A Randomized Open-Label Phase III Study of Single Agent Pembrolizumab versus Single Agent Chemotherapy per Physician*s Choice for Metastatic Triple Negative Breast Cancer (mTNBC) * (KEYNOTE-119)

Published: 01-09-2015
Last updated: 19-04-2024

The purpose of this study is to test the safety, tolerability and anti-tumor activity of the research study drug, Pembrolizumab (MK-3475) compared to other chemotherapy drugs of physician*s choice (which includes Capecitabine, Eribulin, Gemcitabine...

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

Summary

ID

NL-OMON46885

Source
ToetsingOnline

Brief title
MK3474-119

Condition

- Breast neoplasms malignant and unspecified (incl nipple)

Synonym
breast cancer

Research involving

Human

Sponsors and support

Primary sponsor: Merck Sharp & Dohme (MSD)
Source(s) of monetary or material Support: Industrie

Intervention

Keyword: Metastatic, Pembrolizumab, Triple negative breast cancer

Outcome measures

Primary outcome

Primary objectives:

(1) To compare overall survival (OS) in subjects with PD-L1 positive tumors.

(2) To compare OS in all subjects.

The study is considered to have met its primary objective if pembrolizumab is superior to TPC in OS in either subjects with PD-L1 positive tumors or in all subjects.

Secondary outcome

Secondary objectives:

(1) To compare progression-free survival (PFS) based on RECIST 1.1 as assessed by blinded central imaging vendor in all subjects.

(2) To compare overall response rate (ORR) per RECIST 1.1 by blinded central imaging vendor in all subjects.

(3) To evaluate PFS and ORR based on RECIST 1.1 as assessed by blinded central imaging vendor in subjects with PD-L1 positive tumors.

(4) To evaluate duration of response (DOR), and disease control rate (DCR)

based on RECIST 1.1 as assessed by blinded central imaging vendor in subjects

with PD-L1 positive tumors and in all subjects.

(5) To determine the safety and tolerability of pembrolizumab.

Study description

Background summary

Excluding basal cell and squamous cell skin cancers, breast cancer is the most commonly diagnosed malignancy in women, accounting for 29% of all new cancers. It is also the second leading cause of cancer death (after lung cancer) among women. About 232,670 new
cases of breast cancer and 40,000 deaths due to breast cancer are expected in women in the United States in 2014. Triple-negative breast cancer (TNBC) is phenotypically defined by a lack of estrogen receptor (ER) and progesterone receptor (PR) expression and the
absence of human epidermal growth factor receptor-2 (HER2) overexpression and/or amplification. TNBC represents 15-20% of all breast cancers and is overlapping, but not synonymous, with the basal-like subtype defined by gene expression, as about 70% of
TNBCs have basal-like characteristics

Subjects with TNBC whose disease has progressed on at least one systemic treatment for mTNBC have dismal prognosis with a PFS of 2-3 months and OS of 9-12 months. Nearly all have been previously treated with anthracyclines(s) and taxane(s), and will receive
single agent chemotherapy as a 2L+ regimen. As there is no established standard of care (SOC) for mTNBC, any drug approved for the treatment of metastatic breast cancer, such as capecitabine, eribulin, gemcitabine, or vinorelbine, may be used. To date, no mTNBC focused
clinical trial has evaluated the efficacy of any of the above mentioned agents.

Given (1) the poor outcome of subjects with advanced mTNBC, (2) the lack of TNBCspecific standard of care for the treatment of mTNBC, (3) the paucity of published results from Phase III clinical trials prospectively enrolling mTNBC subjects, and (4) the promising antitumor and safety profile of pembrolizumab in heavily pretreated mTNBC as demonstrated by the proof-of-concept KN 012 study, which showed an ORR of 18.5% and response durability, potential use of pembrolizumab as a 2-3L monotherapy for mTNBC will be further investigated in a large randomized open-label Phase 3 study (KN 119) comparing single agent pembrolizumab to TPC monotherapy.

Study objective

The purpose of this study is to test the safety, tolerability and anti-tumor activity of the research study drug, Pembrolizumab (MK-3475) compared to other chemotherapy drugs of physician*s choice (which includes Capecitabine, Eribulin, Gemcitabine, or Vinorelbine) in subjects with Metastatic Triple-Negative Breast Cancer (mTNBC).

Study design

This is a randomized, open-label, active-controlled, multicenter, international Phase III trial of single agent pembrolizumab versus single agent chemotherapy per physician*s choice (Treatment of Physician*s Choice, TPC) for subjects receiving second line (2L) or third line (3L) treatment for metastatic triple negative breast cancer (mTNBC).

Intervention

After the screening phase, eligible subjects will be stratified according to 2 stratification factors [PD-L1 tumor status (positive vs negative), and history of prior (neo)adjuvant therapy vs de novo metastatic disease at initial diagnosis]. Then subjects will be randomized 1:1 to receive single agent pembrolizumab 200 mg IV Q3W or single agent chemotherapy per physician*s choice (TPC): capecitabine, eribulin, gemcitabine, or vinorelbine. For the TPC arm, there is a maximum enrollment cap of 60% for each chemotherapy drug. The TPC dosing and frequency will be handled according to local regulations and guidelines in participating countries.

Study burden and risks

Subjects assigned to the first treatment group will receive pembrolizumab 200mg IV every 3 weeks (1 cycle). There is a maximum of 35 treatments of pembrolizumab with the option of an additional 17 treatments with pembrolizumab during the Second Course. Subjects assigned to the second treatment group will receive one of 4 treatments of physicians choice (Capecitabine, Eribulin, Gemcitabine, or Vinorelbine). . Each study therapy cycle is about 3 weeks.

The following procedures need to be performed that could be experienced as inconvenience and/or a risk: ECG, physical examination and vital signs, tumor imaging (CT or MRI), blood draws, bone scan, X-ray, completing questionnaires and a pregnancy test (if applicable).

Very common side effects of patients treated with pembrolizumab/KEYTRUDA include the following: itching of the skin, feeling tired, lack of energy, feeling not hungry,short of breath and cough. For capecitabine are these: diarrhea, nausea, vomiting, abdominal pain, hand-and-foot syndrome and fatigue

and weakness. For eribuline are these: fever, chills, cough and burning or pain when urinating. For gemcitabine and vinorelbine are some of the severe side effects that could occur in the: circulatory system, digestive system, respiratory system, kidneys, liver, neuropsychiatric, skin, injection site and other.

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

1.Have received either one or two prior systemic treatments for metastatic breast cancer and have documented disease progression on or after their most recent therapy. ;2.Have been previously treated with an anthracycline and/or taxane in the (neo)adjuvant or metastatic setting. ;3.Have centrally confirmed mTNBC (determined by a newly obtained core or excisional biopsy from a metastatic, not previously irradiated, tumor lesion). ;4.Have

measurable disease based on RECIST 1.1 as assessed by site investigator and local radiology review. ;5.Have provided a newly obtained core or excisional biopsy from a metastatic, not previously irradiated, tumor lesion for central determination of triple-negative breast cancer status and PD-L1 biomarker analysis. Adequacy of the biopsy specimen for the above analyses must be confirmed by the central laboratory. Repeat samples may be required if adequate tumor tissue is not provided. ;Note: Subjects for whom fresh tumor biopsies cannot be obtained (e.g. inaccessible tumor site or concern for subject safety) may submit an archived tumor specimen only upon agreement from the Sponsor.;6.Have an ECOG performance status of 0 or 1 assessed within 10 days prior to treatment initiation.

Exclusion criteria

1.Has participated or is currently participating in a study of an investigational agent/device and has received/is receiving the investigational agent/device within 4 weeks of randomization.;Note: A subject who has entered the follow-up phase of an investigational study may participate as long as 4 weeks have elapsed since the last dose of the investigational agent and/or removal of the device.;2.Has had monoclonal antibody (mAb) for direct anti-neoplastic treatment within 4 weeks of randomization;3.Has had chemotherapy, targeted small molecule therapy, or radiation therapy within at least 2 weeks of randomization ;4.Has not recovered from adverse events (i.e., downgraded to * Grade 1 or at baseline) due to a previously administered therapy.;Note: Subjects with * Grade 2 neuropathy or alopecia of any grade are an exception to this criterion and may qualify for the study.;Note: If subject received major surgery, they must have recovered adequately from the toxicity and/or complications from the surgery prior to randomization.;5.Has an active autoimmune disease that has required systemic treatment in the past 2 years (i.e. with use of disease modifying agents, corticosteroids or immunosuppressive drugs). ;Note: Replacement therapy (eg., thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency, etc.) is not considered a form of systemic treatment. ;6.Has a diagnosis of immunodeficiency or is receiving systemic steroid therapy or any other form of immunosuppressive therapy within 7 days of randomization.;7.Has a known additional malignancy that progressed or required active treatment within the last 5 years. Exceptions include basal cell carcinoma of the skin, squamous cell carcinoma of the skin that has undergone potentially curative therapy, and in situ cervical cancer.;8. Has known active brain metastases and/or carcinomatous meningitis.
Note: known brain metastases are considered active, if any of the following criteria is applicable: a. Brain imaging during screening demonstrates progression of existing metastases and/or appearance of new lesions compared to brain imaging performed at least 4 weeks earlier. b. Neurological symptoms attributed to brain metastases have not returned to baseline. c. Steroids were used for brain metastases within 28 days of randomization.
.;9.Has active/history of pneumonitis requiring treatment with steroids or active/history of interstitial lung disease.;10.Has an active infection requiring systemic therapy.;11.Has a history or current evidence of any condition, therapy, or laboratory abnormality that might confound the results of the trial, interfere with the subject*s participation for the full duration

of the trial, or is not in the best interest of the subject to participate, in the opinion of the treating investigator. ;12.Has known psychiatric or substance abuse disorders that would interfere with cooperation with the requirements of the trial.;13.Is pregnant or breastfeeding, or expecting to conceive or father children within the projected duration of the trial, starting with the screening visit through 120 days after the last dose of trial treatment.;14.Has received prior therapy with an anti-PD-1, anti-PD-L1, anti-PD-L2 agent or with an agent directed to another co-inhibitory T-cell receptor (e.g. CTLA-4, OX-40, CD137) or has previously participated in Merck MK-3475 clinical trials.;15.Has a known history of Human Immunodeficiency Virus (HIV) (HIV 1/2 antibodies).;16.Has a known active Hepatitis B (e.g., HBsAg reactive) or Hepatitis C (e.g., HCV RNA [qualitative] is detected).;Has received a live vaccine within 30 days of randomization

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):	23-03-2016
Enrollment:	30
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Halaven
Generic name:	Eribuline
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:	N/A
Generic name:	Vinorelbine
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Xeloda
Generic name:	Capecitabine
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	01-09-2015
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	19-11-2015
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	11-01-2016
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	12-01-2016
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO	

Date:	15-04-2016
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	06-06-2016
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	14-06-2016
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	05-12-2016
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	01-03-2017
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	27-03-2017
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	26-04-2017
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	29-06-2017
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek

	(Assen)
Approved WMO Date:	12-10-2017
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	18-10-2017
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	22-02-2018
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	19-03-2018
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	12-04-2018
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	02-05-2018
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	02-08-2018
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
EudraCT	EUCTR2015-001020-27-NL
CCMO	NL54416.056.15