Monalizumab and trastuzumab In Metastatic HER2-pOStive breAst cancer: MIMOSA-trial

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To determine the activity (as measured by objective response rate by RECIST1.1) of monalizumab and trastuzumab in patients with metastatic HER2-positive breast cancer.

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

Summary

ID

NL-OMON52889

Source
ToetsingOnline

Brief title
MIMOSA

Condition

- Breast neoplasms malignant and unspecified (incl nipple)

Synonym
Breast cancer, HER2 positive

Research involving
Human

Sponsors and support

Primary sponsor: Nederlands Kanker Instituut
Source(s) of monetary or material Support: Astra Zeneca,Farmaceutische industrie

Intervention

Keyword: Accessible lesion for study biopsies, HER2 positive, max 3 lines palliative treatment, Metastatic disease, Min 1

Outcome measures

Primary outcome

Primary Objective:

To determine the activity (as measured by objective response rate by RECIST1.1)

of monalizumab and trastuzumab in patients with metastatic HER2-positive breast

cancer.

Secondary outcome

Secondary Objectives:

• To evaluate activity (as measured by objective response rate by RECIST1.1) in

all included patients

• To evaluate progression-free survival according to RECIST1.1

• To evaluate overall survival

• To evaluate the safety of monalizumab and trastuzumab as the percentage of

patients with toxicity and immune-related adverse events

Study description

Background summary

The cornerstone of the treatment of HER2-positive breast cancer is targeting HER2 with trastuzumab. The mechanism of action of trastuzumab is partly based on the lysis of tumor cells via ADCC, a cell-mediated immune mechanism requiring NK cells. Monalizumab is an antibody targeting the inhibitory receptor NKG2A on NK cells and CD8 T cells and has demonstrated clinical activity when combined with cetuximab (anti-EGFR antibody) in head and neck cancer. We hypothesize that the combination of trastuzumab and monalizumab can

promote anti-tumor immunity by unleashing NK cells and CD8 T cells in HER2-positive breast cancer and thereby induce clinical responses.

Study objective

To determine the activity (as measured by objective response rate by RECIST1.1) of monalizumab and trastuzumab in patients with metastatic HER2-positive breast cancer.

Study design

To get an impression of the pre-existing immunity, levels of tumor-infiltrating lymphocytes will be determined at baseline. Clinical efficacy will be assessed independently of tumor infiltrating-lymphocyte levels.
An optimal Simon*s two-stage design will be used. The null hypothesis that the true response rate is 10% will be tested against a one-sided alternative. In the first stage, 11 patients will be accrued per cohort. If there are 1 or fewer responses in these 11 patients, the cohort will be stopped. Otherwise, 8 additional patients will be accrued for a total of 19 patients. The null hypothesis of a response rate of 10% will be rejected if 4 or more responses are observed in 19 patients. This design yields a type I error rate of 0.1 and power of 0.9 when the true response rate is 35%. Dependent on the interim analysis, a maximum of 19 patients will be included.

Intervention

Patients will be treated with monalizumab (750 mg) and trastuzumab (4 mg/kg) every two weeks until progressive disease or intolerable toxicity.

Study burden and risks

The most important risk associated with the use of monalizumab are infusion-related reactions, as described in the investigator*s brochure (version 10.1, dated on 09 Nov 2021). Activation of NK cells and subset T cells through blockade of inhibitory receptors may potentially lead to immune-related adverse events (AEs). Furthermore, trastuzumab might induce cardiac toxicity with a decrease in left ventricular ejection fraction. This will be carefully monitored throughout the trial. The potential of monalizumab (and trastuzumab) to induce durable responses through reactivation of T cells and NK cells can be of benefit for patients.

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

• Histologically confirmed HER2-positive (immunohistochemistry 2+ with SISH amplification or 3+ reagrdless of SISH amplification) breast cancer.
HER2-positivity must have been assessed on a baseline study biopsy of a metastatic lesion.
• Histological or cytological confirmed locally incurable or metastatic disease
• Accessible lesion for study biopsies.
• Administration of at least one line of palliative treatment with documented progression and a maximum of three lines of palliative chemotherapy in combination with HER2 targeting agents (TDM-1 is considered one line of palliative treatment). Trastuzumab in combination with endocrine treatment is not defined as one line of treatment.
• Documented progression during previous trastuzumab-based therapy
• Measurable disease according to RECIST1.1 (at least one target lesion)
• Left ventricular ejection fraction of 50% or higher
• WHO performance status of 0 or 1
• No signs of a visceral crisis

• Signed written informed consent
- Subjects with brain metastases are eligible if they have been treated, asymptomatic and there is no magnetic resonance imaging (MRI) evidence of progression for at least 4 weeks prior to study registration. There must also be no requirement for immunosuppressive doses of systemic corticosteroids (> 10 mg/day prednisone equivalents) for at least 2 weeks prior to study drug administration

Exclusion criteria

• uncontrolled intercurrent illness including, but not limited to, ongoing or active infection, symptomatic congestive heart failure, unstable angina pectoris
• known leptomeningeal disease localization
• history of having received other anticancer therapies within 2 weeks of start of the study drug
• history of immunodeficiency, autoimmune disease, conditions requiring immunosuppression (>10 mg daily prednisone equivalents) or chronic infections. Subjects with vitiligo, diabetes mellitus type I on a stable insulin regimen, psoriasis not requiring systemic treatment or resolved childhood asthma/atopy would be an exception to this rule. Subjects that require intermittent use of bronchodilators, inhaled steroids, or local steroid injections will not be excluded from the study. Subjects with hypothyroidism stable on hormone replacement, Sjøgren*s syndrome or conditions not expected to recur in the absence of an external trigger will not be excluded from the study. In addition, subjects with Graves* disease stable on hormone replacement will also not be excluded from the study. Adrenal replacement doses >10 mg daily prednisone equivalents are permitted in the absence of active autoimmune disease
• prior treatment with immune checkpoint blockade or other forms of immunotherapy, such as but not limited to: anti-PD-(L)1, anti-PD-L2, anti-CTLA-4, anti-GITR or CD137/OX40 agonists
• prior treatment with HER2-based vaccines
• live vaccine within two weeks prior to start of the study, at any time during the study or within 5 months following the last dose of monalizumab. Inactivated vaccines, such as the seasonal flu vaccination, are allowed
• history of clinically significant or uncontrolled cardiac disease, including congestive heart failure (New York Heart Association functional classification >=3), angina, myocardial infarction within 12 months prior to study treatment or ventricular arrhythmia.
• active other cancer
• positive test for hepatitis B surface virus surface antigen (HBsAg) or hepatitis C virus ribonucleic acid (HCV antibody) indicating acute or chronic infection.
• allogeneic stem cell or organ transplantation, HIV or active tuberculosis
• history of uncontrolled serious medical or psychiatric illness
• Presence of any psychological, familial, sociological or geographical

condition potentially hampering compliance with the study protocol and follow-up schedule
• current pregnancy or breastfeeding. Women of childbearing potential (WOCBP*) must use adequate contraceptive protection. WOCBP must have a negative serum or urine pregnancy test

Study design

Design

Study phase:	2
Study type:	Interventional
Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Diagnostic

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	23-03-2021
Enrollment:	19
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Monalizumab
Generic name:	IPH2201
Product type:	Medicine
Brand name:	Trastuzumab
Generic name:	Trastuzumab
Registration:	Yes - NL intended use

Ethics review

Approved WMO

Date:	04-06-2020
Application type:	First submission
Review commission:	METC NedMec
Approved WMO Date:	14-07-2020
Application type:	First submission
Review commission:	METC NedMec
Approved WMO Date:	11-11-2021
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	15-03-2022
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	09-06-2022
Application type:	Amendment
Review commission:	METC NedMec

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	EUCTR2020-000849-14-NL
ClinicalTrials.gov	NCT04307329

Register	ID
CCMO	NL73029.031.20