Trastuzumab (Herceptin®)

National Drug Monograph

December 2014

VA Pharmacy Benefits Management Services, Medical Advisory Panel, and VISN Pharmacist Executives

The purpose of VA PBM Services drug monographs is to provide a comprehensive drug review for making formulary decisions. Updates will be made when new clinical data warrant additional formulary discussion. Documents will be placed in the Archive section when the information is deemed to be no longer current.

FDA Approval Information[1]

Description/Mechanism of Action	Trastuzumab is a HER2/neu receptor antagonist that mediates antibody-dependent cellular cytotoxicity on HER2 overexpressing tumor cells.
Indication(s) Under Review in this document (may include off label)	**Metastatic Breast Cancer (1998):** trastuzumab is FDA approved • In combination with paclitaxel for first-line treatment of HER2-over-expressing metastatic breast cancer • As a single agent for treatment of HER2-overexpressing breast cancer in patients who have received one or more chemotherapy regimens for metastatic disease **Adjuvant Breast Cancer (2006):** trastuzumab is FDA approved for adjuvant treatment of HER2 overexpressing node positive or node negative (ER/PR negative or with one high risk feature breast cancer • As part of a treatment regimen consisting of doxorubicin, cyclophosphamide and either paclitaxel or docetaxel • With docetaxel and carboplatin • As a single agent following multi-modality anthracycline-based therapy **Metastatic Gastric Cancer (2013):** trastuzumab is FDA approved in combination with cisplatin and capecitabine or 5-fluorouracil, for the treatment of patients with HER2-overexpressing metastatic gastric or gastroesophageal junction adenocarcinoma, who have not received prior treatment for metastatic disease
Dosage Form(s) Under Review	Available a lyophilized powder of 440 mg in a multidose vial
REMS	☐ REMS ☒ No REMS ☐ Postmarketing Requirements *See Other Considerations for additional REMS information*
Pregnancy Rating	Pregnancy Category D

Background

Purpose for review	**FDA-approval in 1998 (prior to current formulary review process)** **Issues to be determined:** What role does trastuzumab have in HER2 overexpressing breast and gastric cancers? What safety issues need to be considered?
Other therapeutic options	**Formulary Alternatives** **HER2-directed agents** — **Other Considerations** None **Non-formulary Alternatives** **HER2-directed agents** — **Other Considerations**

Lapatinib	Oral formulation; TKI against EGFR1 and HER2
Pertuzumab	Injectable; administered in combination with trastuzumab
Ado-trastuzumab emtansine	Injectable; Antibody-Drug Conjugate; activity post-trastuzumab

Efficacy (FDA Approved Indications)

Literature Search Summary

A literature search was performed on PubMed/Medline with focus over the last 10 years using the search terms: meta-analysis, trastuzumab, adjuvant therapy, early breast cancer, metastatic breast cancer, metastatic gastric cancer. The search was limited to studies performed in humans and published in the English language. Reference lists of review articles were searched for relevant clinical trials. All randomized controlled trials published in peer-reviewed journals were included.

Review of Efficacy

Trastuzumab (H) in the Adjuvant Treatment of HER2-Positive Early Breast Cancer (Refer to Table 1)

- A meta-analysis of RCTs was performed to compare adjuvant trastuzumab therapy to observation for patients with HER2-positive early breast cancer. Viani, et al. identified five randomized trials for inclusion. The analysis indicated there was a significant improvement in mortality, recurrence, metastases and secondary tumors (other than breast) with one year of trastuzumab therapy. Cardiac toxicity and brain metastases were significantly more common among those receiving trastuzumab.[2]

- Yin, et al. performed a meta-analysis to assess the benefits of concurrent vs. sequential trastuzumab with adjuvant therapy. Utilizing six eligible studies, the analysis indicates that trastuzumab provided benefit with regard to DFS, OS, locoregional and distant recurrence. CNS recurrence rate was higher in those receiving trastuzumab. Patients receiving concomitant trastuzumab had statistically significant improvements in OS while a higher incidence of CNS recurrence, as compared to the sequential trastuzumab patients who did not achieve significance with regard to OS or CNS recurrence. These findings suggest that concomitant trastuzumab is superior to sequential, with the possibility that CNS recurrence is secondary to prolonged survival.[3]

- A Cochrane review of trastuzumab-containing regimens for early breast cancer included eight trials and a total of 11,991 patients. The intent of the analysis was to evaluate the evidence of efficacy and safety with trastuzumab in the adjuvant setting and its relation to duration and schedule of administration (concurrent vs. sequential). The authors concluded that overall trastuzumab significantly improved OS and DFS in HER2-positive women with early stage breast cancer. Cardiovascular risk, in term of increased risk of CHF and LVEF decline, is increased with trastuzumab therapy. Due to the small numbers of included studies, no conclusions can be made about the schedule of administration.[4]

Table 1. Meta-analyses (MA) of Adjuvant Trastuzumab (H) in Early Breast Cancer (EBC)

Citation	HERA	BCIRG 006	FinHer	NCCTG N9831	NSABP B31	PACS 04	NOAH	Buzdar	Results
Viani, 2007[2] MA of RCTs comparing adjuvant H vs. obs 5 trials: N= 9117	X	X	X	X	X				<u>Adjuvant H vs. obs in EBC</u> Mortality rate (p<0.00001) Recurrence rate (p<0.00001) Second other tumors (p=0.007) Metastases rate (p<0.00001) CV tox (grade 3,4): 4.5 vs. 1.8% Brain mets: 54 vs. 30 events; OR 1.82
Yin, 2011[3] MA of RCTs evaluating adjuvant chemo with (concurrent vs. sequential) H vs. no H 6 trials; N = 13,952	X	X	X	X	X	X			<u>Adjuvant H (Concur vs. Seq) vs. control</u> DFS: OR 0.69 (0.59-0.80); p<0.001 OS: OR 0.69 (0.58-0.83) vs. 0.86 (0.73-1.01) CNS Recurrence rate: OR 1.58 (1.08-2.30) Distant recurrence: OR 0.62 (0.55-0.69)
Moja, 2012[4] MA of RCTs evaluating efficacy & safety of H in adjuvant or neo-adjuvant setting of EBC 8 trials; N= 11,991	X	X	X	X	X	X	X	X	<u>Adjuvant H (Concur vs. Seq) vs. control</u> OS: HR 0.66 (0.57-0.77); p<0.00001 DFS: HR 0.60 (0.50-0.71); p<0.00001) Risk of CHF: RR 5.11 (90% CI: 3-8.72); p<0.00001 Risk of ↓LVEF: RR 1.83 (90% CI: 1.36-2.47); p=0.0008

<u>Trastuzumab (H) in the Treatment of HER2-Positive Metastatic Breast Cancer</u>

A Cochrane review was performed to evaluate the safety and efficacy of trastuzumab in the metastatic breast cancer setting. The review included RCTs that evaluated trastuzumab alone or in combination with cytotoxic chemotherapy or hormonal therapy. A total of 7 trials with 1497 patients met the inclusion criterion. For the endpoint of OS, five of 7 trials reported this outcome with an improvement in overall survival by 5-8 months in the trastuzumab-containing arms compared to control arms OS [HR 0.82 (0.71-0.94) p=0.004]. Three trials evaluated trastuzumab in the first-line MBC setting, while two trials considered trastuzumab beyond progression. OS was improved in the first-line setting [HR 0.79 (0.67-0.94); p=0.006], while OS beyond progression was not significantly different [HR 0.87 (0.68-1.12) p=0.27]. Progression-free survival (PFS) was evaluated in all 7 trials. Trastuzumab extended PFS from 2-11 months compared to control [HR 0.61 (0.54-0.70) p<0.00001]. The benefit was noted as significant whether trastuzumab was given in the first-line or beyond progression setting.[5]

Trastuzumab (H) in the Treatment of HER2-Positive Metastatic Gastric Cancer

FDA-approval of trastuzumab for the treatment of HER2-overexpressing metastatic gastric or gastroesophageal junction (GEJ) adenocarcinoma comes from the ToGA (Trastuzumab for Gastric Cancer) trial. In an open-label, international (including Asia, Central and South America, Europe), phase 3 RCT, patients with overexpressed HER2 gastric or GEJ cancer who had not received previous treatment, were randomized 1:1 to either trastuzumab + chemotherapy (capecitabine + cisplatin or 5-fluorouracil + cisplatin) vs. chemotherapy alone. The primary endpoint of OS was significantly improved with the addition of trastuzumab compared to chemotherapy alone, 13.8 vs. 11.1 months [HR 0.74 (0.60-0.91); p=0.0046]. Median PFS was also improved, 6.7 vs. 5.5 months, respectively [HR 0.71 (0.59-0.85); p=0.0002]. A pre-planned exploratory analysis evaluating degree of HER2 expression and response suggested that the improvement in OS with trastuzumab was greater in those with higher expression of the HER2 protein (IHC 2+/FISH positive or IHC 3+), compared to those with low expression (IHC 0 or 1+/FISH positive) with median OS 16 months vs. 11.8 months [HR 0.65 (0.51-0.83)].[6]

Potential Off-Label Use

The following trials can be found in www.clinicaltrials.gov unless otherwise noted:

- Intrathecal trastuzumab trials for the treatment of leptomeningeal metastases and carcinomatosis meningitis in breast cancer.
- A Phase III Clinical Trial to Evaluate Patient´s Preference of Subcutaneous Trastuzumab (SC) Versus Intravenous (IV) Administration in Patients with HER2 Positive Advanced Breast Cancer (ABC).
- Everolimus, Letrozole and Trastuzumab in HR- and HER2/Neu-positive Breast Cancer Patients
- Evaluation of Carboplatin/Paclitaxel With and Without Trastuzumab (Herceptin) in Uterine Serous Cancer
- Efficacy and Safety Study of Trastuzumab, Paclitaxel and Carboplatin on HER2+ Preoperative Breast Cancer
- Evidence to support the addition of HER2-directed agents to neoadjuvant therapy in HER2-positive breast cancer is based upon the primary endpoint of pathologic complete response rate (pCR). Evidence from the NOAH trial (neoadjuvant chemotherapy with trastuzumab trial), which compared 1 year of treatment with trastuzumab (neoadjuvant and adjuvant) with no trastuzumab showed that 3-year event-free survival was improved with trastuzumab [71 vs. 56%; HR 0.59 (0.38-0.90); p=0.013]. Follow-up to this trial was presented at the ASCO 2013 Annual Meeting. After a median follow-up of 5.4 years, the benefit of improved EFS with trastuzumab was confirmed. The authors note a trend in improved OS.[7, 8]
- Use of trastuzumab in combination with chemotherapy regimens other than cisplatin and a fluoropyrimidine for first-line treatment of gastric or GEJ cancer. An observational study was conducted to evaluate the use of trastuzumab in HER2-positive metastatic gastric cancer. Data from a total of 110 patients was collected over a 2-year period. Only 28% of the population received trastuzumab as labeled with cisplatin and 5-FU or capecitabine. The rest of the patients received the following regimens: cisplatin, 5-FU, leucovorin (17%); 5-FU, leucovorin, oxaliplatin and docetaxel (8%), 5-FU, leucovorin and oxaliplatin (7%), capecitabine (6%) or other combinations (25%). The preliminary PFS was 6.8 months, which the authors note, is consistent with the 6.7 month PFS noted in the ToGA trial.[9]
- Use of trastuzumab in Non-Small Cell Lung Cancer is categorized as an NCCN 2B recommendation (defined as based upon low level of evidence with consensus that the intervention is appropriate) for patients with HER2 mutations.[18]

Safety
(for more detailed information refer to the product package insert)

	Comments
Boxed Warning	• Cardiomyopathy: Trastuzumab can result in sub-clinical and clinical cardiac failure manifesting as CHF, and decreased LVEF, with greatest risk when administered concurrently with anthracyclines. Evaluate cardiac function prior to and during treatment. Discontinue trastuzumab for cardiomyopathy. • Infusion reactions, pulmonary toxicity: Discontinue trastuzumab for anaphylaxis, angioedema, interstitial pneumonitis or acute respiratory distress syndrome. • Embryo-Fetal Toxicity: Exposure to trastuzumab during pregnancy can result in oligohydramnios, in some cases complicated by pulmonary hypoplasia and neonatal death.
Contraindications	• None
Warnings/Precautions	• Cardiomyopathy. Trastuzumab can cause LV cardiac dysfunction, arrhythmias, hypertension, disabling cardiac failure, cardiomyopathy and cardiac death; asymptomatic declines in LVEF are also known effects; the highest incidence of cardiac dysfunction is noted when trastuzumab is given with an anthracycline. Trastuzumab should be withheld in situations where there is $\geq$ 16% absolute decrease in LVEF from baseline values or an LVEF value that is below institutional limits of normal and $\geq$ 10% absolute decrease from baseline values. The following monitoring schedule is recommended: o Baseline cardiac assessment including history, physical exam and LVEF via echocardiogram or MUGA scan o Baseline LVEF immediately prior to start of trastuzumab o LVEF every 3 months during and upon completion of trastuzumab o LVEF at 4-week intervals if trastuzumab is held for significant LV dysfunction o LVEF every 6 months for at least 2 years following completion of trastuzumab for adjuvant therapy • Infusion Reactions. Serious and fatal infusion reactions have been reported among postmarketing data. Severe reactions may include bronchospasm, anaphylaxis, angioedema, hypoxia and severe hypotension. The onset and clinical course of the reactions are variable. Fatalities occurred within hours to days following a serious reaction. Trastuzumab should be interrupted in all patients that experience dyspnea and significant hypotension. Emergent medical therapy may be needed, such as epinephrine, corticosteroids, diphenhydramine, bronchodilators and oxygen. Monitor and evaluate patients until complete resolution of all signs and symptoms. Permanent discontinuation should be considered in all patients with severe infusion reactions. Pre-medication with antihistamines and/or corticosteroids should be considered if therapy is to resume, recognizing that recurrent reactions are possible despite pre-medication. • Embryo-fetal Toxicity. Trastuzumab can cause fetal harm when administered to a pregnant woman. Cases of oligohydramnios and oligohydramnios sequence manifesting as pulmonary hypoplasia, skeletal abnormalities and neonatal death have been noted in post-marketing reports. Women of child-bearing potential should be advised of the potential hazard to the fetus resulting from trastuzumab exposure during pregnancy and provided contraception counseling. • Pulmonary Toxicity. Trastuzumab use can result in serious and fatal pulmonary toxicity. Pulmonary toxicity can occur as sequelae of an infusion reaction. Those with symptomatic intrinsic lung disease or extensive tumor

involvement of the lungs, that results in dyspnea at rest, appear to experience greater lung toxicity.

- Exacerbation of Chemotherapy-induced Neutropenia. The incidences of Grade 3 or 4 neutropenia and febrile neutropenia were higher in the patients who received trastuzumab and myelosuppressive chemotherapy compared to those who received chemotherapy alone.
- HER2 Testing. HER2 protein overexpression is necessary for patient selection for trastuzumab therapy as these are the only patients studied and for whom a benefit has been shown. Use FDA-approved tests for the specific tumor types (breast vs. gastric) as there are differences in the tumor histopathology. HER2 status should be performed by laboratories proficient in utilizing FDA-approved tests to obtain reliable results.

Safety Considerations

- HER2 testing is essential to determine if patients are appropriate for trastuzumab therapy. Selected laboratories need to be proficient with IHC and FISH technology to ensure reliable results.
- Look Alike Sound Alike potential for medication errors due to similarity in names between trastuzumab and ado-trastuzumab emtansine.
- Risk for cardiomyopathy and potential for reduced LVEF are major considerations prior to initiation of trastuzumab therapy. Whether trastuzumab is administered as a single agent or as part of a treatment plan that includes anthracyclines, some degree of myocardial dysfunction can be expected. Appropriate cardiac monitoring is essential throughout the course of therapy.
- Risk of embryo-fetal toxicity, as exposure can result in embryo-fetal death or birth defects. Advise patients of these risks and the need for effective contraception. Perform a pregnancy test before initiating therapy in women of childbearing potential and periodically throughout treatment if risk of pregnancy is questionable.
- Trastuzumab can potentiate the risk of chemotherapy-induced neutropenia when given as part of a treatment plan that includes myelosuppressive chemotherapy. Anticipation of Grade 3, 4 neutropenia and possibly febrile neutropenia should be a consideration prior to initiating therapy with trastuzumab and chemotherapy.
- Infusion-related reactions can be severe and fatal. The onset and clinical course of these reactions has been variable. Trastuzumab infusions should be interrupted for symptomatic patients with careful monitoring until complete resolution. Pre-medication with antihistamines and/or corticosteroids may need to be considered.
- Within the Cochrane review in MBC, all 7 trials reported data on cardiovascular events. Congestive heart failure and cardiac dysfunction NYHA class III and IV events were combined. Overall, trastuzumab use was associated with an increased risk of severe cardiac events [RR 3.49 (1.88-6.47) p=0.0009]. When comparing the type of regimen with cardiac toxicity, trastuzumab with an anthracycline significantly increased risk [RR 5.43 (90% CI 2.28-12.94) p=0.001]. Evaluation of LVEF decline was reported in 6 trials. The pooled analysis indicates an increased risk of decline with trastuzumab [RR 2.65 (90% CI 1.48-4.74) p=0.006]. Risk of LVEF decline was noted in both first-line and beyond-progression settings.[5]
- The ToGA trial reported that Trastuzumab + chemotherapy vs. chemotherapy alone had similar adverse effect profiles. Nausea, neutropenia, vomiting and anorexia were the most common reported events. Grade 3 or 4 events were similar, except for diarrhea, which was reported in a higher number of trastuzumab patients (9 vs. 4%). Rates of grade 3 or 4 cardiac events were similar between both groups and were noted in a minority of patients (6 vs. 6%).[6]
- Use of intrathecal trastuzumab (off-label) will require drug reconstitution with preservative-free diluent, NOT the diluent included from the manufacturer in packaging, which contains 1.1% benzyl alcohol.

Adverse Reactions

Common adverse reactions	**Adjuvant and metastatic breast cancer setting**: fever, nausea, vomiting, infusion reactions, diarrhea, infections, increased cough, headache, fatigue, dyspnea, rash, neutropenia, anemia, myalgia **Metastatic gastric cancer setting**: neutropenia, diarrhea, fatigue, anemia, stomatitis, weight loss, upper respiratory tract infections, fever, thrombocytopenia, mucosal inflammation, nasopharyngitis, dysgeusia
Death/Serious adverse reactions	Severe infusion reactions, neutropenia, infection/febrile neutropenia, pulmonary toxicity, diarrhea, CHF or symptomatic decrease in LVEF
Discontinuations due to adverse reactions	**Adjuvant and metastatic breast cancer setting**: CHF, significant decline in LV cardiac function, severe infusion reactions, pulmonary toxicity **Metastatic gastric cancer setting**: infection, diarrhea, febrile neutropenia

Drug Interactions

Drug-Drug Interactions

- Anthracyclines (doxorubicin, epirubicin, etc.): Avoid use with trastuzumab due to potential of increasing risk of cardiotoxicity.
- Paclitaxel: Mean serum concentration of trastuzumab is increased when administered with paclitaxel.
- Myelosuppressive chemotherapy: Trastuzumab therapy can increase risk of neutropenia.

Risk Evaluation

As of November 24, 2014

Comments

Sentinel event advisories

- No sentinel event advisories. Alerts are related to the name similarity between trastuzumab and ado-trastuzumab emtansine.
- Sources: ISMP, FDA, TJC

Look-alike/sound-alike error potentials

- Sources: Based on clinical judgment and an evaluation of LASA information from three data sources (Lexi-Comp, First Databank, and ISMP Confused Drug Name List)

NME Drug Name	Lexi-Comp	First DataBank	ISMP	Clinical Judgment
Trastuzumab 440mg MDV	Ado-trastuzumab emtansine Pertuzumab	None	Ado-trastuzumab emtansine	Alemtuzumab Tocilizumab Trametinib
Herceptin	None	None	None	Heparin Hepsera Hespan

Sources: Based on clinical judgment and an evaluation of LASA information from three data sources (Lexi-Comp, First Databank, and ISMP Confused Drug Name List)

!High alert medication: The Institute for Safe Medication Practices (ISMP) includes this medication among its list of drug classes which have a heightened risk of causing significant patient harm when used in error.

Other Considerations

General

- HER2 testing is essential to determine if patients are appropriate for trastuzumab therapy in any setting. Selected laboratories need to be proficient with IHC and FISH technology to ensure reliable results in both breast and gastric/GEJ cancer settings.[10, 15]
- Look Alike Sound Alike potential for medication errors due to similarity in names between trastuzumab and ado-trastuzumab emtansine.

Neoadjuvant / Adjuvant Therapy

- The VHA UNDER SECRETARY FOR HEALTH'S INFORMATION LETTER Guidance on Breast Cancer Care (draft dated 10-2014) states that trastuzumab should be considered for all patients with HER2 amplified or over-expressed breast cancer in the adjuvant setting, except for very low risk disease. Current data support the optimal duration of trastuzumab treatment is one year.[11]
- The National Comprehensive Cancer Network (NCCN) Guidelines include trastuzumab as a component of adjuvant therapy (Category 1 recommendation) in HER2-positive tumors that are either node-positive or node-negative with tumor > 1cm.[12]
- The National Institute for Health and Care Excellence (NICE) evidence review group summarized the clinical and cost-effectiveness of trastuzumab in HER2-positive primary breast cancer, supporting the use of trastuzumab for one year or until disease recurrence in patients following surgery, chemotherapy and radiotherapy.[13]

MBC Setting

- The American Society of Clinical Oncology (ASCO) Guidelines on Systemic therapy for patients with advanced HER2-positive breast cancer support the use of HER2-targeted therapy-based combinations as first-line, second-line and third-line treatment.[14]
  Evidence GRADE. First-line setting. Evidence quality: high; strength of recommendation: strong
  Evidence GRADE. Second-line setting. Evidence quality: high; strength of recommendation: strong
  Evidence GRADE. Third-line setting. Evidence quality: intermediate; strength of recommendation: moderate
- The combination of trastuzumab, pertuzumab and a taxane is recommended for first-line therapy, unless contraindication to taxanes exist.
  Evidence GRADE. Evidence quality: high; strength of recommendation: strong
- The National Comprehensive Cancer Network (NCCN) Guidelines include trastuzumab either alone or in combination with other agents in the recurrent or metastatic breast cancer setting. A Category 1 recommendation is given to the combination of pertuzumab, trastuzumab and docetaxel as a preferred first-line regimen in this setting. Trastuzumab alone or in combination with other cytotoxic agents are given a Category 2A recommendation.[12]
- The optimal duration and ideal sequence of HER2-targeted therapy in MBC is unknown at this time.

Gastric/Gastroesophageal Junction Adenocarcinoma Setting

- The benefit of trastuzumab correlated with strong positivity of HER2 status.[6]
- FDA approval is based upon use of trastuzumab with a cisplatin and fluoropyrimidine-based regimen. NCCN guidelines categorize a cisplatin/fluoropyrimidine-based regimen as Category 1, while other active regimens are Category 2A.[16]

Dosing and Administration

- Refer to the package insert for full dosing information.

Special Populations (Adults)

	Comments
Elderly	• Among the adjuvant and metastatic breast cancer trials, the risk of cardiac dysfunction was increased in patients over age 65 years compared to younger patients. The reported clinical experience in breast cancer is not adequate to determine if there is a difference between young and old populations. • No differences in safety or effectiveness were noted between elderly and young patients in the metastatic gastric cancer setting.
Pregnancy	• Pregnancy Category D. Fetal harm can result when trastuzumab is given to a pregnant woman. Cases of oligohydramnios and oligohydramnios sequence manifesting as pulmonary hypoplasia, skeletal abnormalities and neonatal death have been noted in post-marketing reports. Monitor pregnant women exposed to trastuzumab for oligohydramnios, Consider fetal testing appropriate for gestational age and consistent with community standards. Advise women of the potential of harm to her fetus subsequent to trastuzumab exposure.
Lactation	• It is not known if trastuzumab is excreted in human milk, but IgG is; a decision concerning the importance of the drug to the mother with the potential risk to the nursing infant should be addressed.
Renal Impairment	• No specific recommendations for renal impairment have been noted; renal toxicity was identified in the metastatic gastric cancer trial as well as rare cases of nephrotic syndrome identified through post-marketing studies.
Hepatic Impairment	• No data identified.
Pharmacogenetics/genomics	• No data identified.

Projected Place in Therapy

Adjuvant Therapy Setting in EBC

- The VHA UNDER SECRETARY FOR HEALTH'S INFORMATION LETTER Guidance on Breast Cancer Care (draft dated 10-2014) states that trastuzumab should be considered for all patients with HER2 amplified or over-expressed breast cancer in the adjuvant setting, except for very low risk disease. Current data support the optimal duration of trastuzumab treatment is one year.
- The National Comprehensive Cancer Network (NCCN) Guidelines include trastuzumab as a component of adjuvant therapy (Category 1 recommendation) in HER2-positive tumors that are either node-positive or node-negative with tumor > 1cm.

Neoadjuvant (Preoperative) Therapy Setting in EBC

- Evidence to support the addition of HER2-directed agents to neoadjuvant therapy in HER2-positive breast cancer is based upon the primary endpoint of pathologic complete response rate (pCR).

MBC Setting

- The American Society of Clinical Oncology (ASCO) Guidelines on Systemic therapy for patients with advanced HER2-positive breast cancer support the use of HER2-targeted therapy-based combinations as first-line, second-line and third-line treatment.[14]
- The National Comprehensive Cancer Network (NCCN) Guidelines include trastuzumab either alone or in combination with other agents in the recurrent or metastatic breast cancer setting. A Category 1 recommendation is given to the combination of pertuzumab, trastuzumab and docetaxel as a preferred first-line regimen in this setting. Trastuzumab alone or in combination with other cytotoxic agents are given a Category 2A recommendation.[12]

Metastatic Gastric/GEJ Adenocarcinoma Setting

- FDA approval is based upon use of trastuzumab with a cisplatin and fluoropyrimidine-based regimen. NCCN guidelines categorize a cisplatin/fluoropyrimidine-based regimen as Category 1, while other active regimens are Category 2A.

References

1. Herceptin [prescribing information]. South San Francisco, CA: Genentech, Inc. September 1998; revision June 2014.

2. Viani GA, Afonso SL, Stefano EJ, DeFendi LI, Soares FV. Adjuvant Trastuzumab in the Treatment of HER2-Positive Early Breast Cancer: A Meta-Analysis of Published Randomized Trials. BMC Cancer 2007; 7: 153.

3. Yin W, Jiang Y, Shen Z, Shao Z, Lu J. Trastuzumab in the Adjuvant Treatment of HER2-Positive Early Breast Cancer Patients: A Meta-Analysis of Published Randomized Controlled Trials. PLoS ONE 2011; 6:e21030

4. Moja L, Tagliabue L, Balduzzi S, Parmelli E, Pistotti V, Guarneri V, D'Amico R. Trastuzumab containing regimens for early breast cancer. *Cochrane Database of Systematic Reviews* 2012; Issue 4. Art. No.: CD006243.

5. Balduzzi S, Mantarro S, Guarneri V. et al. Trastuzumab-Containing Regimens for Metastatic Breast Cancer. Cochrane Database Syst Rev. 2014; 6: CD006242.

6. Vang YJ, et al. for the ToGA Trial Investigators. Trastuzumab in Combination with Chemotherapy versus Chemotherapy alone for Treatment of HER2-positive Advanced Gastric or Gastro-oesophageal Junction Cancer (ToGA): A Phase 3, open-label, Randomized, Controlled Trial. Lancet 2010: 376: 687.

7. Gianni L, Eierman W, Semiglazov V, et al. Neoadjuvant chemotherapy with trastuzumab followed by adjuvant trastuzumab versus neoadjuvant chemotherapy alone, in patients with HER2-positive locally advanced breast cancer (NOAH trial): a randomized controlled superiority trial with a parallel HER2-negative cohort. Lancet 2010; 375: 377.

8. Gianni L, Eiermann W, Semiglazov V, et al. Follow-up results of NOAH, a randomized phase III trial evaluating neoadjuvant chemotherapy with trastuzumab followed by adjuvant H versus CT alone, in patients with HER2-positive locally advanced breast cancer. J Clin Oncol 2013; 31 (suppl; abstr 503).

9. Hegewisch-Becker S, Moorahrend E, Kroning H, et al. Trastuzumab in combination with different first-line chemotherapies for treatment of HER2-positive metastatic gastric or gastroesophageal junction cancer (MGC): Findings from the German noninterventional observational study HerMES. J Clin Oncol 2012; suppl; abstr 4065.

10. Wolff AC, et al. Recommendations for Human Epidermal Growth Factor Receptor 2 Testing in Breast Cancer: American Society of Clinical Oncology/College of American Pathologists Clinical Practice Guideline Update. Journal of Clinical Oncology 2013; 31: 3997.

11. Department of Veterans Affairs, Veterans Health Administration. UNDER SECRETARY FOR HEALTH'S INFORMATION LETTER Guidance on Breast Cancer Care. Draft dated 10-2014

12. National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology, Breast Cancer (version 3.2014). http://www.nccn.org/professionals/physician_gls/pdf/breast.pdf (Accessed November 2014).

13. Ward S, Pilgrim H, Hind D. Trastuzumab for the Treatment of Primary Breast Cancer in HER2-Positive Women: A Single Technology Appraisal. Health Technol Assess 2009; 13. Suppl 1:1-6. doi: 10.3310/hta13suppl1/01.

14. Giordano SH, Temin S, Kirshner JJ, et al. Systemic Therapy for Patients with Advanced Human Epidermal Growth Factor Receptor-2-Positive Breast Cancer: American Society of Clinical Oncology Clinical Practice Guideline. J Clin Oncol 2014; 32: 2078.

15. Ross JS, Mulcahy M. HER2 Testing in Gastric/Gastroesophageal Junction Adenocarcinomas: Unique Features of a Familiar Test. Gastrointestinal Cancer Research 2011; 4: 62.

16. National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology, Gastric Cancer (version 1.2014). http://www.nccn.org/professionals/physician_gls/pdf/gastric.pdf (Accessed November 2014).

17. Plana, et al. Expert Consensus for Multimodality Imaging Evaluation of Adult Patients during and after Cancer Therapy: A Report from the American Society of Echocardiography and the European Association of Cardiovscular Imaging. J Am Soc Echocardiogr 2014; 27: 911-939.

18. Cappuzzo F, Bemis L, Varella-Garcia M. *HER2* Mutation and Response to Trastuzumab Therapy in Non-Small Cell Lung Cancer. N Engl J Med 2006; 354: 2619-2621

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Appendix A: GRADEing the Evidence

Designations of Quality

Quality of evidence designation	Description
High	Evidence includes consistent results from well-designed, well-conducted studies in representative populations that directly assess effects on health outcomes (2 consistent, higher-quality randomized controlled trials or multiple, consistent observational studies with no significant methodological flaws showing large effects).
Moderate	Evidence is sufficient to determine effects on health outcomes, but the number, quality, size, or consistency of included studies; generalizability to routine practice; or indirect nature of the evidence on health outcomes (1 higher-quality trial with > 100 participants; 2 higher-quality trials with some inconsistency; 2 consistent, lower-quality trials; or multiple, consistent observational studies with no significant methodological flaws showing at least moderate effects) limits the strength of the evidence.
Low	Evidence is insufficient to assess effects on health outcomes because of limited number or power of studies, large and unexplained inconsistency between higher-quality studies, important flaws in study design or conduct, gaps in the chain of evidence, or lack of information on important health outcomes.

Please refer to Qaseem A, et al. The development of clinical practice guidelines and guidance statements of the American College of Physicians: Summary of Methods. Ann Intern Med 2010;153:194-199.

Appendix B: Approval Endpoints (use for oncology NMEs)

Table 1. A Comparison of Important Cancer Approval Endpoints

Endpoint	Regulatory Evidence	Study Design	Advantages	Disadvantages
Overall Survival	Clinical benefit for regular approval	• Randomized studies essential • Blinding not essential	• Universally accepted direct measure of benefit • Easily measured • Precisely measured	• May involve larger studies • May be affected by crossover therapy and sequential therapy • Includes noncancer deaths
Symptom Endpoints (patient-reported outcomes)	Clinical benefit for regular approval	• Randomized blinded studies	• Patient perspective of direct clinical benefit	• Blinding is often difficult • Data are frequently missing or incomplete • Clinical significance of small changes is unknown • Multiple analyses • Lack of validated instruments
Disease-Free Survival	Surrogate for accelerated approval or regular approval*	• Randomized studies essential • Blinding preferred • Blinded review recommended	• Smaller sample size and shorter follow-up necessary compared with survival studies	• Not statistically validated as surrogate for survival in all settings • Not precisely measured; subject to assessment bias, particularly in open-label studies • Definitions vary among studies
Objective Response Rate	Surrogate for accelerated approval or regular approval*	• Single-arm or randomized studies can be used • Blinding preferred in comparative studies • Blinded review recommended	• Can be assessed in single-arm studies • Assessed earlier and in smaller studies compared with survival studies • Effect attributable to drug, not natural history	• Not a direct measure of benefit in all cases • Not a comprehensive measure of drug activity • Only a subset of patients with benefit
Complete Response	Surrogate for accelerated approval or regular approval*	• Single-arm or randomized studies can be used • Blinding preferred in comparative studies • Blinded review recommended	• Can be assessed in single-arm studies • Durable complete responses can represent clinical benefit • Assessed earlier and in smaller studies compared with survival studies	• Not a direct measure of benefit in all cases • Not a comprehensive measure of drug activity • Small subset of patients with benefit
Progression- Free Survival (includes all deaths) or Time to Progression (deaths before progression censored)	Surrogate for accelerated approval or regular approval*	• Randomized studies essential • Blinding preferred • Blinded review recommended	• Smaller sample size and shorter follow-up necessary compared with survival studies • Measurement of stable disease included • Not affected by crossover or subsequent therapies • Generally based on objective and quantitative assessment	• Not statistically validated as surrogate for survival in all settings • Not precisely measured; subject to assessment bias particularly in open-label studies • Definitions vary among studies • Frequent radiological or other assessments • Involves balanced timing of assessments among treatment arms

*Adequacy as a surrogate endpoint for accelerated approval or regular approval is highly dependent upon other factors such as effect size, effect duration, and benefits of other available therapy. See text for details.

Guidance for Industry: Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics. U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER), Center for Biologics Evaluation and Research (CBER), May 2007.