RxAdvance

NEW DRUG APPROVAL

Brand Name	Margenza™
Generic Name	margetuximab-cmkb
Drug Manufacturer	MacroGenics, Inc.

New Drug Approval

FDA Approval Date: December 16, 2020

Review Designation: Standard

Review Type: BLA (761150)

Dispensing Restrictions: Limited distribution is expected but not known at this time.

Place in Therapy

DISEASE DESCRIPTION & EPIDEMIOLOGY

Worldwide, breast cancer is the most common cancer and a primary cause of cancer mortality in women. Lifetime risk of breast cancer in North American females is about 12%. Median age at time of breast cancer diagnosis was 62 during 2012-2016. In the United States (U.S.), breast cancer is the most common cancer in women, with more than 260,000 new cases and 40,000 deaths annually. Metastatic breast cancer is categorized into different histopathological subtypes based on expression of ER, PR, and HER2. Approximately 20 to 25% of breast cancer patients have HER2-positive tumors. HER2 gene amplification or HER2 protein overexpression in breast cancer is associated with a more aggressive tumor and poorer prognosis. Advanced or metastatic HER2-positive breast cancer is incurable.

Efficacy

Efficacy of margetuximab-cmkb plus chemotherapy was evaluated in SOPHIA (NCT02492711), which was a randomized, mulicenter, open-label trial of 536 patients with IHC 3+ or ISH-amplified HER2+ metastatic breast cancer who had received prior treatment with other anti-HER2 therapies. Patients were randomized (1:1) to margetuximab-cmkb plus chemotherapy or trastuzumab plus chemotherapy. Patients were required to have progressed on or after the most recent line of therapy. Prior radiotherapy and hormonal therapy were permitted. Patients received margetuximab-cmkb 15 mg/kg intravenously every 3 weeks or trastuzumab 8 mg/kg intravenously initially and 6 mg/kg intravenously on subsequent doses every 3 weeks. Patients were treated until disease progression or unacceptable toxicity. Major efficacy outcomes were progression-free survival (PFS) and overall survival (OS). Additional efficacy outcomes were objective response rate (ORR) and duration of response (DOR).

Majority of patients were female (99.4%) and White (80%). Patients had an ECOG performance status of 0 (58%) or 1 (42%) at baseline. Median number of prior lines of therapy in the locally advanced/metastatic setting was 2 with a range of 1 to 4. All study patients had previously received trastuzumab; all but one patient has previously received pertuzumab and 91% had previously received ado-trastuzumab emtansine.

Efficacy Result in SOPHIA

	margetuximab-cmkb + chemotherapy	trastuzumab + chemotherapy
N	266	270
Progression-free Survival		

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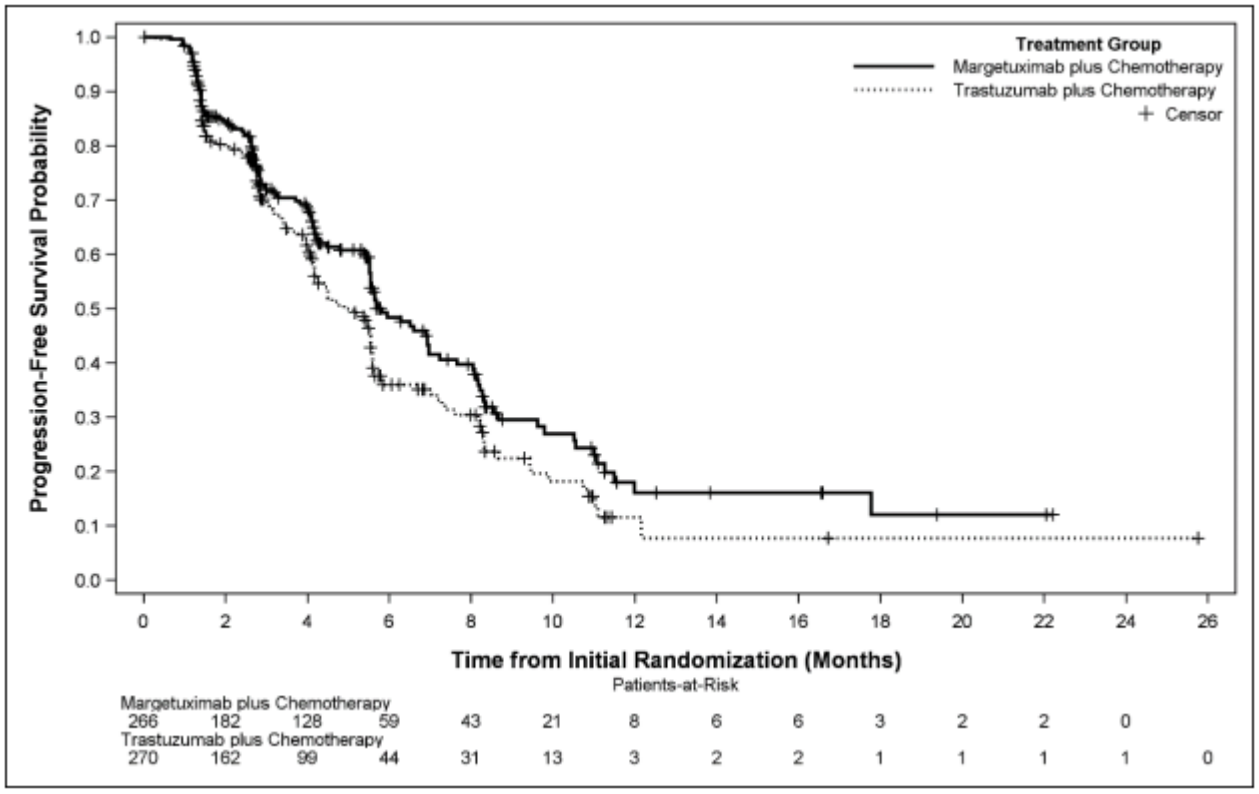
Number of events (%)	130 (48.9)	135 (50)
Disease progression	118 (44.4)	125 (46.3)
Death	12 (4.5)	10 (3.7)
Median, months (95% CI)	5.8 (5.5, 7.0)	4.9 (4.2, 5.6)
Hazard Ratio (95% CI)	0.76 (0.59, 0.98)	
p-value	0.033	
Objective Response for patients with measurable disease (N)	262	262
Confirmed ORR (95% CI)	22 (17, 27)	16 (12, 20)
Duration of Objective Response (N)	58	42
Median, months (95% CI)	6.1 (4.1, 9.1)	6.0 (4.0, 6.9)

Kaplan-Meier Curve for PFS in SOPHIA



The study resulted in a statistically significant difference in PFS when margetuximab-cmkb plus chemotherapy was compared to trastuzumab plus chemotherapy. Investigator-assessed PFS was similar to independent blinded PFS results. Although the PFS improvement is only 0.9 months, margetuximab-cmkb plus chemotherapy represents a replacement therapy for trastuzumab plus chemotherapy and patients may benefit from having an alternative therapy.

Overall survival was immature; however no apparent detriment was observed in patients who received margetuximab-cmkb plus chemotherapy compared to those that received trastuzumab plus chemotherapy. At the protocol pre-specified second interim analysis of OS, the OS data were not mature with 50% of deaths in the overall population.

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Safety

ADVERSE EVENTS

Dosage disruption due to adverse reactions occurred in 11% of patients receiving margetuximab-cmkb plus chemotherapy. Permanent discontinuation of margetuximab-cmkb due to adverse reactions occurred in 3% of patients. Adverse reactions that occur 15% or more in patients are listed:

- Dermatologic: Alopecia (18%)
- Gastrointestinal disorders: Abdominal pain (17%); constipation (19%); diarrhea (25%); increased serum lipase (30%); nausea (33%); and vomiting (21%)
- Hematologic: Decreased hemoglobin (52%); increased INR (24%); leukopenia (40%); lymphocytopenia (31%); prolonged partial thromboplastin time (32%)
- Hepatic: Increased serum alanine aminotransferase (32%), increased alkaline phosphatase (21%); increase aspartate aminotransferase (23%)
- Nervous system disorders: Fatigue (57%); headache (19%); peripheral neuropathy (16%)
- Neuromuscular & skeletal: Asthenia (57%)
- Renal: Increased serum creatinine (68%)
- Miscellaneous: Pyrexia (19%)

WARNINGS & PRECAUTIONS

Margetuximab-cmkb has a black box warning regarding left ventricular dysfunction and embryo-fetal toxicity. It also has a warning regarding infusion-related reactions.

- Left ventricular cardiac dysfunction. Left ventricular cardiac dysfunction occurred in 1.9% of patients treated with margetuximab-cmkb. Margetuximab-cmkb has not been studied in patients with a pre-treatment LVEF less than 50%, a prior history of myocardial infarction or unstable angina within 6 months or congestive heart failure NYHA class II-IV. Withhold margetuximab-cmkb for 16% or greater absolute decrease in LVEF from pre-treatment values or LVEF value below institutional limits of normal and 10% or greater absolute decrease in LVEF from pre-treatment values. Permanently discontinue margetuximab-cmkb if LVEF decline persists for greater than 8 weeks, or if dosing is interrupted on greater than 3 occasions due to LVEF decline.

- Embryo-Fetal Toxicity. Margetuximab-cmkb can cause fetal harm when administered to pregnant women. In post-marketing reports, use of a HER2-directed antibody during pregnancy resulted in cases of oligohydramnios and oligohydramnios sequence manifesting as pulmonary hypoplasia, skeletal abnormalities and neonatal death. Verify pregnancy status of females of reproductive age prior to the initiation of margetuximab-cmkb. Advise women and females of reproductive potential that exposure to margetuximab-cmkb during pregnancy or within 4 months prior to conception can result in fetal harm.

- Infusion-related Reactions. Infusion-related reactions can occur causing fever, chills, arthralgia, cough, dizziness, fatigue, nausea, vomiting, headache, diaphoresis, tachycardia, hypotension, pruritus, rash, urticaria, and dyspnea. Infusion-related reactions were reported in 13% of patients receiving margetuximab-cmkb plus chemotherapy. Monitor patients for infusion-related reactions during margetuximab-cmkb administration and as clinically indicated after the completion of the infusion.

- As with all therapeutic proteins, there is a potential for immunogenicity with margetuximab-cmkb. Detection of antibodies is highly dependent on assay sensitivity and specificity.

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CONTRAINDICATIONS

None.

Clinical Pharmacology

MECHANISMS OF ACTION

Margetuximab-cmkb binds to the extracellular domain of the HER2 oncoprotein. Upon binding to HER2-expressing tumor cells, margetuximab-cmkb inhibitors tumor cell proliferation, reduces shedding of the HER2 extracellular domain, and mediates antibody-dependent cellular cytotoxicity (ADCC).

Dose & Administration

ADULTS

15 mg/kg, administered as an intravenous infusion every 3 weeks (21-day cycle) until disease progression or unacceptable toxicity. The first infusion should be administered over 120 minutes; all subsequent doses can be administered over a minimum of 30 minutes. Margetuximab-cmkb should be administered after chemotherapy completion on days that chemotherapy and margetuximab-cmkb are to be administered. If a dose is missed, administer the dose as soon as possible. Adjust the administration schedule to maintain 3-week intervals between doses.

PEDIATRICS

Safety and efficacy of margetuximab-cmkb in pediatric patients has not been studied.

GERIATRICS

Refer to adult dosing.

RENAL IMPAIRMENT

No formal studies have been conducted.

HEPATIC IMPAIRMENT

No formal studies have been conducted.

Product Availability

DOSAGE FORM(S) & STRENGTH(S)

Injection: 250 mg/10 mL (25 mg/mL) in a single-dose vial

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