



## Positive Quality Intervention: Margetuximab-cmkb (MARGENZA®) Management

### Description:

The purpose of this PQI is to provide guidance for the management and treatment of HER2 positive, metastatic breast cancer using margetuximab-cmkb for patients who have received two or more lines of prior anti-HER2 regimens, one of which is in the metastatic setting.

**Background:** Margetuximab-cmkb is a chimeric monoclonal antibody that binds to human epidermal growth factor receptor 2 protein (HER2) ultimately mediating cellular cytotoxicity and natural killer cell activation. Margetuximab-cmkb was FDA approved on December 16, 2020 in combination with chemotherapy for the treatment of adult patients with metastatic HER2-positive (HER2+) breast cancer who have received at least 2 or more prior lines of therapy with at least one in the metastatic setting.<sup>1</sup> Margetuximab-cmkb recommended dosing is 15 mg/kg intravenously (IV) every 3 weeks until disease progression or unacceptable toxicity. Efficacy and safety of margetuximab-cmkb was evaluated in the open-label phase III SOPHIA trial<sup>2</sup> where 536 HER2+ metastatic breast cancer patients who had progressed after at least 2 HER2-targeted therapies were randomized (1:1) to margetuximab-cmkb plus chemotherapy (margetuximab-cmkb arm) or trastuzumab plus chemotherapy (trastuzumab arm). All patients received investigator selected chemotherapy of either capecitabine, eribulin, gemcitabine or vinorelbine. The main efficacy outcomes in the SOPHIA trial were progression free survival (PFS) and overall survival (OS) in the intention-to-treat population.<sup>2</sup> The final median progression free survival in the margetuximab-cmkb arm was 5.7 months versus 4.4 months in the trastuzumab arm (HR, 0.73; 95% CI, 0.60-0.88; P = 0.001).<sup>3</sup> Final OS analysis did not demonstrate a margetuximab-cmkb advantage over trastuzumab.<sup>3</sup> The most common adverse reactions (>20%) observed with margetuximab-cmkb, in the SOPHIA trial, included fatigue, nausea, neutropenia, and diarrhea. Other common adverse reactions (>20%), per current prescribing information, includes myelosuppression, increased ALT/AST, serum lipase, creatinine and INR. Serious adverse reactions that occurred in patients receiving margetuximab-cmkb included infusion related reactions and febrile neutropenia. Infusion-related reactions of all grades were higher with margetuximab-cmkb (13.6%) than trastuzumab (3.4%), with 5 patients experiencing grade 3 or higher reactions in the margetuximab-cmkb arm versus zero in the trastuzumab group.<sup>3</sup> Similar to its trastuzumab counterpart, margetuximab-cmkb has a black boxed warning advising of potential risk of left ventricular dysfunction (LVEF) and embryo-fetal toxicity.<sup>1</sup> Specifically in the SOPHIA trial, any-grade LVEF occurred at the same rate in both arms at 3%, however trastuzumab required more dose delays or discontinuation as a result of LVEF.

### PQI Process:

- Review the medical record
  - Ensure patient is an appropriate candidate for margetuximab-cmkb
    - Margetuximab-cmkb is indicated, in combination with chemotherapy, for the treatment 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
  - Assess left ventricular ejection fraction (LVEF) and cardiac history prior to initiation
    - Patients with pretreatment LVEF <50% by echocardiogram or multi-gated acquisition scan (MUGA) were not studied<sup>2</sup>
    - Patients with history of myocardial infarction, unstable angina within 6 months or congestive heart failure class II-IV were not studied<sup>2</sup>
  - Assess pregnancy status in females of reproductive potential prior to treatment with a serum or urine pregnancy test for a negative result

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- Review treatment plan
  - Verify infusion rate and administration sequence
    - The initial dose of margetuximab-cmkb is administered over 120 minutes and if tolerated may subsequently be administered over a minimum of 30 minutes
    - Chemotherapy is to be administered first, followed by margetuximab-cmkb last
  - Verify premedication for secondary prevention of infusion related reactions (*if applicable*)
    - Consider use of antihistamines (ie. diphenhydramine), corticosteroids (ie. dexamethasone) and/or acetaminophen for prevention of infusion related reactions if there is history of mild to moderate infusion reactions to margetuximab-cmkb
- Preparation and administration<sup>1</sup>
  - Withdraw required dose volume of margetuximab-cmkb and transfer to a 100 mL or 250 mL 0.9% sodium chloride IV bag (do not use 5% dextrose).
  - Final concentration of diluted product should be between 0.5 mg/mL to 7.2 mg/mL
  - Do not mix with other medications or administer IV push or bolus
  - Administer intravenously through a line containing a sterile, low-protein binding 0.2 or 0.22 micron in-line filter
- Monitoring
  - LVEF: baseline (within 4 weeks) and every 3 months during treatment
    - Withhold for greater than or equal to 16% decrease of LVEF from baseline
    - Withhold if LVEF is below 50% (or institutional limit of normal) and there is a greater than or equal to 10% decrease in LVEF from baseline
    - Margetuximab-cmkb should be permanently discontinued if LVEF decline persists for greater than 8 weeks or if dosing is interrupted greater than 3 occasions due to LVEF decline
  - Infusion reactions: during administration and after completion of infusion
    - For patients that experience mild to moderate infusion reactions:
      - Consider pre-medications for subsequent doses
      - Decrease rate of infusion
    - Permanently discontinue in all patients with severe or life-threatening infusion reactions

### Patient-Centered Activities<sup>1</sup>:

- Provide patient education; [Intravenous Cancer Treatment Education \(IVE\) sheet](#) *Coming Soon*
- Instruct patient to report any symptoms of chills, fever, shortness of breath, headache, cough, fast heartbeat, itching, hives, or other unusual effects during infusion
- Promptly review signs of heart problems such as new or worse cough or shortness of breath, swelling of ankles or legs, abnormal heartbeat, dizziness, passing out or weight gain of more than 5 pounds in 24 hours
- Educate on potential to experience adverse effects such as fatigue, nausea, extremity pain and infusion related reactions.
- Advise females of reproductive potential to use effective contraception during treatment and for 4 months after completion
- Patient Assistance: [NCODA Financial Assistance Tool](#)

### References:

1. [Margenza® \(margetuximab-cmkb\) \[prescribing information\]](#).
2. Rugo HS, Im SA, Cardoso F, et al. Efficacy of Margetuximab vs Trastuzumab in Patients With Pretreated ERBB2-Positive Advanced Breast Cancer: A Phase 3 Randomized Clinical Trial. *JAMA Oncol.* 2021;7(4):573-584.
3. Rugo HS, Im S, Cardosa F, et al. Margetuximab Versus Trastuzumab in Patients With Previously Treated HER2-Positive Advanced Breast Cancer (SOPHIA): Final Overall Survival Results From a Randomized Phase 3 Trial. *J Clin Oncol.* 2022;41(2):198-205