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ADISINSIGHT REPORT

Margetuximab: First Approval

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Abstract
The second-generation anti-human epidermal growth factor receptor2 protein (HER2) monoclonal antibody margetuximab (MARGENZA™, margetuximab-cmkb) is being developed for the treatment of HER2-positive breast cancer, gastric cancer and gastro-oesophageal junction cancer. The antibody has been engineered for increased binding to activating Fcγ receptor IIIA (CD16A) and decreased binding to inhibitory Fcγ receptor IIB (CD32B) relative to trastuzumab with the aim of improving response rates. Based on the results of the phase III SOPHIA trial margetuximab has been approved in the USA for use in combination with chemotherapy as treatment of previously-treated metastatic HER2-positive breast cancer. This article summarizes the milestones in the development of margetuximab leading to this first approval.

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Margetuximab (MARGENZA™): Key points

A monoclonal antibody HER2 inhibitor is being developed by MacroGenics Inc. and International partners for the treatment of HER2-positive breast cancer, gastric cancer and gastro-oesophageal junction cancer.

Received its first approval on 16 December 2020 in the USA

Approved for use 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

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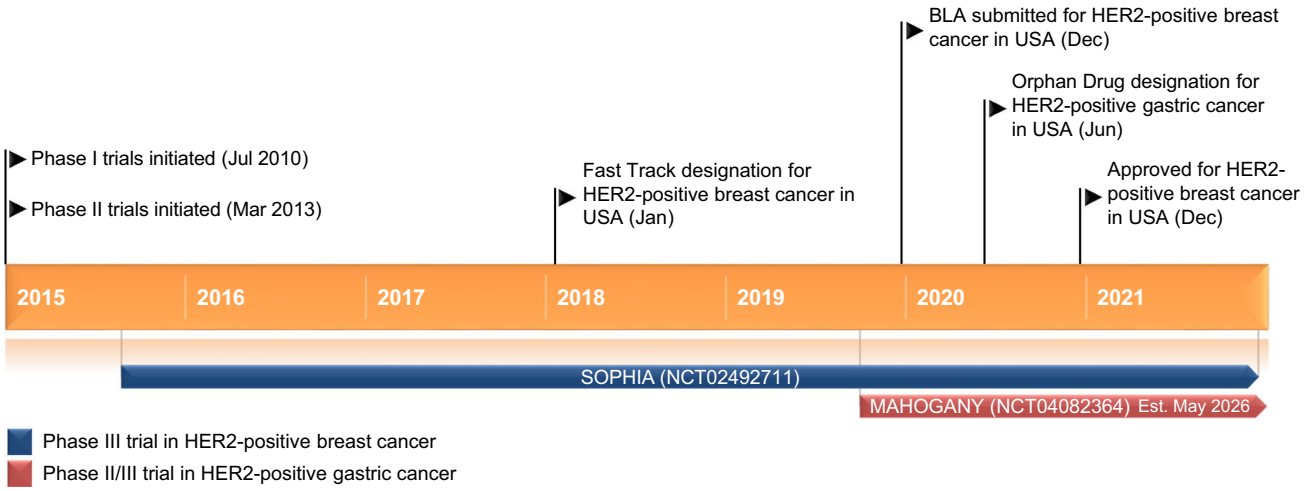
1 Introduction

Margetuximab (MARGENZA™, margetuximab-cmkb) is a second-generation anti-human epidermal growth factor receptor2 protein (HER2) monoclonal antibody being developed by MacroGenics, Inc. and International partners (see company agreements, below) for the treatment of HER2-positive breast cancer, gastric cancer and gastro-oesophageal junction cancer. Monoclonal antibodies targeting HER2-postive tumour cells have demonstrated multiple mechanisms of action including mediating cytolysis of tumour cells via antibody-dependent cell-mediated cytotoxicity (ADCC) and presentation of antigenic determinants of opsonized cells to antigen-presenting cells. The latter mechanism is dependent on the interaction between the Fc domain of the monoclonal antibody and leukocyte Fcγ receptors, with Fcγ receptor polymorphism having been shown to influence clinical response to several monoclonal antibody therapies including trastuzumab [1]. On this basis margetuximab has been engineered for increased binding to activating Fcγ receptor IIIA (CD16A) and decreased binding to inhibitory Fcγ receptor IIB (CD32B) relative to trastuzumab, with the aim of improving activation of innate and adaptive anti-HER2 immune responses [1, 2].

Margetuximab was approved in the USA on 16 December 2020 for use in combination with chemotherapy as treatment for 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 [3,



Key milestones in the development of margetuximab. *BLA* Biologics License Application, *HER2* human epidermal growth factor receptor 2

4]. The recommended dose is 15 mg/kg IV infused over 120 min for the initial dose, then over ≥ 30 min, once every three weeks [4]. As with other HER2 inhibitors, margetuximab has been associated with left ventricular dysfunction and should be withheld or permanently discontinued in patients who experience clinically relevant decreases in left ventricular ejection fraction during treatment. As seen with other anti-HER2 monoclonal antibody therapies, the potential for embryo-fetal harm exists with margetuximab. Based on findings in animals margetuximab can cause embryo-foetal harm. Thus the pregnancy status of female patients must be established prior to initiation of treatment and female patients advised to use effective contraception during and 4 months after treatment.

1.1 Company Agreements

In June 2010 MacroGenics entered into a collaboration agreement with GC Pharma (formerly Green Cross) for the development and commercialization of margetuximab in South Korea.

In October 2015 MacroGenics and Merck entered into a collaboration to conduct a clinical trial to evaluate the combination of margetuximab and pembrolizumab in patients with HER2-positive gastric cancer [5].

In November 2018 MacroGenics entered into an exclusive collaboration and license agreement with Shanghai, China-based Zai Lab to develop and commercialize margetuximab in China, Hong Kong, Macau and Taiwan. Zai Lab will lead clinical development in the licensed territories with both companies intending to initiate a global study using combination regimens containing margetuximab for the treatment of gastric cancer [6].

In November 2020 MacroGenics partnered with commercial services provider EVERSANA to commercialize margetuximab in the USA. Under the terms of the agreement MacroGenics retains ownership of margetuximab, including all manufacturing, regulatory and development responsibilities, with EVERSANA receiving a co-exclusive right to conduct approved commercialization activities [7].

2 Scientific Summary

2.1 Pharmacodynamics

In an antigen-capture enzyme-linked immunosorbent assay margetuximab had an effective concentration for 50% (EC_{50}) HER2 binding of 28.76 ng/mL compared to 27.28 ng/mL for trastuzumab. The two compounds had similar antiproliferative activity against SKBR-3 cells and no activity against JIMT-1 cells indicating the changes to the Fc domain do not affect antigen recognition and antiproliferative activity in the absence of effector cells [1].

The Fc domain of margetuximab had equilibrium dissociation constants (K_Ds) of 89 and 161 nmol/L for the 158V and 158F alleles of human CD16A, respectively, compared to K_Ds of 415 and 1059 nmol/L, respectively, for RES120, a version of the same monoclonal antibody containing the wild-type Fc domain. Conversely the Fc domain of margetuximab had lower affinity for human CD32B compared to RES120 (437 vs. 52 nmol/L) [1].

Margetuximab enhanced ADCC activity of effector cells expressing the CD16A-158F variant isolated from human donors relative to RES120 and had EC_{50} values lower than RES120 against cancer cells expressing HER2 with effector cells from CD16A F/F or V/F donors [1].

In vivo margetuximab had superior anti-tumour efficacy to RES120 in JIMT-1 xenograft-bearing $CD16^{-/-}$ human CD16A-positive mice [1].

2.2 Pharmacokinetics

Margetuximab had geometric mean C_{max} and AUC 0 to day 21 ($AUC_{0\text{-}21d}$) values of 466 μg/mL and 4120 μg • day/mL, respectively, in patients with HER2-positive relapsed or refractory advanced breast cancer treated with the approved recommended dose. The time to reach steady-state was two months with an accumulation ratio of 1.65 (based on $AUC_{0\text{-}21d}$). The geometric mean steady-state volume of distribution is 5.47 L, geometric mean $t_{½}$ is 19.2 days and clearance is 0.22 L/day. Serum concentrations of margetuximab decrease to ≈3% of the steady-state trough levels 4 months after discontinuation of treatment [4].

No clinically significant differences in the pharmacokinetic properties of margetuximab were observed according to age, gender, ethnicity, mild to moderate renal impairment, mild hepatic impairment, HER2 expression level, tumour burden, ECOG score, albumin levels, FCGR3A (CD16A), FCGR2A (CD32A) and FCGR2B (CD32B) genotype, number of metastatic sites, number of prior therapy lines or concurrent chemotherapies [4].

The pharmacokinetic properties of margetuximab have been evaluated in a phase I dose escalation and expansion study (NCT01148849) in patients with relapsed HER2-overexpressing cancers ($n = 66$). A two-compartment model with parallel linear and Michaelis–Menten elimination best described the pharmacokinetic profile of margetuximab in this trial [8].

2.3 Therapeutic Trials

2.3.1 HER2-Positive Metastatic Breast Cancer

Margetuximab plus single agent chemotherapy improved progression free survival compared to trastuzumab plus single agent chemotherapy in patients with previously treated HER2-positive metastatic breast cancer in the phase III SOPHIA trial (NCT02492711). Patients with HER2-positive metastatic breast cancer previously treated with other anti-HER2 regimens (2 or more prior anti-HER2 therapies and 1 to 3 lines of nonhormonal therapy for metastatic disease) were randomized to treatment with margetuximab plus chemotherapy ($n = 266$) or trastuzumab (8 mg/kg IV loading dose then 6 mg/kg once every 3 weeks) plus chemotherapy ($n = 270$). Median progression free survival was 5.8 months in the margetuximab group compared to 4.9 months in trastuzumab recipients, corresponding to a relative risk reduction of 24% with margetuximab (HR 0.76; 95% CI 0.59–0.98; $p = 0.03$). Interim median overall survival was 21.6 months in the margetuximab group compared with 19.8 months in the trastuzumab group ($p = 0.33$). Objective response rate was 22 and 16%, respectively ($p = 0.06$) and clinical benefit rate was 37 and 25%, respectively ($p = 0.003$) [2].

Features and properties of margetuximab

Alternative names	MARGENZA™, Margetuximab-cmkb, MGAH22
Class	Antineoplastics, immunotherapies, monoclonal antibodies
Mechanism of Action	HER2 inhibitor
Route of Administration	IV
Pharmacodynamics	EC_{50} of 28.76 ng/mL for HER2 binding
Pharmacokinetics	C_{max} 466 μg/mL, AUC between 0 and 21 days ($AUC_{0\text{-}21d}$) 4120 μg • day/mL in patients with HER2-positive advanced breast cancer treated with the approved recommended dose. Time to reach steady-state 2 months (accumulation ratio of 1.65), steady-state volume of distribution 5.47 L, $t_{½}$ 19.2 days, clearance 0.22 L/day
Adverse events	
Most frequent	Fatigue/asthenia, nausea, diarrhoea, vomiting, pyrexia, constipation, headache, alopecia, abdominal pain, peripheral neuropathy, cough, decreased appetite, arthralgia/myalgia, palmar-plantar erythrodysesthesia, dyspnoea, infusion-related reaction, pain in extremity
Occasional	Left ventricular dysfunction, dizziness, stomatitis, decreased weight, dysgeusia, rash, insomnia, hypertension syncope, febrile neutropenia, viral pneumonia, aspiration pneumonia
ATC codes	
WHO ATC code	L01X-C
EphMRA ATC code	L1G
Chemical Name	Immunoglobulin G1, anti-(human neu (receptor)) (human-Mus musculus monoclonal MGAH22 clone ch4D5 heavy chain), disulfide with human-Mus musculus monoclonal MGAH22 clone ch4D5 light chain, dimer

2.3.2 HER2-Positive Gastro-Oesophageal Adenocarcinoma

Combination treatment with margetuximab and pembrolizumab had synergistic antitumor activity in a phase Ib/II dose escalation trial (NCT02689284) in patients with locally advanced unresectable or metastatic HER2-positive gastric or gastro-oesophageal junction cancer who had progressed after at least one previous line of therapy with trastuzumab plus chemotherapy. In the dose-escalation phase of the study patients were treated with margetuximab 10 mg/kg IV plus pembrolizumab 200 mg IV every three weeks ($n = 3$) or margetuximab 15 mg/kg plus pembrolizumab 200 mg IV every three weeks ($n = 6$); the phase II expansion enrolled an additional 86 patients who received the latter regimen. Excluding patients treated at the lower margetuximab dose, 17 of 92 patients (18.5%) had an objective response and 49 (53%) had disease control. Median progression free survival and median overall survival were 2.7 and 12.5 months, respectively. No relationship between CD16A-158 genotype and response or stable disease was observed [9].

2.4 Adverse Events

In the phase III SOPHIA trial, margetuximab plus chemotherapy had an acceptable tolerability profile that was generally similar to that of trastuzumab plus chemotherapy [2]. Adverse reactions occurring in >10% of patients treated with margetuximab plus chemotherapy in the phase III SOPHIA trial described above included fatigue/asthenia (57% all grades and 7% grade three or four), pyrexia (19 and 0.4%), nausea (33 and 1.1%) diarrhoea (25 and 2.3%), vomiting (21 and 0.8%), constipation (19 and 0.8%), abdominal pain (17 and 1.5%), alopecia (18 and 0%), palmar-plantar erythrodysesthesia (13 and 0%), headache (19 and 0%), peripheral neuropathy (16 and 1.1%), cough (14 and 0.4%), dyspnoea (13 and 1.1%), decreased appetite (14 and 0.4%) arthralgia/myalgia (14 and 0.4%), extremity pain (11 and 0.8%) and infusion-related reactions (13 and 1.5%) [4]. Adverse events considered clinically relevant that occurred in ≤10% of patients included dizziness (10%), stomatitis (10%), decreased weight (6%), dysgeusia (6%), rash (6%), insomnia

Key clinical trials of margetuximab

Drug(s)	Indication	Phase	Status	Sponsor	Location(s)	Identifier
Margetuximab, trastuzumab, capecitabine, eribulin, gemcitabine, vinorelbine	Metastatic HER-2 positive breast cancer	III	Ongoing	MacroGenics	Multinational	NCT02492711, SOPHIA
Margetuximab, trastuzumab, paclitaxel, pertuzumab	HER2-positive breast cancer	II	Ongoing	Dana Farber Cancer Institute	USA	NCT04425018, MARGOT
Margetuximab, trastuzumab, capecitabine, vinorelbine, gemcitabine	HER2 metastatic breast cancer	II	Ongoing	Zai Lab	Taiwan	NCT04262804
Margetuximab	Pharmacokinetics in HER2 -positive metastatic breast cancer	I	Ongoing	Zai Lab	China	NCT04398108
Margetuximab	Relapsed or refractory advanced breast cancer; tumours express HER2 at the 2+ Level by immunohistochemistry and lack evidence of HER2 gene amplification by FISH	II	Completed	MacroGenics	USA	NCT01828021
Margetuximab	HER2-positive breast cancer, HER2-positive carcinoma expanded access	N/A	N/A	MacroGenics	N/A	NCT03133988
Margetuximab, retifanlimab, tebotelimab, trastuzumab, chemotherapy	HER2-positive gastric cancer	II/III	Ongoing	MacroGenics, Zai Lab	Multinational	NCT04082364, MAHOG-ANY
Margetuximab, pembrolizumab	Advanced metastatic HER2-positive gastric or gastroesophageal junction cancer	Ib/II	Ongoing	MacroGenics, Merck Sharp & Dohme	Multinational	NCT02689284
Margetuximab	HER2-positive breast cancer and other HER2-positive carcinomas	I	Ongoing	MacroGenics, Green Cross Corporation	USA, South Korea	NCT01148849
Margetuximab, MGD013	Unresectable or metastatic neoplasms	I	Ongoing	MacroGenics, Zai Lab	Multinational	NCT03219268

(6%), hypertension (5%) and syncope (1.5%). Left ventricular dysfunction occurred in 1.9% of patients [4].

Serious adverse reactions occurred in 16% of patients treated with margetuximab in SOPHIA; those occurring in >1% of patients included febrile neutropenia (1.5%), neutropenia/decreased neutrophil count (1.5%) and infusion related reactions (1.1%). Fatal adverse reactions occurred in 1.1% of patients and included viral pneumonia (0.8%) and aspiration pneumonia (0.4%). Adverse reactions led to permanent discontinuation of margetuximab in 3% of patients in SOPHIA and included left ventricular dysfunction and infusion related reactions, which occurred in >1% of patients. Eleven percent of patients required dosage interruptions because of adverse reactions, mostly infusion related reactions, which occurred in > 5% of patients [4].

Select laboratory abnormalities (≥ 20%) that worsened from baseline in patients treated with margetuximab plus chemotherapy in SOPHIA included decreased haemoglobin levels (52% all grades and 3.2% grade three or four), decreased leukocytes (40 and 5%) decreased neutrophils (34 and 9%), increased activated partial thromboplastin time (32 and 3.4%), decreased lymphocytes (31 and 4.4%), increased prothrombin international normalized ratio (24 and 1.2%), increased creatinine levels (68 and 0.4%), increased ALT levels (32 and 2%), increased lipase levels (30 and 6%), increased AST levels (23 and 2%) and increased alkaline phosphatase levels (21 and 0%) [4].

In SOPHIA, samples were taken from patients receiving margetuximab for immunogenicity testing at baseline, then once every two cycles and at end of therapy. Treatment-emergent anti-margetuximab antibodies emerged in four patients (1.7%); prior to cycle seven of margetuximab treatment in one, and more than two months after the last margetuximab dose in three. In an infusion sub-study, treatment-emergent anti-margetuximab antibodies were detected in two patients (3.8%); prior to cycle three of treatment in one, and more than six months after the last margetuximab dose in the other [4].

2.5 Ongoing Clinical Trials

The phase III SOPHIA trial and the phase Ib/II trial in patients with metastatic HER2-positive gastro-oesophageal adenocarcinoma (NCT02689284) described above are ongoing. The phase II MARGOT trial (NCT04425018) is comparing combination treatment with paclitaxel, margetuximab and pertuzumab to paclitaxel, trastuzumab and pertuzumab for 12 weeks prior to surgery in patients with anatomic stage II-III HER2 positive breast cancer and who are CD16A F carriers. A further phase II study (NCT04262804) is evaluating the efficacy and safety of margetuximab plus chemotherapy in Chinese patients with HER2 positive metastatic breast cancer. Also ongoing is a phase I study (NCT01148849) evaluating margetuximab in patients with refractory HER2-positive breast cancer and in patients with other carcinomas that overexpress HER2. The phase II/III MAHOGANY trial (NCT04082364) is evaluating the efficacy and tolerability of margetuximab plus retifanlimab with or without chemotherapy and margetuximab plus tebotelimab with chemotherapy as treatment for first-line unresectable metastatic/locally advanced gastroesophageal junction adenocarcinoma [10].

3 Current Status

Margetuximab received its first approval on 16 December 2020 in the USA for use in combination with chemotherapy as treatment for metastatic HER2-positive breast cancer in adult patients who have received two or more prior anti-HER2 regimens, at least one of which was for metastatic disease [3].

Declarations

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Ethics approval, Consent to participate, Consent to publish, Availability of data and material, Code availability Not applicable.

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