A Phase 3, Randomized Study of Margetuximab Plus Chemotherapy vs Trastuzumab Plus Chemotherapy in the Treatment of Patients with HER2+ Metastatic Breast Cancer Who Have Received Prior Anti-HER2 Therapies and Require Systemic Treatment.

Published: 23-07-2015
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Primary Objective:The primary objective of this study is to evaluate the efficacy, as measured by progression-free survival (PFS) assessed by independent review and overall survival (OS), of margetuximab plus chemotherapy compared to trastuzumab…

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Breast neoplasms malignant and unspecified (incl nipple)
Study type	Interventional

Summary

ID

NL-OMON47874

Source
ToetsingOnline

Brief title
SOPHIA

Condition

- Breast neoplasms malignant and unspecified (incl nipple)

Synonym
Breast cancer

Research involving
Human

Sponsors and support

Primary sponsor: MacroGenics, Limited
Source(s) of monetary or material Support: Sponsor MacroGenics;Inc.

Intervention

Keyword: Breast Cancer, Margetuximab, Phase 3, Trastuzumab

Outcome measures

Primary outcome

Statistical Methods:

Sample Size Determination

There are 2 primary endpoints in this study. The first primary endpoint is centrally determined PFS and the second primary endpoint is OS. These two endpoints will be assessed in a hierarchical manner with PFS being assessed first. OS will only be assessed if a statistically significant difference is obtained in PFS.

It is estimated that the median PFS for patients treated with trastuzumab and chemotherapy is 4 months. To detect a 2 month improvement in median PFS from 4 months to 6 months (HR=0.67) in patients treated with margetuximab plus chemotherapy, a total of 257 PFS events are required to provide 90% power at a 2-sided alpha=0.05. The analysis of the primary PFS endpoint will occur when about 257 events have occurred and when all patients have enrolled and had at least one post-baseline assessment or in the absence of a post-baseline tumor assessment, have experienced clearly documented clinical disease progression, whichever occurs later.

The sample size is calculated to ensure 80% power for the analysis of OS. The median OS for patients treated with trastuzumab plus chemotherapy is estimated to be 12 months. This study is designed to detect an increase to a median OS of 16 months in patients treated with margetuximab plus chemotherapy (hazard ratio [HR]=0.75). To detect a 4-month improvement in OS from 12 months to 16 months, a total of 385 events are required to provide 80% power at a 2-sided alpha=0.05. It is anticipated that about 530 patients will be accrued to achieve this number of events. Patients will be enrolled over 18 months, and estimated to remain on study for an average of 18 months, for a total anticipated study duration of approximately 36 months.

Efficacy Analyses

Primary Efficacy Endpoints

The primary analysis for PFS will be conducted when about 257 PFS events have occurred. Analysis of OS will be conducted at the time of PFS analysis and subsequently when 50% of the OS events and a final OS analysis when about 385 survival events have occurred.

For both PFS and OS, Kaplan-Meier methods will be used to generate survival curves and estimate the median OS and PFS along with corresponding 95% CIs for each treatment group. A log-rank test stratified by protocol defined stratification factors will be used to compare both time-to-event endpoints between the two treatment groups. In addition, hazard ratios and 95% CIs will be assessed using Cox proportional hazards models with protocol defined

stratification factors as covariates.

Secondary outcome

Analysis of Secondary Endpoints:

The secondary endpoints of investigator-assessed PFS and ORR will be assessed using the Hochberg step-up procedure for multiplicity adjustment. P-values will be assessed in descending order. If the least significant p-value<0.05, then both hypotheses are rejected. Otherwise, this endpoint is retained and the second p-value is tested at p<0.025. If a p-value<0.025 (0.05/2) is obtained, this hypotheses is rejected. Otherwise, both hypotheses are retained.

Investigator-assessed PFS will be analyzed using the same methods as described above for the primary endpoint of PFS.

Response rate based on the RECIST 1.1 criteria will be compared between groups using a Mantel-Haenszel statistic stratified by protocol defined stratification factors. This analysis will be based on objective responses confirmed at least 28 days after initial response.

Study description

Background summary

Among women, invasive adenocarcinoma of the breast is the most common non-dermatological cancer and the second leading cause of death in the United States (US). While early detection and treatment have reduced the death rate associated with breast cancer, for women diagnosed with metastatic breast cancer (MBC) in the US the overall prognosis remains poor, with an estimated 40,300 deaths due to this disease in 2014. In the European Union (EU), mortality associated with breast cancer was estimated to affect 92,000 individuals in 2012. Metastatic breast cancer can be identified either as the initial presentation of the disease, or after recurrence following previous treatment for local disease. Prior to the era of targeted therapies, patients

with HER2+ tumors had more aggressive tumors that foretold a shorter survival. The introduction of trastuzumab into clinical practice in 1998 and subsequent therapeutic developments dramatically altered the natural history of HER2+ MBC. Direct targeting of the HER2 oncoprotein lengthened survival in patients with HER2+ MBC to the point that now patients with HER2+ disease have a much more favorable prognosis than prior to the introduction of trastuzumab.
In the US and elsewhere, several agents are approved for the treatment of HER2+ breast cancer. For patients who require systemic therapy as part of definitive surgical resection, either neo-adjuvant therapy with trastuzumab - and increasingly - pertuzumab, or adjuvant therapy with trastuzumab, both in combination with cytotoxic chemotherapy, is the treatment of choice. Treatment at the time of recurrence is determined in part by the length of the original treatment-free interval. Patients who recur late after adjuvant treatment are often treated with the same or similar anti-HER2 regimen (trastuzumab +/- pertuzumab) used in the neo-adjuvant or adjuvant setting. Patients who recur shortly after initial neoadjuvant/adjuvant therapy (within 6 months) will often proceed to a second-line regimen, preferentially ado-trastuzumab emtansine. The progression of therapies for de novo MBC is similar, with trastuzumab (+/- pertuzumab) used in combination with chemotherapy in first-line and ado-trastuzumab emtansine used in the second-line. Of note, ado-trastuzumab emtansine, an antibody-drug conjugate of trastuzumab and emtansine, is only approved for use in patients who have previously received trastuzumab, and the benefit of this agent as first-line therapy, either alone or in combination with pertuzumab, has not yet been demonstrated. Trastuzumab is also approved for use as a monotherapy in patients who have received previous chemotherapy, although its use is limited in this indication. After treatment with ado-trastuzumab emtansine, there are no data to support a specific therapeutic approach. Lapatinib, a small molecule tyrosine kinase inhibitor of both HER1 (EGFR) and HER2, has been approved in the US for use in combination with capecitabine in patients who have previously received an anthracycline, a taxane and trastuzumab and additionally in Europe in combination with trastuzumab. In theory this allows for lapatinib use immediately after ado-trastuzumab emtansine: however, in practice, lapatinib is more often used in a later line of therapy for patients with HER2+ tumors. Given the effectiveness of neoadjuvant, adjuvant, and first- and second-line therapies in HER+ disease, more patients are surviving and suitable for later-line therapy. However, recurrence of disease is common, and additional treatments are needed.

Study objective

Primary Objective:
The primary objective of this study is to evaluate the efficacy, as measured by progression-free survival (PFS) assessed by independent review and overall survival (OS), of margetuximab plus chemotherapy compared to trastuzumab plus chemotherapy in patients with advanced HER2+ breast cancer who have received prior treatment with trastuzumab, pertuzumab, and ado-trastuzumab emtansine in the neoadjuvant, adjuvant, or metastatic setting, and who have received at

least one, and no more than three, lines of therapy in the metastatic setting.

Secondary Objectives
Secondary objectives of this study are:
* To evaluate PFS, as assessed by study investigators, of margetuximab plus chemotherapy vs. trastuzumab plus chemotherapy in these patients.
* To evaluate by independent review the objective response rate (ORR) of margetuximab plus chemotherapy vs. trastuzumab plus chemotherapy in these patients.

Tertiary Objectives:
* To evaluate health-related quality of life (HRQoL), as assessed using the Network-Functional Assessment of Cancer Therapy-Breast Cancer Symptom Index (NFBSI) -16 and EQ-5D-5L, associated with margetuximab plus chemotherapy vs. trastuzumab plus chemotherapy in these patients.
* To characterize the safety profile of margetuximab plus chemotherapy vs. trastuzumab plus chemotherapy in these patients.
* To evaluate the clinical benefit rate (CBR) of margetuximab plus chemotherapy vs. trastuzumab plus chemotherapy in these patients.
* To evaluate the response duration of margetuximab plus chemotherapy vs. trastuzumab plus chemotherapy in these patients.
* To characterize the population pharmacokinetics (PPK) and exposure-response (E-R) relationships of margetuximab in these patients.
* To evaluate anti-drug antibodies (ADA) directed against margetuximab and its effects on pharmacokinetics (PK), efficacy, and safety in these patients.

Exploratory Objective(s)

* To evaluate the effect of allelic variation in CD16A on the efficacy of margetuximab in these patients.

Study design

This is a Phase 3, randomized, open-label, controlled study comparing margetuximab to trastuzumab, each in combination with chemotherapy, for the treatment of patients with advanced HER2+ breast cancer who have received prior treatment with trastuzumab, pertuzumab, and ado-trastuzumab ematansine in the neoadjuvant, adjuvant, or metastatic settings and have received at least one, and no more than two, lines of therapy in the metastatic setting. Patients must have progressed on or following the most recent therapy. Eligible patients will be assigned to chemotherapy of the investigator*s choice to be chosen from capecitabine, eribulin, gemcitabine, or vinorelbine. Upon meeting all entry criteria, patients enrolled in the study will be randomized 1:1 to receive either margetuximab or trastuzumab to be administered in combination with the chosen chemotherapy. Patients will be treated until disease progression, death, withdrawal of consent, or request by the treating physician to discontinue treatment. Following completion of (or discontinuation from) treatment,

patients will be followed for survival.

Intervention

Through an infusion, the patient will receive margetuximab plus chemotherapy or trastuzumab plus chemotherapy. The study doctor will choose which chemotherapy the patient will receive. He can choose between capecitabine, eribulin, gemcitabine, or vinorelbine.

Study burden and risks

Number of visits to the study doctor/hospital: minimum of 5 visits, this depends on number of cycles that patient will have. For example if the patient on average will have 7 cycles, then the number of visits will be 17.
Intravenous infusions: 21 x (if patient will have on average 7 cycles). Patient might experience local discomfort from needle during IV injection.
Physical examinations: will occur at screening, at day 1 of cycle 1 and odd cycles, and at day 1 of cycle 2 and even cycles, and at End of Treatment visit.
Check of vital signs (blood pressure, heart rate, breathing rate, and temperature) will be checked 2 to 4 times during IV administration and 1 hour after the infusion is done. Patient might not experience any burden or risk from these examinations.
Health Related Quality of Life questionnaires: 3 times, at cycle 1 and odd cycles, and at cycle 2 and even cycles.
Additional blood tests: if patient completed on average 7 cycles of treatment then the total number of times blood is taken would be taken 18 times if assigned to Margetuximab and 9 times if assigned to Trastuzumab, at screening visit, at day 1 of cycle 1 and odd cycles, and at day 1 of cycle 2 and even cycles, and at End of Treatment visit and Post-Treatment Follow-up visit. The amount of blood taken at each visit will generally be 16-21 mL, with the most being about 27 mL. After Cycle 7 (about 21 weeks), about 21 mL of blood will be taken in each cycle.Patient might experience discomfort from needle during blood draw.
Urine test : 3 x, at day 1 of cycle 1 and odd cycles, and at day 1 of cycle 2 and even cycles, and at End of Treatment visit.
Electrocardiogram : 4 x. At screening, at day 1 of cycle 1 and odd cycles, and at day 1 of cycle 2 and even cycles, and at End of Treatment. Patient might experience local discomfort from the sticky padges.
MUGA scan or echocardiogram: 3 x. At screening and at day 1 of cycle 1 and odd cycles, and at End of Treatment. Small amount of radiation.
CT or MRI scans to evaluate cancer tumors: 2 x. At screening and at day 1 of cycle 1 and odd cycles. If tumors appear smaller compared to previous scans, the CT/MRI scan will be repeated in at least 28 days (will be done more often than in standard of care). Small amount of radiation.
Patient might experience side effects.
If patient has skin lesions the study doctor may need to take pictures of these

lesions to see how they change during the course of the study. Patient will not experience extra burden or risk from this procedure.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

Inclusion Criteria;To be included in this study, patients must:
General
1. Be able to provide informed consent and documentation of informed consent prior to initiation of any study-related tests or procedures that are not part of standard-of-care for the patient*s disease. Patients must also be willing and able to comply with study procedures, including the acquisition of specified research specimens and completion of HRQoL assessments.
2. Be * 18 years old. Patients may be male or female.

3. Have histologically-proven, metastatic or locally-advanced, relapsed/refractory HER2+ (3+ by IHC or ISH-amplified as per American Society of Clinical Oncology [ASCO] and the College of American Pathologists [CAP] Guidelines) breast cancer based on the most recently available tumor biopsy collected from the patient. HER2 status must be documented from a reference laboratory that conforms to standards set for accreditation by CAP or an equivalent accreditation authority. Confirmatory IHC testing is not required for study entry. Tumors may be estrogen receptor (ER)/progesterone receptor (PR) positive or negative.
4. Have received prior treatment with pertuzumab, trastuzumab, and ado-trastuzumab emtansine in the neoadjuvant, adjuvant, or metastatic setting. Prior radiotherapy, hormonal therapies, and other anti-HER2 therapies are allowed.
5. Have received treatment with at least one, and no more than three, lines of therapy in the metastatic setting. Prior neo-adjuvant or adjuvant therapy that resulted in relapse within 6 months of the completion of therapy will be considered a line of treatment for metastatic disease. Eligible patients must have progressed on or following, the most recent line of therapy.
6. Resolution of all chemotherapy or radiation-related toxicities to * Grade 1 (with exception of * Grade 2 alopecia, stable sensory neuropathy, or stable electrolyte disturbances that are managed by supplementation).
7. Have Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 (Appendix 4).
8. Have life expectancy * 12 weeks.
9. Have measurable or evaluable disease as per RECIST 1.1 criteria and documented by CT and/or MRI.;Laboratory Features
10. Have acceptable laboratory parameters as follows:
a. Platelet count * 100 × 103/µL without having received a transfusion or growth factor support within 4 weeks prior to the initiation of study drug.
b. Hemoglobin * 9.0 g/dL without having received a transfusion within 4 weeks prior to the initiation of study drug.
c. Absolute neutrophil count * 1.5 × 103/µL in the absence of any growth factor support given within 4 weeks prior to the initiation of study drug.
d. Alanine aminotransferase (ALT)/ aspartate aminotransferase (AST) * 3.0 × the upper limit of normal (ULN), except patients with liver metastases, who may enroll with ALT/AST * 5.0 × ULN.
e. Total bilirubin * 1.5 × ULN, except patients with Gilbert*s syndrome, who may enroll if the conjugated bilirubin is within laboratory normal limits.
f. Creatinine < 1.5 mg/dL, or a calculated or measured creatinine clearance > 50 mL/min.;Reproductive Features
11. Female patients of childbearing potential (not surgically sterilized and between menarche and 1 year post menopause) must have a negative result from a serum pregnancy test performed within 7 days of randomization and on the day of first study treatment. All study subjects must agree to use highly effective contraceptive measures during the entire study period and 120 days after the last dose of study medication.
Further, female patients of childbearing potential must agree to use effective barrier contraceptive measures from the time of informed consent through 120 days after last dose of study drug. Two forms of contraception must be utilized. Effective methods of contraception include oral, transdermal, injectable, or implantable contraceptives; intrauterine device (IUD); female condom; diaphragm with spermacide; cervical cap; use of a

condom by the sexual partner; or a sterile sexual partner.
12. Male patients with partners of childbearing potential must use barrier contraception. In addition, male patients should also have their partners use another method of contraception from the time of informed consent through 120 days after last dose of study drug.

Exclusion criteria

Exclusion Criteria: ;Patients who meet any of the following criteria will be excluded from the study:
1. Patients with known, untreated brain metastasis. Patients with signs or symptoms of brain metastasis must have a CT or MRI performed within 4 weeks prior to randomization to specifically exclude the presence of radiographically-detectable brain metastases. Patients with known, treated metastases should have a baseline MRI within 4 weeks of study entry and are eligible provided all therapy for the metastases concluded at least 4 weeks prior to the initiation of study drug, or, if continued steroid therapy is indicated following therapy, they have been on a stable dose of steroids (* 10 mg of prednisone or equivalent) for at least 4 weeks with no symptoms.
2. History of uncontrolled seizures within 6 months of randomization.
3. History of prior allogeneic bone marrow, stem-cell, or solid organ transplantation.
4. Treatment with any local or systemic anti-neoplastic therapy or any investigational therapy within the 2 weeks prior to the initiation of study drug. Bisphosphonates and receptor activator of nuclear factor kappa B ligand (RANKL) inhibitors are allowed provided treatment starts prior to the start of study therapy.
5. Treatment with corticosteroids (i.e., > 10 mg prednisone per day or equivalent) or other immune suppressive drugs within the 2 weeks prior to the initiation of study drug. Steroids for topical use, inhalational use, nasal spray, or ophthalmic solution are allowed.
6. History of clinically significant cardiovascular disease including but not limited to:
a. Myocardial infarction or unstable angina within 6 months prior to the initiation of study drug.
b. Stroke or transient ischemic attack within 6 months prior to the initiation of study drug
c. Clinically significant cardiac arrhythmias.
d. Uncontrolled (persistent) hypertension defined as systolic blood pressure (SBP) >180 mmHg or diastolic blood pressure (DBP) >100 mmHg.
e. Congestive heart failure (New York Heart Association [NYHA] class II-IV).
f. Pericarditis or clinically significant pericardial effusion.
g. Myocarditis.
h. Left ventricle ejection fraction (LVEF) < 50% by echocardiogram or multi-gated acquisition (MUGA) scan.
7. Clinically-significant pulmonary compromise, including a requirement for supplemental oxygen use to maintain adequate oxygenation.
8. Evidence of active viral, bacterial, or systemic fungal infection requiring parenteral treatment within 7 days prior to the initiation of study drug.
9. Known positive testing for human immunodeficiency virus or acquired immune deficiency syndrome.
10. Active hepatitis B or hepatitis C infection or positive test for hepatitis B surface antigen,

hepatitis B core antigen, or hepatitis C polymerase chain reaction (PCR).
11. Second primary malignancy that has not been in remission for at least 2 years from the anticipated start of study treatment. Exceptions of treated malignancies that do not require a 2 year remission include: non-melanoma skin cancer; cervical carcinoma in situ; squamous intraepithelial lesion; localized prostate cancer (Gleason score < 6); resected melanoma in situ or ductal carcinoma in situ. Patients with second primary breast cancers within 2 years are eligible provided that both primary tumors were HER2+ (3+ by IHC or ISH amplified).
12. History of trauma or major surgery within 4 weeks prior to the initiation of study drug.
13. Any serious underlying medical or psychiatric condition that would impair the ability of the patient to receive or tolerate the planned treatment at the investigational site.
14. Known hypersensitivity to recombinant proteins, polysorbate 80, benzyl alcohol, or any excipient contained in the drug formulation for margetuximab, trastuzumab or other study treatments. Previous infusion reactions to trastuzumab or other monoclonal antibodies will not preclude enrollment provided no contraindication to trastuzumab therapy remains.
15. Any condition that would be a contraindication to receiving trastuzumab as described in the approved local label or a condition that would prevent treatment with the physician*s choice of chemotherapy.
16. Vaccination with any live virus vaccine within 4 weeks prior to the initiation of study drug. Inactivated annual influenza vaccination is allowed at any time.
17. Dementia or altered mental status that would preclude understanding and rendering of informed consent.
18. Active or history of alcohol or other substance abuse within 1 year prior to the initiation of study drug.
19. Pregnant or breast feeding.
20. Prior participation in a margetuximab clinical study.
21. Any investigative site personnel directly affiliated with this study.
22. Employees of MacroGenics, Inc.
23. Prisoners or other individuals who are involuntarily detained.
24. Any issue or condition that in the opinion of the investigator would contraindicate the patient*s participation in the study or confound the results of the study.

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)
Control:	Active

Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	24-08-2015
Enrollment:	11
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Herceptin®
Generic name:	Trastuzumab
Registration:	Yes - NL outside intended use
Product type:	Medicine
Brand name:	Margetuximab
Generic name:	Margetuximab

Ethics review

Approved WMO Date:	23-07-2015
Application type:	First submission
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	24-09-2015
Application type:	First submission
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	18-12-2015
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	14-03-2016
Application type:	Amendment

Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	26-04-2016
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	10-05-2016
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	21-06-2016
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	19-07-2016
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	21-07-2016
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	30-03-2017
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	05-04-2017
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	29-06-2017
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	04-07-2017
Application type:	Amendment

Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	12-07-2017
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	07-09-2017
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	11-10-2017
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	12-04-2018
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	30-04-2018
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	15-08-2018
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	29-08-2018
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	20-02-2019
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	05-03-2019
Application type:	Amendment

Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	25-03-2019
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	27-03-2019
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
EudraCT	EUCTR2015-000380-13-NL
CCMO	NL53565.028.15

Study results

Date completed:	25-04-2019
Actual enrolment:	8