A Randomized, Double-blind, Placebo-controlled, Phase 3 Study of Pembrolizumab Plus Chemotherapy Versus Placebo Plus Chemotherapy for the Treatment of Chemotherapy-Candidate Hormone Receptor-Positive, Human Epidermal Growth Factor Receptor 2-Negative (HR+/HER2-) Metastatic Breast Cancer

Published: 13-04-2021
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This study has been transitioned to CTIS with ID 2023-506752-24-00 check the CTIS register for the current data. 1) Objective: To compare pembrolizumab plus chemotherapy to placebo plus chemotherapy with respect to PFS

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

Summary

ID

NL-OMON51870

Source
ToetsingOnline

Brief title
MK3475-B49

Condition

- Breast neoplasms malignant and unspecified (incl nipple)

Synonym
Breast cancer, Breast carcinoma

Research involving
Human

Sponsors and support

Primary sponsor: Merck Sharp & Dohme (MSD)
Source(s) of monetary or material Support: Merck Sharp & Dohme;soms samenwerkende studies

Intervention

Keyword: breast cancer, pembrolizumab, Phase 3

Outcome measures

Primary outcome

- To compare pembrolizumab plus chemotherapy to placebo plus chemotherapy with respect to PFS

- To compare pembrolizumab plus chemotherapy to placebo plus chemotherapy with respect to OS

Secondary outcome

- To compare pembrolizumab plus chemotherapy to placebo plus chemotherapy with respect to ORR

- To compare pembrolizumab plus chemotherapy to placebo plus chemotherapy with respect to DCR

- To evaluate DOR

- To evaluate the safety and tolerability of pembrolizumab plus chemotherapy.

Study description

Background summary

Breast cancer is the most frequently diagnosed malignancy and the leading cause of cancer deaths in women worldwide. Respectively HR+/HER2- breast cancer represents ~73% of all breast cancer cases. The 5-year OS rate for HR+/ HER2- breast cancer is stage-dependent and ranges between 98% to 75% for Stages I-III, respectively, whereas the 5-year OS rate in patients with distant metastasis is no more than 30%.Once endocrine therapy resistance occurs, as it does in all cases, sequential chemotherapy becomes the mainstay of current treatment for HR+/HER2- MBC, where PFS and OS remain poor.

Pembrolizumab is a potent humanized IgG4 monoclonal antibody (mAb) with high specificity of binding to the programmed cell death 1 (PD-1) receptor, thus inhibiting its interaction with ligand PD-L1 and ligand PD-L2. Based on preclinical in vitro data, pembrolizumab has high affinity and potent receptor blocking activity for PD-1. Pembrolizumab has an acceptable preclinical safety profile and is in clinical development as an intravenous (IV) immunotherapy for advanced malignancies. Keytruda® (pembrolizumab) is indicated for the treatment of patients across a number of indications.

The PD-1 receptor-ligand interaction is a major pathway hijacked by tumors to suppress immune control. The normal function of PD-1, expressed on the cell surface of activated T- cells under healthy conditions, is to down-modulate unwanted or excessive immune responses, including autoimmune reactions. As a consequence, the PD-1/PD-L1 pathway is an attractive target for therapeutic intervention of HR+/HER2- MBC.

Study objective

This study has been transitioned to CTIS with ID 2023-506752-24-00 check the CTIS register for the current data.

1) Objective: To compare pembrolizumab plus chemotherapy to placebo plus chemotherapy with respect to PFS

Study design

This is a randomized, double-blind, placebo-controlled, Phase 3 Study of Pembrolizumab plus chemotherapy versus placebo plus chemotherapy for the treatment of chemotherapy-candidate Hormone Receptor-Positive, Human Epidermal Growth Factor Receptor 2-Negative (HR+/HER2-) Locally Recurrent Inoperable or Metastatic Breast Cancer.

Approximately 800 participants will be randomly assigned (with about 400 participants with CPS >=10) to two subgroups. After a screening phase of up to 28 days, each participant will be randomly assigned to receive study intervention until one of the conditions for discontinuation of study intervention is met.

Participants who complete study intervention after receiving 35 administrations of pembrolizumab, and participants who attain a complete response and stop study intervention may be eligible for the Second Course and receive up to 17 additional administrations of pembrolizumab (approximately 1 year) upon experiencing disease progression.

At the end of treatment, each participant will be followed for the occurrence of AEs and spontaneously reported pregnancy.

Participants who discontinue for reasons other than radiographic disease progression will have posttreatment follow-up imaging for disease status until any of the conditions for discontinuation of imaging are met.

All participants will be followed for overall survival until death, withdrawal of consent, or the end of the study.

Intervention

Twee intervention groups

Drug: Dose Strength: Dose
Frequency: Admin: Treatment period: Use:

Arm 1: Pembrolizumab 200 mg Day
1 IV Every 21 days
Experimental
Paclitaxel 90 mg/m2 Day 1, day
8, day 15 IV Every 28 days Background Treatment
Nab-Paclitaxel 100 mg/m2 Day 1, day 8,
day 15 IV Every 28 days Background Treatment
Liposomaal doxorubicine 50 mg/m2 Day
1 IV Every 28 days Background
Treatment
Capecitabine 1000 mg/m2 BID days
1-14 PO Every 21 days Background
Treatment

Arm 2: Normal saline or dextrose N/A
N/A IV Every 21
days Placebo
Paclitaxel 90 mg/m2 Day 1, day 8, day

15 IV Every 28 days Background Treatment
Nab-Paclitaxel 100 mg/m2 Day 1, day 8, day
15 IV Every 28 days Background Treatment
Liposomaal doxorubicine 50 mg/m2 Day
1 IV Every 28 days Background
Treatment
Capecitabine 1000 mg/m2 BID days
1-14 PO Every 21 days Background
Treatment

Abbreviations: Admin = administration; BID = twice daily; IV = intravenously; PO = orally.

Study burden and risks

For this study, patients will be subjected to invasive procedures such as blood collection, Biopsy, CT-MRI or bone scans, physical exams, possibly confrontational questionnaires, and patients will be asked to visit the hospital regularly. Patients will be administered with different kinds of medication (Pembro + Chemo OR Placebo + Chemo), during three-week cycles up to a maximum of 35 treatments.

It cannot be guaranteed that participants in clinical studies will directly benefit from study intervention during participation, as clinical studies are designed to provide information about the safety and effectiveness of an investigational medicine. Pembrolizumab has been administered in a large number of cancer participants with a well characterized safety profile and has received regulatory approval for multiple malignancies. Overall, pembrolizumab is well tolerated at doses up to 10 mg/kg every 2 weeks (Q2W). Pembrolizumab has also demonstrated anticancer clinical activity and efficacy in a broad range of cancer indications.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)

Inclusion criteria

The main inclusion criteria are listed here. For a complete list of inclusion please refer to the research protocol.
1. Has locally recurrent inoperable or metastatic HR+/HER2- breast cancer, which has not been previously treated with cytotoxic chemotherapy in the noncurative setting.
2. Has progressed on prior endocrine therapy and is now a chemotherapy candidate, meeting the characteristics in regard to previous treatments of one of the 4 groups.
3. Has presented a documented radiographic disease progression
4. Is a chemotherapy candidate that meets the criteria as described in the protocol.
5. Provides a new or the last obtained core biopsy.
6. Has centrally confirmed PD-L1 CPS >=1 and HR+ (ER and/or PgR) /HER2- breast cancer as defined by the most recent ASCO/CAP guidelines on most recent tumor biopsy.
7. Has an ECOG Performance Status of 0 or 1, as assessed within 7 days prior to the first dose of study treatment.
8. Demonstrates adequate organ function, within 10 days prior to the start of study treatment, as defined in the protocol.
9. Participants are at least 18 years of age on the day of signing informed consent
10. Male participants are eligible to participate if they agree to the criteria as defined in the protocol during the study intervention period and for at least 6 months after the last dose of chemotherapy.
11. A female participant is eligible to participate if she is not pregnant or breastfeeding, and at least 1 of the conditions defined in the protocol.

12. The participant (or legally acceptable representative if applicable) provides documented informed consent for the study.

Exclusion criteria

The main exclusion criteria are listed here. For a complete list of exclusion please refer to the research protocol.
1. Has breast cancer amenable to treatment with curative intent.
2. Has a history or current evidence of any condition, therapy, or laboratory abnormality as defined in the protocol.
3. Has significant cardiac disease as defined in the protocol
4. Has advanced/metastatic, symptomatic visceral spread at risk of rapidly evolving into life-threatening complications, see more information in the study protocol.
5. Has skin only disease. Participants who have metastatic disease fulfilling the previous criteria in addition to skin disease can be enrolled.
6. Has a known germline BRCA mutation and has not received previous treatment with PARP inhibition either in the adjuvant or metastatic setting. Single-agent PARP inhibitor therapy does not count as a line of endocrine therapy.
7. Has received prior chemotherapy for locally recurrent inoperable or metastatic breast cancer.
8. Has received prior therapy with an anti-PD-1, anti-PD-L1, or anti-PD-L2 agent or with an agent directed to another stimulatory or coinhibitory T-cell receptor (eg, CTLA-4, OX-40, CD137).
9. Has received prior systemic anticancer therapy with other investigational agents within 4 weeks prior to randomization.
10. Has received prior radiotherapy within 2 weeks of start of study intervention or radiation-related toxicities requiring corticosteroids.
11. Has received a live or live attenuated vaccine within 30 days prior to the first dose of study intervention.
12. Has received an investigational agent or has used an investigational device within 4 weeks prior to study intervention administration.
13. Has a diagnosis of immunodeficiency or is receiving chronic systemic steroid therapy or any other form of immunosuppressive therapy as defined in the protocol.
14. Has a known additional malignancy that is progressing or has required active treatment within the past 3 years.
15. Has known active CNS metastases as defined in the protocol.

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	04-02-2022
Enrollment:	24
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Abraxane
Generic name:	Nab-Paclitaxel
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Capecitabine, Xeloda
Generic name:	Capecitabine
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Keytruda
Generic name:	pembrolizumab
Registration:	Yes - NL outside intended use
Product type:	Medicine
Brand name:	Liposomal doxorubicin
Generic name:	Liposomal doxorubicin
Registration:	Yes - NL intended use
Product type:	Medicine

Brand name:	Paclitaxel, Paxene, Taxol, Pazenir
Generic name:	Paclitaxel
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	13-04-2021
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	07-06-2021
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	20-08-2021
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	20-09-2021
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	24-09-2021
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	16-10-2021
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO	

Date:	18-02-2022
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	01-04-2022
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	18-06-2022
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	27-06-2022
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	10-09-2022
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	12-09-2022
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	29-10-2022
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	02-11-2022
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek

	(Assen)
Approved WMO Date:	06-02-2023
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)

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
EU-CTR	CTIS2023-506752-24-00
EudraCT	EUCTR2020-005407-38-NL
CCMO	NL76778.056.21