Margetuximab-cmkb (Margenza)
National Drug Monograph
December 2023

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

The purpose of VA PBM Services drug monographs is to provide a focused drug review for making formulary decisions. Updates will be made if new clinical data warrant additional formulary discussion. The Product Information or other resources should be consulted for detailed and most current drug information.

FDA Approval Information

Description/Mechanism of Action

- Margetuximab-cmkb binds to the extracellular domain of the human epidermal growth factor receptor 2 protein (HER2). Through this binding, it inhibits tumor cell proliferation, reduces shedding of the HER2 extracellular domain, and mediates antibody-dependent cellular cytotoxicity.

Indication(s) Under Review in This Document

- Treatment, in combination with chemotherapy, of adult patients with metastatic HER2-positive breast cancer who have received two or more prior anti-HER2 regimens, at least one of which was for metastatic disease

Dosage Form(s) Under Review

- Dosage form: 250 mg/10 mL single-dose vial
- Margetuximab-cmkb is dosed at 15 mg/kg IV every 3 weeks (21-day cycle) until disease progression or unacceptable toxicity. It is administered over 120 minutes for the initial dose, then over a minimum of 30 minutes for all subsequent doses.
- On days where it is administered with chemotherapy, it may be administered immediately after chemotherapy completion.

Clinical Evidence Summary

Efficacy Considerations

- The efficacy of margetuximab-cmkb was evaluated in SOPHIA, a phase III study of patients with advanced breast cancer who had previously been treated with multiple lines of therapy including pertuzumab. The phase I showed partial response in patients with pretreated ERBB2-positive carcinomas. The FDA-approval is based on the results from this phase III trial of adults with metastatic HER2-positive breast cancer who had received two or more prior anti-HER2 regimens, at least one of which was for metastatic disease.
- Efficacy data from the SOPHIA trial are summarized in Table 1

Table 1: Efficacy results of SOPHIA and Final Overall Survival Results

Design	Results
SOPHIA Trial: **Phase III**, open-label, randomized controlled trial **Inclusion:** Age ≥18, confirmed ERBB2-positive advanced breast cancer, progressive disease after ≥2 lines of prior ERBB2-targeted therapy (Including pertuzumab and 1 to 3 lines of nonhormonal metastatic breast cancer therapy), ECOG PS of 0 to 1 **Exclusion:** Active, untreated brain metastasis, history of uncontrolled seizures within 6 months of randomization, history of prior allogenic bone marrow, stem-cell, or solid organ transplantation, receipt of local or systemic antineoplastic therapy within 2 weeks of randomization, receipt of corticosteroids (>10 mg prednisone per day or equivalent) or other immune suppressive drugs in two weeks prior to randomization, history of clinically significant cardiovascular disease including (But not limited to): MI, stroke, or transient ischemic attack within 6 months of randomization, clinically significant cardiac arrhythmias, uncontrolled hypertension, congestive heart failure (NYHA class II-IV), pericarditis, myocarditis, LVEF <50% **Intervention:** Margetuximab-cmkb 15 mg/kg IV on day 1 of each 21-day cycle plus chemotherapy of the investigator's choice[a] or trastuzumab 8 mg/kg loading dose followed by 6 mg/kg IV on day 1 of each 21-day cycle plus chemotherapy of investigators choice prior to randomization to margetuximab-cmkb or trastuzumab. The following chemotherapy choices were allowed: Capecitabine 1000 mg/m^2 PO twice daily for 14 days followed by 7 days off, eribulin 1.4 mg/m^2 IV before antibody infusion on day 1, gemcitabine 1000 mg/m^2 IV before antibody infusion on day 1, or vinorelbine 25-30 mg/m^2 before antibody infusion on day 1 **Primary Endpoints:** PFS as determined by central blind analysis (CBA) and OS **Secondary Endpoints:** Investigator-assessed (IA) PFS and CBA-assessed ORR	**Median cycles received:** 6 cycles of margetuximab-cmkb versus 5 cycles of trastuzumab **Primary PFS analysis was triggered by last randomization (October 10, 2018) after 265 PFS events. At that time 30% of patients remained on margetuximab-cmkb and 22% remained on trastuzumab** **OS analysis was triggered on September 10, 2019, after 270 total deaths.** **Primary Endpoints (Margetuximab-cmkb vs trastuzumab):** **mPFS (CBA):** 5.8 vs 4.9 mo (HR 0.76; 95% CI, 0.59-0.98; P = 0.03) **mOS:** 21.6 vs 19.8 mo (HR 0.89; 95% CI, 0.69-1.13; P = 0.33) • **3-mo OS:** 75% vs 75% • **6-mo OS:** 60% vs 56% • **9-mo OS:** 44% vs 40% **Secondary Endpoints (Margetuximab-cmkb vs trastuzumab):** **mPFS (IA):** 5.6 vs 4.2 mo (HR 0.70; 95% CI, 0.56-0.87; P = 0.001) **ORR (CBA):** 22% vs 16% (P = 0.06) **CBR:** 36.6% s 24.8% (P = 0.0026)

Demographic	Margetuximab (n = 266)	Trastuzumab (n = 270)
Age, median (Range)	55 (29-83)	56 (27-86)
Gender, % female	100	98.9
ECOG PS 1, %	44.0	40.4
Metastatic disease, %	97.7	97.8
ER (+), PR (+), or both, %	61.7	63.0
>2 prior lines of therapy, %	34.2	33.3
Baseline metastases, %		
Bone	57.5	57.4
Lymph node	52.6	55.9
Lung	46.6	46.7
Liver	35.0	35.2
Breast	16.5	13.7
Skin	15.4	11.9
Brain	13.9	12.6
Prior systemic therapy, %		
Taxane	94.7	92.2
Anthracycline	44.4	40.7
Platinum	12.8	14.8
Prior ERBB2 therapy, %		
Trastuzumab	100	100
Pertuzumab	100	99.6
Ado-trastuzumab emtansine	91.0	91.5
Lapatinib	15.4	14.4
Other	2.3	2.2
Prior endocrine therapy, %	47.4	49.3

Additional Endpoints: Safety, clinical benefit rate (CBR), investigator-assessed ORR, response duration, and antidrug antibodies **Exploratory Analyses:** Evaluation of FcγR allelic variation on efficacy **SOPHIA Trial Follow-Up Data:** **Final Analysis:** Overall survival **Exploratory Analyses:** CD16A genotyping OS	**Second Interim Analysis of PFS (IA) (September 10, 2019):** **mPFS (IA):** 5.7 vs 4.4 mo (HR 0.71; 95% CI, 0.58-0.86; P < 0.001) **Additional Endpoints (Margetuximab-cmkb vs trastuzumab):** **CBR:** 48% vs 36% (P = 0.003) **ORR (IA):** 25% vs 14% (P < 0.001) **mDoR:** 6.1 vs 6.0 mo (10/10/2018) and 6.9 vs 7.0 mo (09/10/2019) **SOPHIA Trial Final Overall Final Results:** **Final Results (Margetuximab-cmkb vs trastuzumab):** **mOS:** 21.6 vs 21.9 mo (HR 0.95; 95% CI, 0.77-1.17; P = 0.620) • **12-mo OS:** 75% vs 76% • **18-mo OS:** 60% vs 57% • **24-mo OS:** 46% vs 44% **Subgroup Analysis:** **CD16A-158F mOS:** 23.3 vs 20.8 mo (HR 0.86; 95% CI, 0.69-1.08) • **12-mo OS:** 75% vs 75% • **18-mo OS:** 61% vs 57% • **24-mo OS:** 48% vs 43% **CD16A-158FF mOS:** 23.6 vs 19.2 mo (HR 0.72; 95% CI, 0.52-1.00) • **12-mo OS:** 83% vs 72% • **18-mo OS:** 65% vs 54% • **24-mo OS:** 49% vs 41% **CD16A-158FV:** 21.3 vs 22.0 mo (HR 0.96; 95% CI, 0.71-1.30) • **12-mo OS:** 69% vs 77% • **18-mo OS:** 58% vs 59% • **24-mo OS:** 48% vs 44% **CD16A-158VV mOS:** 22.0 vs 31.1 mo (HR 1.77; 95% CI, 1.01-3.12) • **12-mo OS:** 80% vs 91% • **18-mo OS:** 66% vs 68% • **24-mo OS:** 43% vs 58%

[a] Investigator's choice of chemotherapy included vinorelbine (n = 191, 35.6%), capecitabine (n = 143, 26.7%), eribulin (n = 136, 25.4%), and gemcitabine (n = 66, 12.3%)

Definitions: DoR = time from initial response to date of first documented disease progression or death from any cause; CBR = proportion of patients achieving a best response of CR, PR, or SD of duration >6 months; ORR = percent of patients documented to have a confirmed CR or PR; PFS = time from randomization to disease progression or death from any cause; OS = time from randomization to death from any cause and was to be assessed only if PFS was positive;

- In this phase III, randomized clinical trial, margetuximab-cmkb plus chemotherapy had a statistically significant improvement in progression free survival as compared to trastuzumab plus chemotherapy in patients with ERBB2-positive advanced breast cancer after progression on 2 or more prior anti-ERBB2 therapies.
- Treatment with margetuximab-cmkb led to a mPFS of 5.8 months, mOS of 21.6 months, and ORR of 22%.
- Follow-up overall survival data did not show a significant difference between the margetuximab-cmkb and trastuzumab arms, but did show a possible differences in the exploratory median overall survival of CD16A genotype subgroups with CD16A-158FF showing improved mOS for margetuximab-cmkb and CD16A-158VV showing improved mOS for trastuzumab.

Safety Considerations

Safety Results from Clinical Trials:

- The safety of margetuximab-cmkb was evaluated in the SOPHIA trial, a phase III trial of patients with ERBB2-positive advanced breast cancer in combination with chemotherapy when compared to trastuzumab and chemotherapy
- Common adverse events (≥20% of patients; margetuximab vs. trastuzumab) included fatigue (42% vs 35.3%), nausea (32.6% vs. 32.3%), diarrhea (25% vs 25.2%), and neutropenia (28.4% vs 20.7%), and vomiting (20.5% vs 14.3%)
- The most common grade 3 or greater events (≥1%; margetuximab vs trastuzumab) included neutropenia (19.7% vs 12.4%), neutrophil count decrease (8.7% vs 10.5%), anemia (4.9% vs 6.4%), fatigue (4.9% vs 3.0%), AST increase (2.7% vs 1.1%), ALT increase (1.9% vs 1.5%), WBC decrease (1.9% vs 3.0%), leukopenia (5.3% vs 0.4%), nausea (1.1% vs 0.4%), diarrhea (2.3% vs 2.3%), asthenia (2.3% vs 1.9%), infusion-related reaction (1.5% vs 0), dyspnea (1.1% vs 2.3%), abdominal pain (1.5% vs 1.1%), hypokalemia (1.5% vs 0.8%), hypertension (1.9% vs 0.8%), pneumonia (1.9% vs 2.6%), and syncope (1.5% vs 0)

Table 2: Safety results from SOPHIA

Event	No. (%) Margetuximab + Chemotherapy (n = 264)		No. (%) Trastuzumab + Chemotherapy (N = 266)	
Adverse Event	All Grade[a]	Grade ≥3[b]	All Grade	Grade ≥3
Nonhematologic				
Fatigue	111 (42.0)	13 (4.9)	94 (35.3)	8 (3.0)
Nausea	86 (32.6)	3 (1.1)	86 (32.3)	1 (0.4)
Diarrhea	66 (25.0)	6 (2.3)	67 (25.2)	6 (2.3)
Constipation	51 (19.3)	2 (0.8)	44 (16.5)	2 (0.8)
Vomiting	54 (20.5)	2 (0.8)	38 (14.3)	4 (1.5)
Pyrexia	50 (18.9)	1 (0.4)	37 (13.9)	1 (0.4)
Headache	47 (17.8)	0	42 (15.8)	0
Alopecia	47 (17.8)	0	39 (14.7)	0
Asthenia	47 (17.8)	6 (2.3)	33 (12.4)	5 (1.9)
Decreased appetite	38 (14.4)	1 (0.4)	36 (13.5)	1 (0.4)
Infusion-related reaction[c]	35 (13.3)	4 (1.5)	9 (3.4)	0
Cough	37 (14.0)	1 (0.4)	31 (11.7)	0
PPE syndrome	33 (12.5)	1 (0.4)	41 (15.4)	8 (3.0)
Dyspnea	34 (12.9)	3 (1.1)	28 (10.5)	6 (2.3)
Pain in extremity	30 (11.4)	2 (0.8)	23 (8.6)	0
Arthralgia	27 (10.2)	0	23 (8.6)	1 (0.4)
Stomatitis	27 (10.2)	2 (0.8)	21 (7.9)	0
Hematologic				
Neutropenia	75 (28.4)	52 (19.7)	55 (20.7)	33 (12.4)
Anemia	49 (18.6)	13 (4.9)	62 (23.3)	17 (6.4)
Neutrophil count decr	33 (12.5)	23 (8.7)	39 (14.7)	28 (10.5)
ALT increased	24 (9.1)	5 (1.9)	26 (9.8)	4 (1.5)
AST increased	22 (8.3)	7 (2.7)	34 (12.8)	3 (1.1)
WBC decreased	19 (7.2)	5 (1.9)	27 (10.2)	8 (3.0)
Leukopenia	14 (5.3)	4 (1.5)	10 (3.8)	1 (0.4)
Febrile neutropenia	8 (3.0)	8 (3.0)	13 (4.9)	13 (4.9)

Abbreviations: ALT: alanine aminotransferase; AST: aspartate aminotransferase; PPE: palmar-plantar erythrodysesthesia; WBC: white blood cell.
[a] All-grade adverse events with _>10% incidence in either group
[b] Grade_>3 with an incidence of _>2% in either group
[c] Infusion-related reactions include hypersensitivity/anaphylactic/anaphylactoid reactions

- **Boxed warnings:** None
- **Contraindications:** None
- **Other warnings / precautions**:
    - **Left ventricular dysfunction**: Left ventricular dysfunction occurred in 1.9% of patients treated with margetuximab-cmkb versus 1.5% in those treated with trastuzumab in the SOPHIA trial. Margetuximab-cmkb has not been studied in patients with pretreatment LVEF values of <50%, prior history of myocardial infarction or unstable angina within 6 months, or congestive heart failure NYHA class II-IV.
    - **Embryo-fetal toxicity:** Based on animal studies and mechanism of action, margetuximab-cmkb can cause fetal harm when administered to pregnant women. There is no currently available data on the use of margetuximab-cmkb in pregnant women.
    - **Infusion-related reactions:** Infusion-related reactions were reported in 13% of patients on margetuximab-cmkb in the SOPHIA trial. Most of the reactions occurred during cycle 1. Grade 3 reactions were reported in 1.5% of patients for the margetuximab-cmkb arm versus 0 reported events in the trastuzumab arm. All reactions resolved within 24 hours regardless of severity. Consider premedications, including antihistamines, corticosteroids, and antipyretics, in patients who experience mild or moderate reactions.
- **Adverse reactions**
    - **Common (≥20%):** Fatigue/asthenia, nausea, diarrhea, vomiting, decreased hemoglobin, decreased leukocytes, decreased neutrophils, increased aPTT, decreased lymphocytes, increased INR, increased creatinine, increased ALT, increased lipase, increased AST, increased alkaline phosphatase
    - **Serious Adverse events / Deaths / Discontinuation:**
        - The most common grade 3 or higher treatment-related adverse events were diarrhea, decreased hemoglobin, increased aPTT, decreased lymphocytes, and increased lipase
        - Three grade 5 fatal events were reported including viral pneumonia and aspiration pneumonia, none were considered treatment-related
        - Permanent discontinuation due to adverse events occurred in 3% of patients. Adverse events that resulted in this permanent discontinuation included left ventricular dysfunction and infusion-related reaction. Dosage interruptions due to adverse events occurred in 11% of patients. Adverse reactions in which required dosage interruption in >5% of patients included infusion-related reactions

Other Considerations

- **Appropriate use:** Select patients for treatment of advanced breast cancer based on the presence of ERBB-2 mutation in tumor sample. Information on approved tests for the detection of ERBB-2 mutation is available at http://www.fda.gov/CompanionDiagnostics
- **Pregnancy considerations:** In animal reproduction studies, intravenous administration of margetuximab-cmkb resulted in oligohydramnios and delayed infant kidney development near the recommended human dose
- **Breastfeeding considerations:** It is unknown if margetuximab-cmkb is present in breast milk. Due to the potential for serious adverse reactions in the breastfed infant, consideration of developmental and health benefits of breastfeeding along with the mother's clinical need should be weighed
- **Dose modifications:**
    - Withhold margetuximab-cmkb for at least 4 weeks for any of the following:
        - ≥16% absolute decrease in LVEF from pretreatment values
        - LVEF below institutional limits of normal (or 50% if no limits are available) and ≥10% absolute decrease in LVEF from pretreatment value
    - Margetuximab-cmkb may be resumed if, within 8 weeks, LVEF returns to normal limits and absolute decrease from baseline is ≤15%
    - Permanently discontinue margetuximab-cmkb if LVEF decline persists for >8 weeks or if dosing is interrupted on >3 occasions for LVEF decline
    - For infusion-related reactions, decrease the rate of infusion for mild or moderate infusion-related reactions. Interrupt infusion for dyspnea or clinically significant hypotension. Discontinue in patients with severe or life-threatening infusion-related reactions

Risk-Benefit Assessment (for Oncology NMEs only)

- **Outcome in clinically significant area:** margetuximab + chemo vs. trastuzumab + chemo
    - **mPFS:** 5.8 mo
    - **mOS (Final analysis):** 21.6 mo
    - **ORR:** 22%
- **Effect Size:**
    - **mPFS:** HR 0.76 **(**95% CI, 0.59-0.98); p = 0.03
    - **mOS (Final analysis):** HR 0.95 **(**95% CI, 0.77-1.17); p = 0.62
    - **ORR:** 95% CI, 17.11-27.16; p = 0.06
- **Potential Harms:** Significant
- **Net Clinical Benefit:** Negative: Improvement of mPFS, but no improvement seen in mOS when compared to trastuzumab

Other Therapeutic Options

Supporting efficacy and safety data for other HER2-targeted agents and chemotherapy options in the second-line and beyond settings (Following two or more prior anti-HER2 regimens, including pertuzumab) are summarized in Table 3

<table>
<tr>
<td>Trastuzumab + docetaxel or vinorelbine</td>
<td>F</td>
<td>FDA-approved indication for this regimen: Metastatic, HER2+ breast cancer

VHA Clinical Pathway for this regimen in breast cancer: For patients with stage IV any ER/PR, HER2+ breast cancer who have received ≥4 previous lines of anti-HER2 therapy including pertuzumab.

<u>Efficacy:</u>
Trastuzumab + docetaxel or vinorelbine:
Phase III study of patients with HER2+ metastatic or locally advanced breast cancer treated first line with docetaxel plus trastuzumab or vinorelbine plus trastuzumab

mTTP: 12.4 vs 15.3 mo (HR 0.94; 95% CI, 0.71-1.25; P=0.67)
mOS: 35.7 vs 38.8 mo (HR 1.01; 95% CI, 0.71-1.42; P=0.98)
ORR: 59.3% in both arms</td>
<td>Dosing: Trastuzumab: 8 mg/kg followed by a maintenance dose of 6 mg/kg every 21 days until disease progression or unacceptable toxicity. Docetaxel: 100 mg/m^2 every 21 days until disease progression or unacceptable toxicity. Vinorelbine: 25 mg/m^2 every 7 days until disease progression or unacceptable toxicity

PK: Trastuzumab: Half-life: ~16 days; metabolism: N/A. Docetaxel: Half-life: 92-135 hr; metabolism: primarily hepatic via CYP3A4. Vinorelbine: Half-life: 28-44 hr; metabolism: primary hepatic via CYP3A4

Drug-drug interactions: Trastuzumab: N/A. Docetaxel: CYP3A4 inducers or inhibitors. Vinorelbine: CYP3A4 inducers or inhibitors

Warnings and precautions:
Trastuzumab: Cardiomyopathy; infusion-related reactions; pulmonary toxicity; renal toxicity. Docetaxel: Bone marrow suppression; cutaneous reactions; extravasation; fluid retention; gastrointestinal toxicity; neurosensory symptoms; ocular toxicity; weakness Vinorelbine: Bone marrow suppression; extravasation; gastrointestinal toxicity; hepatotoxicity; neuropathy; pulmonary toxicity

Safety (Trastuzumab + Docetaxel):
<table>
<tr><th>Event</th><th>%</th></tr>
<tr><td colspan="2">Common (≥20%)</td></tr>
<tr><td>Leukopenia</td><td>47.5</td></tr>
<tr><td>Neutropenia</td><td>46.8</td></tr>
<tr><td>Febrile neutropenia</td><td>37.4</td></tr>
<tr><td>Nausea</td><td>23.0</td></tr>
<tr><td>Infection</td><td>46.7</td></tr>
<tr><td>Pain</td><td>59.0</td></tr>
<tr><td>Fatigue</td><td>54.6</td></tr>
<tr><td>Diarrhea</td><td>25.9</td></tr>
<tr><td>Sensory neuropathy</td><td>49.6</td></tr>
<tr><td>Edema</td><td>31.7</td></tr>
<tr><td>Nail changes</td><td>37.4</td></tr>
<tr><td colspan="2">Grade ≥3 (≥5%)</td></tr>
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Leukopenia	40.3
Neutropenia	43.9
Febrile neutropenia	37.4
Infection	23.7
Pain	17.3
Fatigue	12.9
Diarrhea	8.6
Sensory neuropathy	30.9
Edema	5.8
Dyspnea	5.7
Nail changes	7.9

Event	**%**
Common (≥20%)	
Leukopenia	51.4
Neutropenia	44.4
Infection	34.0
Pain	42.0
Fatigue	42.0
Grade ≥3 (≥5%)	
Leukopenia	21.0
Neutropenia	41.5
Febrile neutropenia	10.8
Infection	13.0
Pain	18.1
Fatigue	7.9

<table>
<tr>
<td>Lapatinib and capecitabine</td>
<td>F (Lapatinib is NF)</td>
<td>FDA-approved indication for this regimen: Advanced or metastatic, HER2+ breast cancer after treatment with prior anthracycline, taxane, and trastuzumab therapy

VHA Clinical Pathway for this regimen in breast cancer: For patients with stage IV any ER/PR, HER2+ breast cancer who have received ≥4 previous lines of anti-HER2 therapy including pertuzumab.

<u>Efficacy:</u>
Lapatinib + Capecitabine:
Phase III study of patients with progressive, HER2+, locally-advanced or metastatic breast cancer who had previously been treated with a minimum of an anthracycline, taxane, and trastuzumab being treated with lapatinib and capecitabine or capecitabine alone

mTTP: 8.4 vs 4.4 mo (HR 0.49; 95% CI, 0.34-0.71; P<0.001)
ORR: 22% vs 14% (P=0.09)
Disease progression or death from any cause: 49 vs 79 events (HR 0.47; 95% CI, 0.33-0.67; P<0.001)</td>
<td>Dosing: Lapatinib: 1250 mg once daily until disease progression or unacceptable toxicity. Capecitabine: 1,000 mg/m^2 twice daily on days 1 to 14 of a 3-week cycle until disease progression or unacceptable toxicity

PK: Lapatininb: Half-life: ~24 hr; metabolism: hepatic via CYP3A4 and CYP3A5 primarily, lesser metabolism via CYP2C19 and CYP2C8.
Capecitabine: Half-life: ~0.75 hr; metabolism: hepatic and tissue

Drug-drug interactions: Lapatinib: CYP3A4 inducers or inhibitors, QTC prolonging agents, P-glycoprotein/ABCB1 inhibitors.
Capecitabine: Drugs that prolong QT interval; proton-pump inhibitors

Warnings and precautions: Lapatinib: Cardiotoxicity; dermatologic toxicity; diarrhea; hepatotoxicity; pulmonary toxicity; QT prolongation.
Capecitabine: Hepatotoxicity

Safety:
<table>
<tr><th>Event</th><th># (%)</th></tr>
<tr><td colspan="2">Common (≥20%)</td></tr>
<tr><td>Diarrhea</td><td>98 (60)</td></tr>
<tr><td>Nausea</td><td>72 (44)</td></tr>
<tr><td>Vomiting</td><td>43 (26)</td></tr>
<tr><td>Hand-foot syndrome</td><td>80 (49)</td></tr>
<tr><td>Rash</td><td>45 (27)</td></tr>
<tr><td colspan="2">Grade ≥3 (≥5%)</td></tr>
<tr><td>Diarrhea</td><td>21 (13)</td></tr>
<tr><td>Hand-foot syndrome</td><td>12 (7)</td></tr>
</table>
Emetic risk: Minimal to low (<30%)</td>
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<tr>
<td>Neratinib + capecitabine</td>
<td>TBD</td>
<td>FDA-approved indication for this regimen: Advanced or metastatic, HER2-positive breast cancer in combination with capecitabine

VHA Clinical Pathway for breast cancer: For patients with stage IV any ER/PR, HER2+ breast cancer who have received ≥4 previous lines of anti-HER2 therapy including pertuzumab.

<u>Efficacy:</u>
Neratinib + capecitabine:
Phase III study of patients with Her2-positive, metastatic breast cancer with ≥2 previous HER2-directed regimens being treated with neratinib plus capecitabine or lapatinib plus capecitabine
mPFS: 8.8 vs 6.6 mo (HR 0.76; 95% CI, 0.63-0.93; P=0.0003)
ORR: 32.8% (84/256) vs 26.7% (72/270)
OS: 24 vs 22.2 mo (HR 0.88; 95% CI 0.72-1.07)
DoR: 8.5 vs 5.6 mo (HR 0.50; 95% CI, 0.33-0.74; P=0.0004)</td>
<td>Dosing: Neratinib: 240 mg once daily on days 1 to 21 of 21-day cycle until disease progression or unacceptable toxicity. Capecitabine: 750 mg/m2 twice daily on days 1 to 14 of a 3-week cycle until disease progression or unacceptable toxicity

PK: Neratinib: Half-life: 7-17 hr; metabolism: hepatic via CYP3A4 (major) and flavin-containing monooxygenase (minor). Capecitabine: Half-life: ~0.75 hr; metabolism: hepatic and tissue

Drug-drug interactions: Neratinib: Strong CYP3A4 inducers or inhibitors. Capecitabine: Drugs that prolong QT interval; proton-pump inhibitors

Warnings and precautions: Neratinib: Gastrointestinal toxicity; hepatotoxicity. Capecitabine: Hepatotoxicity

Safety:
<table>
<tr><th>Event</th><th># (%)</th></tr>
<tr><td colspan="2">Common (≥20%)</td></tr>
<tr><td>Diarrhea</td><td>252 (83.2)</td></tr>
<tr><td>Nausea</td><td>161 (53.1)</td></tr>
<tr><td>PPE syndrome</td><td>139 (45.9)</td></tr>
<tr><td>Vomiting</td><td>138 (45.5)</td></tr>
<tr><td>Decr appetite</td><td>107 (35.3)</td></tr>
<tr><td>Fatigue</td><td>104 (34.3)</td></tr>
<tr><td>Constipation</td><td>94 (31.0)</td></tr>
<tr><td>Stomatitis</td><td>62 (20.5)</td></tr>
<tr><td colspan="2">Grade ≥3 (≥5%)</td></tr>
<tr><td>Diarrhea</td><td>74 (24.4)</td></tr>
<tr><td>PPE syndrome</td><td>29 (9.6)</td></tr>
</table>
Emetic Risk: Minimal to low (<30%)</td>
</tr>
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Projected Place in Therapy

- Breast cancer is the most common type of cancer for women in the United States per the CDC with nearly triple the rate of cases compared to the next leading cancer type. In terms of death, breast cancer is the second most common cause of cancer-related death among women in the United States.
- In the Veterans Affairs Healthcare System, the most common diagnosed cancer among female Veterans was breast cancer at 30%.
- ERBB2 (Or HER2) amplification is found in approximately 15-20% of breast cancers.
- First-line treatment for breast cancer in the HER2+, advanced or metastatic setting is well established with the combination of a taxane and HER2 directed therapy (Trastuzumab, pertuzumab) as shown in the VHA clinical pathway for breast cancer.
- For patients with HER2+, advanced or metastatic breast cancer who continue to progress following multiple treatments with a variety of different HER2 targeted therapies and chemotherapies, guidelines recommend margetuximab-cmkb in combination with chemotherapy as subsequent therapy following progression after multiple lines of HER2 targeted therapies and chemotherapy.
- The SOPHIA trial, a phase III trial, evaluated margetuximab-cmkb in combination with chemotherapy in patients with advanced breast cancer who had previously been treated with multiple lines of therapy, including pertuzumab, when compared to trastuzumab in combination with chemotherapy. The objective response rate was 22%, the median progression free survival was 5.8 months, and the median overall survival was 21.6 months.
    - The initial results showed a statistically significant improvement in progression free survival when comparing margetuximab-cmkb and chemotherapy with trastuzumab and chemotherapy.
    - The follow-up overall survival data did not show a significant difference between the two treatment arms.
- Due to the lack of overall survival benefit in margetuximab + chemotherapy as compared to trastuzumab + chemotherapy, as well as the toxicity and expense, margetuximab + chemotherapy is not included in the VHA clinical pathway for breast cancer.

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