A Randomized, Double-Blind, Phase III Study of Pembrolizumab (MK-3475) plus Chemotherapy vs Placebo plus Chemotherapy for Previously Untreated Locally Recurrent Inoperable or Metastatic Triple Negative Breast Cancer * (KEYNOTE-355)

Published: 13-09-2016
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The purpose of this study is to test the safety, tolerability and anti-tumor activity of the research study drug, Pembrolizumab (MK-3475) in combination with chemotherapy drugs of physician's choice (which includes Nab-paclitaxel, Paclitaxel or...

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

Summary

ID

NL-OMON47725

Source
ToetsingOnline

Brief title
MK3475-355

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: Breast Cancer, Pembrolizumab

Outcome measures

Primary outcome

Part 1 (Safety Run-In):

- To evaluate the safety and tolerability of 3 pembrolizumab + chemotherapy combinations, namely, pembrolizumab + paclitaxel, pembrolizumab + nab paclitaxel, and pembrolizumab + gemcitabine/carboplatin.

Part 2 (Phase III study):

- To compare progression-free survival (PFS) based on Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST 1.1) as assessed by a blinded central imaging vendor (CIV) in all subjects.
- To compare PFS based on RECIST 1.1 as assessed by a blinded CIV in subjects with programmed cell death ligand 1 (PD-L1) positive tumors.
- To compare overall survival (OS) in all subjects.
- To compare OS in subjects with PD-L1 positive tumors.

Secondary outcome

Part 2 (Phase III study):

- To compare objective response rate (ORR) based on RECIST 1.1 as assessed by

a blinded CIV in all subjects.

- To compare ORR based on RECIST 1.1 as assessed by a blinded CIV in subjects with PD-L1 positive tumors.

- To evaluate duration of response (DOR) based on RECIST 1.1 as assessed by a blinded CIV in all subjects and in subjects with PD L1 positive tumors.

- To compare disease control rate (DCR) based on RECIST 1.1 as assessed by a blinded CIV in all subjects and in subjects with PD-L1 positive tumors.

- To evaluate the safety and tolerability of 3 pembrolizumab + chemotherapy combinations.

- To evaluate changes in health-related quality-of-life (QoL) assessments from baseline in all subjects and in all subjects with PD-L1 positive tumors using the European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire Core 30 (EORTC QLQ-C30) and EORTC Breast Cancer-Specific Quality of Life Questionnaire (EORTC QLQ-BR23)

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 (US) in 2014. TNBC is phenotypically defined by a lack of estrogen receptor and progesterone receptor (EG/PGR) expression and the absence of human epidermal growth factor receptor-2 (HER2) overexpression and/or amplification. TNBC represents 15% to 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.
TNBC is a molecularly heterogeneous disease and includes tumor subsets with

different prognosis. Recent gene expression profiling has identified up to 6 distinct TNBC subtypes (2 basal-like, an immunomodulatory, a mesenchymal, a mesenchymal stem-like, and a luminal androgen receptor [AR] subtype).

TNBC is associated with younger age at diagnosis, premenopausal status, African American race, more advanced disease stage, higher grade, high mitotic indices, family history of breast cancer, breast cancer 1 (BRCA1) mutations, and more aggressive behavior than other breast cancer subtypes. As reported in a seminal study on TNBC, 34% of all subjects with TNBC experience distant recurrence with a median distant recurrence-free survival (DRFS) of 2.6 years, compared to a distant recurrence rate of 20% and a median DRFS of 5 years in other breast cancer subtypes; the peak of recurrence for TNBC is within 1 to 3 years after initial diagnosis, and decreases significantly thereafter; subjects with TNBC also have shorter median OS compared to subjects with non-TNBC (4.2 vs 6.0 years) [39]. Finally, subjects with TNBC tend to relapse with distant metastases rather than local recurrences and are more likely to develop visceral metastases, including central nervous system (CNS) involvement.

Treatment of TNBC is challenging and represents an area of unmet medical need, as these tumors lack therapeutic targets, such as ER and HER2, and become rapidly resistant to chemotherapy upon local recurrence and/or metastasis (even though they are often sensitive to cytotoxic drugs at initial presentation). The majority of subjects with metastatic TNBC (mTNBC) have experienced relapse after neoadjuvant or adjuvant therapy for early or locally advanced disease. In a frequently referenced study, the median OS of all (at any line of therapy) subjects with mTNBC was 13.3 months.

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) in combination with chemotherapy drugs of physician's choice (which includes Nab-paclitaxel, Paclitaxel or Gemcitabine/Carboplatin) in comparison with placebo in combination with chemotherapy drugs in subjects with previously untreated locally recurrent inoperable or Metastatic Triple Negative Breast Cancer (mTNBC).

Study design

KN355 is a randomized, double-blind, Phase III clinical study, as this is the gold standard for demonstrating superiority of a therapeutic regimen compared to another.

Intervention

Part 1:

Approximately 30 subjects will be partially-randomized (unblinded open-label) among 3 treatment arms: (1) pembrolizumab + nab-paclitaxel, (2) pembrolizumab + paclitaxel and (3) pembrolizumab + gemcitabine/carboplatin.
Part 2:
Approximately 828 subjects will be randomized (double-blind) in a 2:1 ratio between 2 treatment arms: (1) pembrolizumab + chemotherapy and (2) placebo + chemotherapy. Stratification factors are as follows:
1. Chemotherapy on study (taxane [i.e., paclitaxel or nab paclitaxel] vs gemcitabine/carboplatin).
2. Tumor PD-L1 status (positive vs negative).
3. Prior treatment with same class of chemotherapy in the (neo)adjuvant setting (yes vs no).

Study burden and risks

Treatment cycles will take three weeks, of which pembrolizumab will be administered on day 1. At every visit, a physical examination will be performed, vital signs will be measured and blood samples will be collected. The subjects will also be asked to complete questionnaires on their health and symptoms.
There will be a tumor biopsy at screening (this can be omitted in case there is adequate tumor tissue available).
Trial subjects may experience physical and/or psychological discomfort with some of the study procedures, such as blood sampling, administration of the IV line, CT/MRI/bone scans, and tumor biopsy.
The main side effects reported with the trial medication include fatigue, itching, rash, frequent or irregular bowel movements, pain in joints, muscles, or bones, stomach ache and nausea.

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 signed informed consent to study participation. The subject may also provide consent for Future Biomedical Research (FBR). However, the subject may participate in the main trial without participating in FBR.
2. Be at least 18 years of age on the day of signing informed consent.
3.Have locally recurrent inoperable breast cancer not previously treated with chemotherapy and which cannot be treated with curative intent.
OR
Have metastatic breast cancer not previously treated with chemotherapy.
Note: Subjects with a history of locally recurrent breast cancer, which was previously treated with curative intent, may be eligible.
4.Have centrally confirmed TNBC, as defined by the most recent ASCO/CAP guidelines.
Note: Subjects initially diagnosed with hormone receptor*positive and/or HER2 positive breast cancer must have central confirmation of TNBC in a tumor biopsy obtained from a local recurrence or distant metastasis site.
5.Have completed treatment for Stage I-III breast cancer, if indicated, and *6 months elapsed between the completion of treatment with curative intent (e.g., date of primary breast tumor surgery or date of last adjuvant chemotherapy administration, whichever occurred last) and first documented local or distant disease recurrence.
Note: Adjuvant radiation therapy is not considered treatment with curative intent for the purpose of calculating the *6 month interval requirement described above.
Note: First documentation of local or distant disease recurrence must be in the form of a dated biopsy, pathology, or imaging study report. A laboratory report indicating tumor marker elevation cannot be used as documentation of local or distant disease recurrence, unless accompanied by dated biopsy, pathology, or imaging study report.
Note: Subjects who received taxane, gemcitabine, or platinum agents in the (neo)adjuvant setting can be treated with same class of chemotherapy (taxane or gemcitabine/carboplatin), if *12 months have elapsed between the completion of treatment with curative intent (e.g., date of primary breast tumor surgery or date of last adjuvant chemotherapy administration,

whichever occurred last) and first documented local or distant disease recurrence.
6.Have been treated with (neo)adjuvant anthracycline, if they received systemic treatment in the (neo)adjuvant setting, unless anthracycline was contraindicated or not considered the best treatment option for the subject in the opinion of the treating physician.
Note: Subjects presenting with de novo metastatic TNBC are eligible for the study, if anthracycline is contraindicated or not considered the best treatment option for the subject in the opinion of the treating physician.
7.Have measurable disease based on RECIST 1.1 as determined by local radiology review.
Note: Target lesions situated in a previously irradiated area are considered measurable, only if they have shown unequivocal progression based on RECIST 1.1 after radiation therapy.
Note: Chest wall recurrence can be used as a target lesion, only if measurable by diagnostic quality imaging modality (digital photography alone is not adequate).
8.Have provided recently or newly obtained core or excisional biopsy from a locally recurrent inoperable or metastatic tumor lesion for central determination of TNBC status and PD-L1 expression, unless contraindicated due to site inaccessibility and/or subject safety concerns.
Note: Adequacy of biopsy specimen for the above analyses must be confirmed by the central laboratory. Submission of another tumor specimen may be required, if adequate tumor tissue was not provided the first time.
Note: An archival tumor specimen obtained before the diagnosis of locally recurrent inoperable or metastatic breast cancer may be submitted after consultation with the Sponsor, if neither a recently nor a newly obtained biopsy from a locally recurrent inoperable or a metastatic site is available.
9.Have an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1, as assessed within 10 days prior to the start of study treatment.
10.Have life expectancy *12 weeks from randomization.
11.Demonstrate adequate organ function, within 10 days prior to the start of study treatment. Refer to protocol for complete list.
12. Female subjects of childbearing potential must have a negative urine or serum pregnancy test within 72 hours prior to receiving the first dose of study treatment. If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required.
13. Female subjects of childbearing potential must be willing to use an adequate method of contraception as outlined in Section 5.7.2 * Contraception, for the course of the study through 120 days (or longer as specified by local institutional guidelines) after the last dose of study treatment.
Note: Abstinence is acceptable if this is the usual lifestyle and preferred contraception for the subject.
14. Male subjects of childbearing potential must agree to use an adequate method of contraception as outlined in Section 5.7.2 * Contraception, starting with the first dose of study therapy through 120 days (or longer as specified by local institutional guidelines) after the last dose of study therapy.
Note: Abstinence is acceptable if this is the usual lifestyle and preferred contraception for the subject.

Exclusion criteria

1.Is currently participating in a clinical study and receiving an investigational agent and/or using an investigational device, or has participated in a clinical study and received an investigational agent and/or used an investigational device within 4 weeks prior to randomization.
Note: Subjects who have entered the follow-up phase of a clinical study may participate as long as 4 weeks have elapsed since the last dose of the investigational agent and/or removal of the device.
Note: Subjects who were treated with radiation therapy may participate as long as at least 2 weeks have elapsed since the last dose of radiation therapy was administered.
2.Has not recovered (e.g., to *Grade 1 or to baseline) from AEs due to a previously administered therapy.
Note: Alopecia of any grade is an exception to this criterion.
Note: Prior to randomization, the subject must have recovered adequately from any toxicity and/or complications associated with any recent procedure.
3.Has neuropathy *Grade 2.
4.Has an active autoimmune disease that has required systemic treatment in the past 2 years (e.g., with use of disease modifying agents, corticosteroids, or immunosuppressive drugs). Replacement therapy (e.g., thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency) is not considered a form of systemic treatment.
5.Has a diagnosis of immunodeficiency or is receiving systemic steroid therapy or any other form of immunosuppressive therapy within 7 days prior to randomization.
6.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.
7.Has known active CNS metastases and/or carcinomatous meningitis. Subjects with known brain metastases may participate provided that the brain metastases have been previously treated (except with chemotherapy) and are radiographically stable. To demonstrate radiographic stability of previously treated brain metastases, a minimum of 2 post-treatment brain imaging assessments are required: 1) The first brain imaging must be acquired after treatment of brain metastases has been completed 2) The second brain imaging must be obtained during screening (i.e. within 28 days of randomization) and *4 weeks afters the previous post-treatment brain imaging.
Note: Known brain metastases are considered active, if any of the following criteria are 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. Radiographic stability of previously treated brain metastases is based on local radiology/investigator review, but dated reports of 2 imaging studies (the most recent performed during screening) documenting stability of brain metastasis(es) over *4 weeks must be submitted to the Sponsor. Such brain imaging studies should be available at the site for submission to CIV, if later needed.
b.Neurological symptoms attributed to brain metastases have not returned to baseline
c.Steroids were used for management of symptoms related to brain metastases within 28 days of randomization
8. Has history of (non-infectious) pneumonitis that required steroids or current pneumonitis.
9. Has active, or a history of, interstitial lung disease.

10. Has a known history of active TB (Bacillus Tuberculosis)
11. Has an active infection requiring systemic therapy.
12. Has a history of class II-IV congestive heart failure or myocardial infarction within 6 months of randomization.
13. Has a history or current evidence of any condition, therapy, or laboratory abnormality that might confound the results of the study, interfere with subject participation for the full duration of the study, or render study participation not compatible with the subject*s best interest, in the opinion of the treating Investigator.
14. Has a known psychiatric or substance abuse disorders that would interfere with cooperation with the requirements of the study.
15. Is pregnant or breastfeeding, or expecting to conceive or father children within the projected duration of the study, starting with the screening visit through 120 days (or longer as specified by local institutional guidelines) after the last dose of study treatment.
16.Has received prior therapy with an anti*PD-1, anti*PD-L1, or anti*PD-L2 agent or with an agent directed to another co-inhibitory T cell receptor (such as CTLA-4, OX 40, CD137) or has previously participated in Merck pembrolizumab (MK-3475) clinical studies. Refer to protocol for compete list.
17. Has a known history of human immunodeficiency virus (HIV) (HIV 1/2 antibodies).
18. Has known active hepatitis B (e.g., hepatitis B surface antigen [HBsAg] reactive) or hepatitis C (e.g., HCV RNA [qualitative] is detected).
19. Has received a live vaccine within 30 days prior to randomization.
20. Has a known history of hypersensitivity or allergy to pembrolizumab and any of its components and/or to any of the study chemotherapies (e.g., nab-paclitaxel, paclitaxel, gemcitabine, or carboplatin) and any of their components.
21. Is receiving any medication prohibited in combination with study chemotherapies as described in the respective product labels, unless medication was stopped within 7 days prior to randomization.

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:	Recruitment stopped
Start date (anticipated):	23-02-2017
Enrollment:	12
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Abraxane
Generic name:	Paclitaxel
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:	Carboplatin
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	N/A
Generic name:	Gemcitabine
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	N/A
Generic name:	Nab-paclitaxel
Registration:	Yes - NL intended use

Ethics review

Approved WMO

Date:	13-09-2016
Application type:	First submission

Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	21-11-2016
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	21-11-2016
Application type:	First submission
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	07-12-2016
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	12-12-2016
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	01-02-2017
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	07-02-2017
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	01-03-2017
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	14-03-2017
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	22-03-2017
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Approved WMO Date:	27-03-2017
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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:	01-09-2017
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	13-09-2017
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	20-09-2017
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	18-10-2017
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	09-11-2017
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:	26-04-2018
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	08-08-2018
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:	19-11-2018
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	05-12-2018
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	11-04-2019
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	08-05-2019
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	EUCTR2016-001432-35-NL
CCMO	NL58849.028.16