumor cells cluster with faint or barely perceptible membranous reactivity irrespective of percentage of tumor cells stained.
- IHC2+ is “HER2 equivocal”. Surgical specimens have weak to moderate complete, basolateral or lateral membranous reactivity in  $\geq 10\%$  of tumor cells. Biopsy specimens have tumor cells that cluster with weak to moderate complete, basolateral or lateral membranous activity irrespective of percentage of tumor cells stained.

- IHC3+ is HER2 positive. Surgical specimens have Strong complete, basolateral or lateral membranous reactivity in  $\geq 10\%$  of tumor cells. Biopsy specimens show tumor cell cluster\* with strong complete, basolateral or lateral membranous activity irrespective of percentage of tumor cells stained

For an equivocal (IHC 2+) result in either breast or gastric cancer, 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 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 (53).

**For the complete algorithms for evaluation of HER2 protein expression using IHC or ISH, please see the American Society of Clinical Oncology (ASCO) / College of American Pathologists (CAP) clinical practice guideline update, located here ( 4 , 44 , 52 ).**

## Therapeutic Recommendations based on Genotype

**This section contains excerpted<sup>1</sup> 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)

Select individuals 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 or gastric cancers 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>.

Assessment of HER2 protein overexpression and *HER2* gene amplification in metastatic gastric cancer should be performed using FDA-approved tests specifically for gastric cancers due to differences in gastric vs. breast histopathology, including incomplete membrane staining and more frequent heterogeneous expression of *HER2* seen in gastric cancers.

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)**

**FDA-approved medical devices for HER2 can be searched for [here](#).**

<sup>1</sup> 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.



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

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 an individual with breast cancer to guide decision to pursue HER2-targeted therapy. This should be especially considered for an individual 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 individual status (comorbidities, prognosis, and so on) and individual 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 ( 22 ) and 2018 update ( 4 ).

## 2016 American Society of Clinical Oncology (ASCO) /College of American Pathologists (CAP) Recommendations for Gastroesophageal Adenocarcinoma (GEA)

### Key Points and Recommendations for Clinicians

- Recommendation 1.1: In individuals with advanced GEA who are potential candidates for HER2-targeted therapy, the treating clinician should request HER2 testing on tumor tissue (Type: evidence based; Quality of evidence: high; Strength of recommendation: strong).
- Recommendation 1.2: Treating clinicians or pathologists should request HER2 testing on tumor tissue in the biopsy or resection specimens (primary or metastasis) preferably prior to the initiation of trastuzumab therapy if such specimens are available and adequate. HER2 testing on FNA specimens (cell blocks) is an acceptable alternative (Type: evidence based; Quality of evidence: moderate/intermediate; Strength of recommendation: recommendation/moderate).
- Recommendation 1.3: Treating clinicians should offer combination chemotherapy and HER2-targeted therapy as the initial treatment for appropriate individuals with HER2 positive tumors who have advanced GEA (Type: evidence based; Quality of evidence: moderate/intermediate; Strength of recommendation: strong).

### **Key Points and Recommendations for Pathologists**

- Recommendation 2.1: Laboratories/pathologists must specify the antibodies and probes used for the test and ensure that assays are appropriately validated for HER2 IHC and ISH on GEA specimens (Type: evidence based; Quality of evidence: moderate/intermediate; Strength of recommendation: strong).
- Recommendation 2.2: When GEA HER2 status is being evaluated, laboratories/pathologists should perform/order IHC testing first, followed by ISH when IHC result is 2+ (equivocal). Positive (3+) or negative (0 or 1+) HER2 IHC results do not require further ISH testing (Type: evidence based; Quality of evidence: high; Strength of recommendation: strong).
- Recommendation 2.3: Pathologists should use the Ruschoff/Hofmann method in scoring HER2 IHC and ISH results for GEA (Type: evidence based; Quality of evidence: moderate/intermediate; Strength of recommendation: strong).
- Recommendation 2.4: Pathologists should select the tissue block with the areas of lowest grade tumor morphology in biopsy and resection specimens. More than one tissue block may be selected if different morphologic patterns are present (Type: evidence based; Quality of evidence: moderate/intermediate; Strength of recommendation: recommendation/moderate).
- Recommendation 2.5: Laboratories should report HER2 test results in GEA specimens in accordance with the CAP “Template for Reporting Results of HER2 (ERBB2) Biomarker Testing of Specimens From Individuals With Adenocarcinoma of the Stomach or Esophagogastric Junction” (Type: evidence based; Quality of evidence: moderate/intermediate; Strength of recommendation: strong).
- Recommendation 2.6: Pathologists should identify areas of invasive adenocarcinoma and also mark areas with strongest intensity of HER2 expression by IHC in GEA specimen for subsequent ISH scoring when required (Type: evidence based; Quality of evidence: moderate/intermediate; Strength of recommendation: strong).
- Recommendation 2.7: Laboratories must incorporate GEA HER2 testing methods into their overall laboratory quality improvement program, establishing appropriate quality improvement monitors as needed to ensure consistent performance in all steps of the testing and reporting process. In particular, laboratories performing GEA HER2 testing should participate in a formal proficiency testing program, if available, or an alternative proficiency assurance activity (Type: evidence based; Quality of evidence: moderate/intermediate; Strength of recommendation: strong).
- Recommendation 2.8: There is insufficient evidence to recommend for or against genomic testing in GEA individuals at this time.

**Please review the complete ASCO/CAP recommendations here ( 52 ).**



## Nomenclature for Selected Genes Associated with Trastuzumab Response

Official gene symbol	Alternative gene symbols
<i>EGFR</i>	<i>ERBB1</i> <i>ERBB</i> <i>HER1</i>
<i>ERBB2</i>	<i>HER2</i> <i>HER-2</i> <i>HER-2/neu</i> <i>NEU</i>
<i>ERBB3</i>	<i>HER3</i>
<i>ERBB4</i>	<i>HER4</i>

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## Version History

The first edition of this summary, published August 5<sup>th</sup>, 2015 is available [here](#).

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