SUMMARY OF PRODUCT CHARACTERISTICS

NAME OF THE MEDICINAL PRODUCT

MARGENZA

QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains:

Active ingredient: Margetuximab 25 mg/mL.

Each single-dose 10ml vial contains 250 mg Margetuximab.

PHARMACEUTICAL FORM

Concentrate For Solution For Infusion.

1 INDICATIONS AND USAGE

MARGENZA 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 *[see Dosage and Administration (**2.1**) and Clinical Studies (**12**).*

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Doses and Schedules

The recommended dose of MARGENZA is 15 mg/kg, administered as an intravenous infusion every 3 weeks (21-day cycle) until disease progression or unacceptable toxicity.

Administer MARGENZA as an intravenous infusion at 15 mg/kg over 120 minutes for the initial dose, then over a minimum of 30 minutes every 3 weeks for all subsequent doses.

On days when both MARGENZA and chemotherapy are to be administered, MARGENZA may be administered immediately after chemotherapy completion.

Refer to the respective Prescribing Information for each therapeutic agent administered in combination with MARGENZA for the recommended dosage information, as appropriate.

2.2 Dose Modification or Important Dosing Considerations

If a patient misses a dose of MARGENZA, administer the scheduled dose as soon as possible. Adjust the administration schedule to maintain a 3-week interval between doses.

*Left Ventricular Dysfunction [see Warnings and Precautions (**5.1**)]*

Assess left ventricular ejection fraction (LVEF) before starting MARGENZA and regularly during treatment. Withhold MARGENZA dosing 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 values.

MARGENZA dosing may be resumed if, within 8 weeks, LVEF returns to normal limits and absolute decrease from baseline is ≤ 15%. Permanently discontinue MARGENZA if LVEF decline persists for greater than 8 weeks, or if dosing is interrupted on greater than 3 occasions for LVEF decline.

*Infusion-Related Reactions [see Warnings and Precautions (**5.3**)]*

Decrease the rate of infusion for mild or moderate infusion-related reactions (IRRs). Interrupt the infusion for dyspnea or clinically significant hypotension. Permanently discontinue MARGENZA dosing in patients with severe or life-threatening IRRs.

2.3 Preparation for Administration

Administer as an intravenous infusion after dilution.

Preparation for Intravenous Infusion

Prepare solution for infusion, using aseptic technique, as follows:

- Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. The solution is clear to slightly opalescent, colorless to pale yellow or pale brown. Some visible, translucent, inherent proteinaceous particles may be present.
- **Swirl the vial(s) gently.** Do not shake the vial(s).
- Calculate the required volume of MARGENZA needed to obtain the appropriate dose according to patient's body weight. The calculated total dose volume should be rounded to the nearest 0.1 mL.
- Withdraw appropriate volume of MARGENZA solution from the vial(s) using a syringe.
- Transfer MARGENZA into an intravenous bag containing 100 mL or 250 mL 0.9% Sodium Chloride for Injection, USP (normal saline). Polyvinyl chloride (PVC) intravenous bags or intravenous bags made with polyolefins (polyethylene and polypropylene) and polyamide or polyolefins only or copolymer of olefins may be used. Do not use 5% Dextrose Injection, USP solution.

- The final concentration of the diluted solution should be between 0.5 mg/mL to 7.2 mg/mL.
- **Gently invert the intravenous bag to mix the diluted solution.** Do not shake the intravenous bag.
- Discard any unused portion left in the vial(s).

Do not administer as an intravenous push or bolus. Do not mix MARGENZA with other drugs.

Storage of Diluted Solution

- The product does not contain a preservative. If diluted infusion solution is not used immediately, it can be stored at room temperature up to 4 hours or stored refrigerated at 2°C to 8°C up to 24 hours. If refrigerated, allow the diluted solution to come to room temperature prior to administration. **Do not freeze.**

Administration

- Administer diluted infusion solution intravenously over 120 minutes for the initial dose, then over a minimum of 30 minutes every 3 weeks for all subsequent doses. Administer through an intravenous line containing a sterile, non-pyrogenic, low-protein binding polyethersulfone (PES) 0.2 micron in-line or add-on filter.
- Do not co-administer other drugs through the same infusion line.

3 DOSAGE FORMS AND STRENGTHS

Concentrate For Solution For Infusion: 250 mg/10 mL (25 mg/mL) clear to slightly opalescent, colorless to pale yellow or pale brown solution in a single-dose vial.

4 CONTRAINDICATIONS

- Hypersensitivity to the active substance or to any of the excipients listed in section 9.

5 WARNINGS AND PRECAUTIONS

5.1 Left Ventricular Dysfunction

Left ventricular cardiac dysfunction can occur with MARGENZA. In SOPHIA, left ventricular dysfunction occurred in 1.9% of patients treated with MARGENZA. MARGENZA has not been studied in patients with a pretreatment LVEF value of < 50%, a prior history of myocardial infarction or unstable angina within 6 months, or congestive heart failure NYHA class II-IV.

Withhold MARGENZA for ≥ 16% absolute decrease in LVEF from pretreatment values or LVEF value below institutional limits of normal (or 50% if no limits are available) and ≥ 10% absolute

decrease in LVEF from pretreatment values. Permanently discontinue MARGENZA if LVEF decline persists for greater than 8 weeks, or if dosing is interrupted on greater than 3 occasions due to LVEF decline *[see Dosage and Administration (**2.2**)]*.

Cardiac Monitoring

Conduct thorough cardiac assessment, including history, physical examination, and determination of LVEF by echocardiogram or MUGA scan. The following schedule is recommended:

- Baseline LVEF measurement within 4 weeks prior to initiation of MARGENZA
- LVEF measurements (MUGA/echocardiogram) every 3 months during and upon completion of MARGENZA
- Repeat LVEF measurement at 4-week intervals if MARGENZA is withheld for significant left ventricular cardiac dysfunction *[see Dosage and Administration (**2.2**)]*.

5.2 Embryo-Fetal Toxicity

Based on findings in animals and mechanism of action, MARGENZA can cause fetal harm when administered to a pregnant woman. There are no available data on the use of MARGENZA in pregnant women to inform the drug-associated risk. 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. In an animal reproduction study, intravenous administration of margetuximab-cmkb to pregnant cynomolgus monkeys once every 3 weeks starting at gestational day (GD) 20 until delivery resulted in oligohydramnios and delayed infant kidney development. Animal exposures were ≥ 3 times the human exposures at the recommended dose, based on Cmax.

Verify pregnancy status of females of reproductive potential prior to initiation of MARGENZA. Advise pregnant women and females of reproductive potential that exposure to MARGENZA during pregnancy or within 4 months prior to conception can result in fetal harm. Advise females of reproductive potential to use effective contraception during treatment and for 4 months following the last dose of MARGENZA *[see Use in Specific Populations (**8.1, 8.3**)]*.

5.3 Infusion-Related Reactions

MARGENZA can cause infusion-related reactions (IRRs) *[see Adverse Reactions (**0**)]*. Symptoms may include fever, chills, arthralgia, cough, dizziness, fatigue, nausea, vomiting, headache, diaphoresis, tachycardia, hypotension, pruritus, rash, urticaria, and dyspnea.

In SOPHIA, IRRs were reported by 13% of patients on MARGENZA plus chemotherapy. Most of the IRRs occur during Cycle 1. Grade 3 IRRs were reported in 1.5% of MARGENZA-treated patients. All IRRs resolved within 24 hours, irrespective of severity. In SOPHIA, IRRs leading to

interruption of treatment occurred in 9% of patients treated with MARGENZA and chemotherapy. One patient (0.4%) on MARGENZA discontinued treatment due to IRR.

An infusion substudy in 88 patients in SOPHIA evaluated MARGENZA administered over 120 minutes for the initial dose, then 30 minutes from Cycle 2 forward. IRRs were ≤ Grade 2 and most occurred during the first (120 minutes) administration of MARGENZA. From Cycle 2 onward, one patient (1.1%) had an IRR (Grade 1).

Monitor patients for IRRs during MARGENZA administration and as clinically indicated after completion of infusion. Have medications and emergency equipment to treat IRRs available for immediate use. Monitor patients carefully until resolution of signs and symptoms.

In patients who experience mild or moderate IRRs, consider premedications, including antihistamines, corticosteroids, and antipyretics. Decrease the rate of infusion for mild or moderate IRRs. Interrupt MARGENZA infusion in patients experiencing dyspnea or clinically significant hypotension and intervene with medical therapy which may include epinephrine, corticosteroids, diphenhydramine, bronchodilators and oxygen. Patients should be evaluated and carefully monitored until complete resolution of signs and symptoms. Permanently discontinue MARGENZA in all patients with severe or life-threatening IRRs.

5.4 Effects on Ability to Drive and Use Machines

Margenza has a minor influence on the ability to drive or use machines. Dizziness and somnolence may occur during treatment with Margenza. Patients experiencing infusion-related symptoms should be advised not to drive and use machines until symptoms abate.

6 ADVERSE REACTIONS

The following adverse reactions are discussed in greater detail in other sections of the SPC:

- Left Ventricular Dysfunction *[see Warnings and Precautions (**5.1**)]*
- Embryo-Fetal Toxicity *[see Warnings and Precautions (**5.2**)]*
- Infusion-Related Reactions *[see Warnings and Precautions (**5.3**)]*

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product.

Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form https://sideeffects.health.gov.il

and emailed to the Registration Holder's Patient Safety Unit at:
drugsafety@neopharmgroup.com

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect rates observed in practice.

The safety of MARGENZA was evaluated in HER2-positive breast cancer patients who received two or more prior anti-HER2 regimens in SOPHIA *[see Clinical Studies (**12**)]*.

Patients were randomized (1:1) to receive either MARGENZA 15 mg/kg every 3 weeks plus chemotherapy or trastuzumab plus chemotherapy. Among patients who received MARGENZA, 40% were exposed for 6 months or longer and 11% were exposed for greater than one year.

Serious adverse reactions occurred in 16% of patients who received MARGENZA. Serious adverse reactions in > 1% of patients included febrile neutropenia (1.5%), neutropenia/neutrophil count decrease (1.5%) and infusion related reactions (1.1%). Fatal adverse reactions occurred in 1.1% of patients who received MARGENZA, including viral pneumonia (0.8%) and aspiration pneumonia (0.4%).

Permanent discontinuation due to an adverse reaction occurred in 3% of patients who received MARGENZA. Adverse reactions which resulted in permanent discontinuation in > 1% of patients who received MARGENZA included left ventricular dysfunction and infusion-related reactions.

Dosage interruptions due to an adverse reaction occurred in 11% of patients who received MARGENZA. Adverse reactions which required dosage interruption in > 5% of patients who received MARGENZA included infusion-related reactions.

Table 1 summarizes the adverse reactions in SOPHIA.

Table 1 Adverse Reactions (>10%) in Patients with Metastatic HER2-Positive Breast Cancer Who Received MARGENZA in SOPHIA

Adverse Reaction	MARGENZA + Chemotherapy (n = 264)		Trastuzumab + Chemotherapy (n = 266)	
	All Grades (%)	Grade 3 or 4 (%)	All Grades (%)	Grade 3 or 4 (%)
General disorders and administration site conditions				
Fatigue/Asthenia	57	7	47	4.5
Pyrexia	19	0.4	14	0.4
Gastrointestinal disorders				
Nausea	33	1.1	32	0.4
Diarrhea	25	2.3	25	2.3
Vomiting	21	0.8	14	1.5
Constipation	19	0.8	17	0.8
Abdominal pain[a]	17	1.5	21	1.5
Skin and Subcutaneous tissue				
Alopecia	18	0	15	0
Palmar-plantar erythrodysesthesia	13	0	15	3
Nervous System Disorders				
Headache[b]	19	0	16	0
Peripheral neuropathy[c]	16	1.1	15	2.3
Respiratory, thoracic and mediastinal disorders				
Cough	14	0.4	12	0
Dyspnea	13	1.1	11	2.3
Metabolism and nutrition disorders				
Decreased appetite	14	0.4	14	0.4
Musculoskeletal and connective tissue disorders				
Arthralgia/Myalgia	14	0.4	12	0.8
Extremity pain	11	0.8	9	0
Injury, poisoning and procedural complications				
Infusion-related reaction	13	1.5	3	0

a Includes abdominal pain, abdominal discomfort, lower abdominal pain and upper abdominal pain

b Includes headache and migraine

c Includes peripheral neuropathy, peripheral sensory neuropathy, peripheral motor neuropathy, and neuropathy

Clinically relevant adverse reactions in ≤10% of patients who received MARGENZA in combination with chemotherapy included: dizziness and stomatitis (10%) each, decreased weight, dysgeusia, rash, and insomnia (6%) each, hypertension (5%), and syncope (1.5%).

Table 2 summarizes the laboratory abnormalities in SOPHIA.

Table 2 Select Laboratory Abnormalities (≥20%) That Worsened from Baseline in Patients with Metastatic HER2-Positive Breast Cancer Who Received MARGENZA in SOPHIA

Laboratory Abnormality	MARGENZA + Chemotherapy[1]		Trastuzumab + Chemotherapy[1]	
	All Grades (%)	Grade 3 or 4 (%)	All Grades (%)	Grade 3 or 4 (%)
Hematology				
Decreased hemoglobin	52	3.2	43	2.4
Decreased leukocytes	40	5	36	3.2
Decreased neutrophils	34	9	28	9
Increased aPTT	32	3.4	34	4.3
Decreased lymphocytes	31	4.4	38	4.4
Increased INR	24	1.2	25	0.4
Chemistry				
Increased creatinine	68	0.4	60	0
Increased ALT	32	2	30	0.8
Increased lipase	30	6	24	3.2
Increased AST	23	2	22	0.8
Increased alkaline phosphatase	21	0	23	0.8

[1] The denominator used to calculate the rate varied from 229 to 253 based on the number of patients with a baseline value and at least one post-treatment value.
aPTT: activated partial thromboplastin time; INR: prothrombin international normalized ratio; ALT: alanine aminotransferase; AST: aspartate aminotransferase

7 DRUG INTERACTIONS

Anthracyclines

Patients who receive anthracyclines less than 4 months after stopping MARGENZA *[see Clinical Pharmacology (**10.3**)]* may be at increased risk of cardiac dysfunction. While this interaction has not been studied with MARGENZA, clinical data from other HER2-directed antibodies warrants consideration. Avoid anthracycline-based therapy for up to 4 months after stopping MARGENZA. If concomitant use is unavoidable, closely monitor patient's cardiac function.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Based on findings in animals and mechanism of action, MARGENZA can cause fetal harm when administered to a pregnant woman. There are no available data on use of MARGENZA in

pregnant women to inform the drug-associated risk. In postmarketing 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. In an animal reproduction study, intravenous administration of margetuximab-cmkb to pregnant cynomolgus monkeys once every 3 weeks, starting at gestational day (GD) 20 until delivery, resulted in oligohydramnios and delayed infant kidney development. Animal exposures were ≥ 3 times the human exposures at the recommended dose, based on Cmax *(see Data)*. Advise patients of potential risks to a fetus. There are clinical considerations if MARGENZA is used during pregnancy or within 4 months prior to conception *(see Clinical Considerations).*

Estimated background risk of major birth defects and miscarriage for the indicated population is unknown. In the U.S. general population, background risks of major birth defects and miscarriage in clinically recognized pregnancies are 2 - 4% and 15 - 20%, respectively.

Clinical Considerations

Fetal/Neonatal Adverse Reactions

Monitor women who received MARGENZA during pregnancy or within 4 months prior to conception for oligohydramnios. If oligohydramnios occurs, perform fetal testing that is appropriate for gestational age and consistent with community standards of care.

Data

Animal Data

In an enhanced pre- and post-natal development study, pregnant cynomolgus monkeys received intravenous doses of 50 or 100 mg/kg margetuximab-cmkb once every 3 weeks starting on GD 20 and until delivery. Animal exposures at doses of 50 and 100 mg/kg were 3 and 6 times, respectively, the human exposures at the recommended dose, based on Cmax. Treatment with 50 and 100 mg/kg margetuximab-cmkb resulted in oligohydramnios beginning on GD 75.

An infant mortality occurred on post-natal day 63 following maternal exposure to 100 mg/kg margetuximab-cmkb. Clinical findings included tubular degeneration/necrosis and tubular dilatation in the kidney. Maternal doses of 50 and 100 mg/kg resulted in decreased infant kidney weights and histologic immature nephrons. Measurable serum concentrations of margetuximab-cmkb were observed in infant animals, which is consistent with margetuximab-cmkb crossing the placenta.

8.2 Lactation

Risk Summary

There is no information regarding presence of MARGENZA in human milk, effects on the breastfed child, or effects on milk production. Published data suggest human IgG is present in

human milk but does not enter neonatal or infant circulation in substantial amounts. Consider developmental and health benefits of breastfeeding along with the mother's clinical need for MARGENZA treatment and any potential adverse effects on the breastfed child from MARGENZA or from the underlying maternal condition. This consideration should also take into account the MARGENZA washout period of 4 months *[see Clinical Pharmacology (**10.3**)]*.

8.3 Females and Males of Reproductive Potential

MARGENZA can cause fetal harm when administered to a pregnant woman.

Pregnancy Testing

Verify pregnancy status of females of reproductive potential prior to initiation of MARGENZA.

Contraception

Females

Advise females of reproductive potential to use effective contraception during treatment and for 4 months following the last dose of MARGENZA *[see Use in Specific Populations (**8.1**) and Clinical Pharmacology (**10.3**)]*.

8.4 Pediatric Use

Safety and effectiveness of MARGENZA have not been established in pediatric patients.

8.5 Geriatric Use

Of the 266 patients treated with MARGENZA 20% were 65 years of age or older and 4% were 75 years or older. No overall differences in efficacy were observed between patients ≥ 65 years of age compared to younger patients. There was a higher incidence of Grade ≥ 3 adverse reactions observed in patients age 65 years or older (56%) compared to younger patients (47%), as well as adverse reactions associated with potential cardiotoxicity (35% vs 18%).

9 DESCRIPTION

Margetuximab-cmkb, a HER2/neu receptor antagonist, is a chimeric Fc-engineered IgG1 kappa monoclonal antibody.

Margetuximab-cmkb is produced by recombinant DNA technology in a mammalian cell (Chinese Hamster Ovary) culture. Margetuximab-cmkb has an approximate molecular weight of 149 kDa.

MARGENZA (margetuximab-cmkb) concentrate for solution for infusion is a sterile, preservative-free, clear to slightly opalescent, colorless to pale yellow or pale brown solution that requires dilution for intravenous use. Some visible, translucent, inherent proteinaceous particles

may be present. Each mL of solution contains the following excipients: sucrose, L-arginine hydrochloride, sodium chloride, sodium phosphate monobasic monohydrate, sodium phosphate dibasic heptahydrate, polysorbate 80, and Water for Injection USP at a pH of approximately 6.1.

This medicinal product contains 50.4 mg sodium per dose (60 kg patient, 15mg/kg dose), equivalent to 2.5% of the WHO recommended maximum daily intake of 2 g sodium for an adult.

10 CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

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

In vitro, the modified Fc region of margetuximab-cmkb increases binding to activating Fc receptor FCGR3A (CD16A) and decreases binding to inhibitory Fc receptor FCGR2B (CD32B). These changes lead to greater in vitro ADCC and NK cell activation.

10.2 Pharmacodynamics

The exposure-response relationship and time course of pharmacodynamic response for the safety and effectiveness of margetuximab-cmkb have not been fully characterized.

10.3 Pharmacokinetics

Following the approved recommended dosage, the steady-state geometric mean (%CV) C_{max} of margetuximab-cmkb is 466 (20%) µg/mL and AUC_{0-21d} is 4120 (21%) µg.day/mL in patients with HER2-positive relapsed or refractory advanced breast cancer. Margetuximab-cmkb undergoes both linear and nonlinear elimination. After a single dose, margetuximab-cmkb C_{max} and AUC_{0-21d} increase in an approximately dose proportional manner from 10 to 18 mg/kg (0.67 to 1.2 times the approved recommended dose). At the approved recommended dosage, time to steady-state was 2 months, and accumulation ratio was 1.65 based on AUC_{0-21d}. No clinically significant differences in margetuximab-cmkb exposure were observed when infusion time was reduced from 120 minutes to 30 minutes.

Distribution

Margetuximab-cmkb geometric mean (%CV) steady-state volume of distribution is 5.47 L (22%).

Elimination

The geometric mean (%CV) terminal half-life of margetuximab-cmkb is 19.2 days (28%) and clearance is 0.22 L/day (24%). Four months after margetuximab-cmkb discontinuation, concentrations decrease to approximately 3% of the steady-state trough serum concentration.

Metabolism

Margetuximab-cmkb is expected to be metabolized into small peptides by catabolic pathways.

Specific Populations

No clinically significant differences in margetuximab-cmkb PK were observed based on age (29 to 83 years), sex, race (Caucasian, Black, Asian), mild to moderate (CLcr 30 to 89 mL/min estimated using the Cockcroft-Gault equation) renal impairment, mild hepatic impairment (total bilirubin ≤ ULN and AST > ULN, or total bilirubin 1 to 1.5 ULN and any AST), HER2 expression level (0 to 3 by IHC), tumor burden (2 – 317 mm), ECOG score (0 to 2), albumin (24 to 50 g/L), FCGR3A (CD16A), FCGR2A (CD32A) and FCGR2B (CD32B) genotype, number of metastatic sites (≤ 2 or > 2), number of prior therapy lines (≤ 2 or > 2) or concurrent chemotherapies (capecitabine, gemcitabine, eribulin and vinorelbine).

The effect of severe renal impairment (CLcr 15 to 29 mL/min), end-stage renal disease with or without hemodialysis, and moderate (total bilirubin > 1.5 to ≤ 3 ULN and any AST) or severe hepatic impairment (total bilirubin >3 ULN and any AST) on margetuximab-cmkb PK is unknown.

10.4 Immunogenicity

The observed incidence of anti-drug antibodies is highly dependent on the sensitivity and specificity of the assay. Differences in assay methods preclude meaningful comparisons of the incidence of anti-drug antibodies in the studies described below with the incidence of anti-drug antibodies in other studies, including those of MARGENZA or of other margetuximab products.

In patients who received MARGENZA in combination with chemotherapy in SOPHIA (up to 68 months) or the Infusion substudy (up to 42 months), the incidence of anti-margetuximab antibodies was 2% (7/350). No patients developed treatment-emergent neutralizing antibodies.

Given the low incidence of anti-margetuximab antibodies, the effect of anti-margetuximab antibodies on the pharmacokinetics, pharmacodynamics, safety, and/or effectiveness of margetuximab-cmkb is unknown.

11 NONCLINICAL TOXICOLOGY

11.1 Carcinogenesis, Mutagenesis, and Impairment of Fertility

Studies have not been performed to evaluate carcinogenic or mutagenic potential of margetuximab-cmkb.

Animal fertility studies have not been conducted with margetuximab-cmkb. In repeat-dose toxicity studies of up to 13-week duration, margetuximab-cmkb had no effect on male and female reproductive organs in sexually mature cynomolgus monkeys.

12 CLINICAL STUDIES

12.1 Metastatic Breast Cancer

The efficacy of MARGENZA plus chemotherapy was evaluated in SOPHIA (NCT02492711), a randomized, multicenter, 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 MARGENZA plus chemotherapy or trastuzumab plus chemotherapy. Randomization was stratified by chemotherapy choice (capecitabine, eribulin, gemcitabine, or vinorelbine), number of lines of therapy in the metastatic setting (≤ 2, > 2), and number of metastatic sites (≤ 2, > 2). Patients were required to have progressed on or after the most recent line of therapy. Prior radiotherapy and hormonal therapy were allowed. Patients received MARGENZA intravenously at a dose of 15 mg/kg every 3 weeks administered over 120 minutes for the initial administration and then over 30 to 120 minutes thereafter. Trastuzumab was given intravenously at an initial dose of 8 mg/kg over 90 minutes, followed by 6 mg/kg over 30 minutes every 3 weeks thereafter. Patients were treated with MARGENZA or trastuzumab in combination with chemotherapy until disease progression or unacceptable toxicity.

Major efficacy outcome measures were progression-free survival (PFS) by blinded independent central (BICR) review and overall survival (OS) of MARGENZA plus chemotherapy, compared with trastuzumab plus chemotherapy. Additional efficacy outcome measures were objective response rate (ORR) and duration of response (DOR) assessed by BICR.

The median age was 56 years (range: 27-86); 78% of patients were < 65 years. The majority of patients were female (99.4%), and the majority were White (80%). Patients had an ECOG performance status of 0 (58%) or 1 (42%) at baseline. Forty seven percent had visceral disease, 57% had bone metastases, and 13% had brain metastases. Sixty percent were hormone receptor positive. The median number of prior lines of therapy in the locally advanced/metastatic setting was 2 (range: 1-4). All study patients had previously received trastuzumab, all but 1 patient had previously received pertuzumab, and 91% had previously received ado-trastuzumab emtansine.

Efficacy results are summarized in **Table 3** and **Figure 1**.

Table 3 Efficacy Results in SOPHIA

	MARGENZA + Chemotherapy (n = 266)	**Trastuzumab + Chemotherapy (n = 270)**
Progression-free Survival [a]		
Number of events (%)	130 (48.9)	135 (50.0)
Disease progression	118 (44.4)	125 (46.3)
Death	12 (4.5)	10 (3.7)
Median, months (95% CI) [b]	5.8 (5.5, 7.0)	4.9 (4.2, 5.6)
Hazard Ratio (HR) (95% CI) [c]	0.76 (0.59, 0.98)	
p-value [d]	0.033	
Objective Response for Patients with Measurable Disease [a]	**(n = 262)**	**(n = 262)**
Confirmed Objective Response Rate (95% CI)	22 (17, 27)	16 (12, 20)
Duration of Objective Response	**(n = 58)**	**(n = 42)**
Median (months) (95% CI) [b]	6.1 (4.1, 9.1)	6.0 (4.0, 6.9)

a Assessed per BICR.

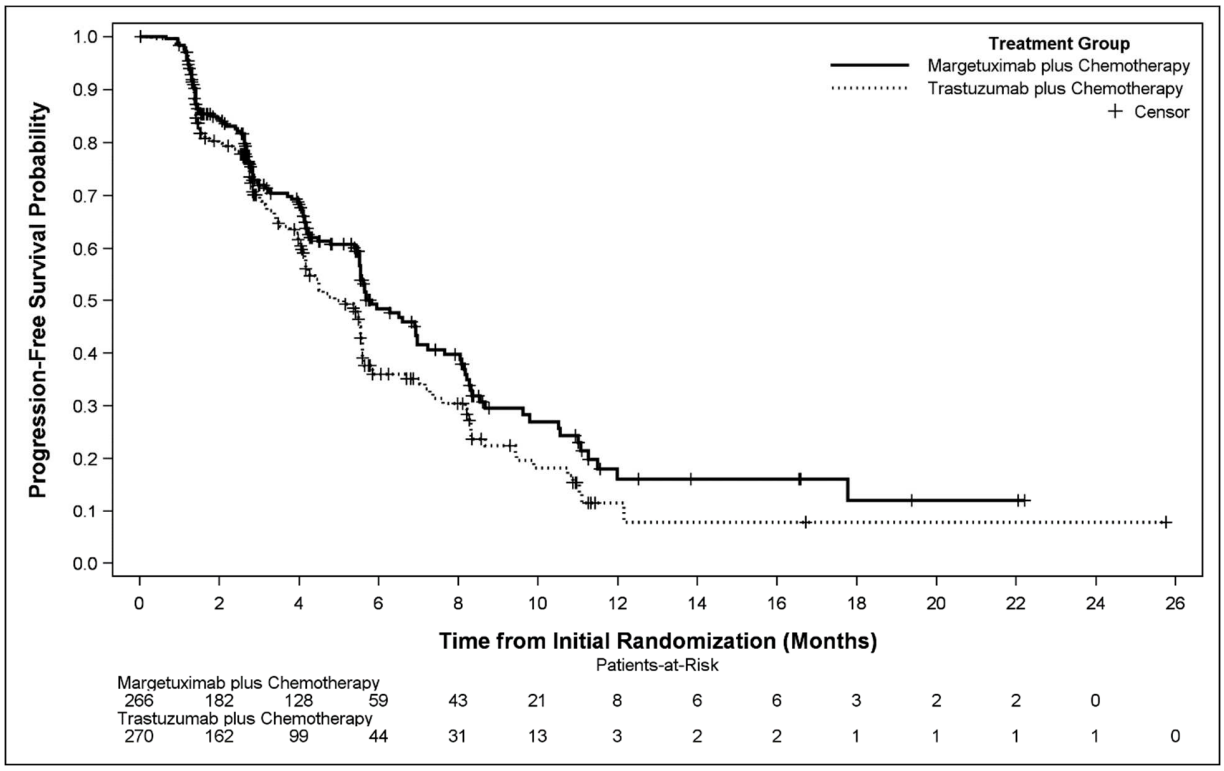
b Based on Kaplan-Meier estimates.

c Based on stratified Cox Model.

d p-value based on 2-sided stratified log rank test.

CI: confidence interval; n: number of patients.

Figure 1 Kaplan-Meier Curve for Progression-Free Survival in SOPHIA



Results for investigator-assessed PFS were similar to the independent blinded PFS results. At the protocol pre-specified second interim analysis of OS, the OS data were not mature with 50% of deaths in the overall population.

A treatment benefit with MARGENZA in terms of PFS was observed in pre-specified patient subgroups based on stratification factors and in an exploratory analysis with a key baseline characteristic, CD16A genotype. In the subgroup of patients who received capecitabine (n = 143), the hazard ratio was 0.77 (95% CI: 0.47, 1.26). In the subgroup of patients who received eribulin (n = 136), the hazard ratio was 0.66 (95% CI: 0.42, 1.05). In the subgroup of patients who received gemcitabine (n = 66), the hazard ratio was 0.58 (95% CI: 0.29, 1.18). In the subgroup of patients who received vinorelbine (n = 191), the hazard ratio was 0.90 (95% CI: 0.60, 1.35). In the subgroup of patients who received ≤ 2 prior metastatic lines of therapy (n = 355), the hazard ratio was 0.81 (95% CI: 0.60, 1.10). In the subgroup of patients who received >2 prior metastatic lines of therapy (n = 181), the hazard ratio was 0.72 (95% CI: 0.48, 1.08). In the subgroup of patients with 1-2 metastatic sites (n = 282), the hazard ratio was 0.94 (95% CI: 0.67, 1.31). In the subgroup of patients with >2 metastatic sites (n = 254), the hazard ratio was 0.63 (95% CI: 0.44, 0.89). In the subgroup of patients who were CD16A-158F allele carriers (n = 437), the hazard ratio was 0.68 (95% CI: 0.52, 0.90). In the subgroup of patients who were CD16A-158V/V homozygotes (n = 69), the hazard ratio was 1.78 (95% CI: 0.87, 3.62).

13 HOW SUPPLIED/STORAGE AND HANDLING

13.1 How Supplied

MARGENZA (margetuximab-cmkb) concentrate for solution for infusion is a clear to slightly opalescent, colorless to pale yellow or pale brown solution in a single-dose vial supplied as:

Carton Contents

One 250 mg/10 mL (25 mg/mL) single-dose vial

Four 250 mg/10 mL (25 mg/mL) single-dose vials

13.2 Storage

Store vials refrigerated at 2°C to 8°C in the original carton to protect from light.

Do not freeze. Do not shake.

14 SHELF LIFE

The expiry date of the product is indicated on the packaging materials.

15 MANUFACTURER

Macrogenics Inc.

9704 medical center drive, Rockville, MD 20850, USA.

16 REGISTRATION HOLDER

Neopharm Ltd.,

Hashiloach 6, P.O.B 7063, Petach Tikva 4917001, Israel.

17 REGISTRATION NUMBER

172-18-37089-00

Revised in March 2025.