A Phase 3, Randomized, Placebo-Controlled Clinical Study to Evaluate the Safety and Efficacy of Stereotactic Body Radiotherapy (SBRT) with or without Pembrolizumab (MK-3475) in Participants with Unresected Stage I or II Non-Small Cell Lung Cancer (NSCLC) (KEYNOTE-867)

Published: 29-11-2021
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This study has been transitioned to CTIS with ID 2022-500413-11-00 check the CTIS register for the current data. The objective of the study is to compare event free surivial (EFS) and overall survival (OS) when administering pembrolizumab + SBRT vs...

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Other condition
Study type	Interventional

Summary

ID

NL-OMON52095

Source
ToetsingOnline

Brief title
MK3475-867

Condition

- Other condition
- Respiratory and mediastinal neoplasms malignant and unspecified

Synonym

Lung Cancer, Non-Small Cell Lung Cancer

Health condition

Niet-kleincellige longkanker

Research involving
Human

Sponsors and support

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

Intervention

Keyword: NSCLC, Pembrolizumab, Radiotherapy

Outcome measures

Primary outcome

Objective: To compare the Event-free Survival (EFS).

Endpoint: EFS: The time from randomization to an event defined as local,

regional, or distant recurrence of the treated NSCLC or death from any cause.

Objective: To compare Overall Survival (OS).

Endpoint: OS: The time from randomization to death from any cause.

Secondary outcome

Objective: To compare the time to death or distant metastases.

Endpoint: Time to death or distant metastases: The time from randomization to

the first documented distant metastases or death from any cause, whichever

occurs first.

Objective: To evaluate the safety and tolerability of SBRT + pembrolizumab.

Endpoint: Adverse events and Study intervention discontinuations due to AEs

Objective: To compare the change from baseline scores in global health status/quality of life (QoL), cough, chest pain, dyspnea, and physical functioning scale.

Endpoint: Change from baseline scores, calculated for the following scales/items at a pre-specified time point: global health status/QoL (EORTC QLQ-C30 Items 29 and 30), cough (EORTC QLQ-LC13 Item 1), chest pain (EORTC QLQ-LC13 Item 10), dyspnea (EORTC QLQ-C30 Item 8), and physical functioning (EORTC QLQ-C30 Items 1-5).

Study description

Background summary

Pembrolizumab is a potent humanized immunoglobulin G4 (IgG4) monoclonal antibody (mAb) with high specificity of binding to the programmed cell death 1 (PD-1) receptor, thus inhibiting its interaction with programmed cell death ligand 1 (PD-L1) and programmed cell death ligand 2 (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. For more details on specific indications, refer to the Investigator*s Brochure (IB).

Study objective

This study has been transitioned to CTIS with ID 2022-500413-11-00 check the CTIS register for the current data.

The objective of the study is to compare event free surivial (EFS) and overall survival (OS) when administering pembrolizumab + SBRT vs placebo +SBRT.

Study design

This is a multisite, placebo-controlled, randomized, double-blind study designed to compare the efficacy and safety of SBRT + pembrolizumab versus SBRT + placebo in participants with unresected Stage I or II NSCLC (AJCC 8th edition). Eligible patients must have histologically or cytologically confirmed Stage I or II NSCLC that has not been previously treated.

The study will be conducted in conformance with Good Clinical Practices (GCP). Approximately 530 participants will be randomized. After a screening phase of up to 42 days, each eligible participant will be randomized in a 1:1 ratio to receive SBRT + pembrolizumab 200 mg Q3W × 17 cycles or SBRT + placebo Q3W × 17 cycles. SBRT will be given as outlined in Table 3. The first SBRT administration will preferably start on Cycle 1 Day 1 (+7 days allowed up to Cycle 1 Day 8, inclusive) following pembrolizumab/placebo administration. All randomized patients will receive either pembrolizumab or placebo regardless if they complete SBRT. Randomization will be stratified by stage of disease (Stage I vs Stage IIA), Eastern Cooperative Oncology Group (ECOG) performance scale (0 or 1 vs 2), geographic region of enrollment site (East Asia vs non-East Asia), and reason for not receiving surgery (medically inoperable vs refused surgery).

Intervention

In this study the patient will undergo the experimental treatment of Pembrolizumab (IV infusion) (Q3W regimen) + SBRT or be part of the control group placebo (IV infusion) (Q3W regimen) + SBRT

Study burden and risks

It cannot be guaranteed that participants in clinical studies will directly benefit from treatment during participation, as clinical studies are designed to provide information about the safety and effectiveness of an investigational medicine. However, pembrolizumab and SBRT are independently effective in the treatment of NSCLC. Available evidence demonstrates that the 2 modalities can be administered in close proximity without increased toxicity [Theelen, W. S. M. E., et al 2019] [Campbell, A. M., et al 2018].

Additional details regarding specific benefits and risks for participants in this clinical study may be found in the accompanying IB and informed consent documents.

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. Has previously untreated NSCLC diagnosed by histology or cytology and confirmed as Stage I or II (T1 to limited T3, N0, M0) NSCLC (AJCC 8th edition) by chest CT and PET scan. Prospective participants with mediastinal lymph nodes measured on chest CT as >1 cm in the short axis or PET avid lymph nodes may be eligible if the lymph node(s) in question is biopsied and is histologically benign. Note: participants with pericardium invasion, >2 nodules or 2 nodules that cannot be treated in one field (>2 cm apart and/or total planned target volume [PTV] >163 cc) and diaphragm elevation suggestive of phrenic nerve invasion are excluded.

2. Cannot undergo thoracic surgery due to existing medical illness(es) or anatomically unresectable tumor as determined by the site*s multidisciplinary tumor board. Medically operable participants who decide to treat with SBRT as definitive therapy rather than surgery are also eligible, if patient*s unwillingness to undergo surgical resection is clearly documented. If there is no tumor board, then this decision will be made by the investigator in consultation with a thoracic surgeon and a radiation oncologist if the investigator is not a radiation oncologist.

3. Has an ECOG performance status of 0, 1, or 2.

4. Is able to receive SBRT and does not have an ultra-centrally located tumor as defined in
the radiation manual.

5. Has adequate organ function as defined in Table 2 of protocol. Specimens must be collected within 7 days prior to the start of study intervention.

6. Is male or female >=18 years of age, at the time of signing the informed consent.

Male Participants
7. Male participants are eligible to participate if they agree to the following during the intervention period and for at least 90 days after the last dose of radiotherapy:
• Refrain from donating sperm
PLUS either:
• Be abstinent from heterosexual intercourse as their preferred and usual lifestyle (abstinent on a long-term and persistent basis) and agree to remain abstinent
OR
• Must agree to use contraception, unless confirmed to be azoospermic (vasectomized or secondary to medical cause, documented from the site personnel*s review of the participant*s medical records, medical examination, or medical history interview) as detailed below:
- Agree to use a male condom plus partner use of an additional contraceptive method when having penile-vaginal intercourse with a WOCBP (see Section 10.5) who is not currently pregnant. Note: Male participants with a pregnant or breastfeeding partner must agree to remain abstinent from penile-vaginal intercourse or use a male condom during each episode of penile-vaginal penetration.
- Contraceptive use by men should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies. If the contraception requirements in the local label for any of the study interventions is more stringent than the requirements above, the local label requirements are to be followed.

Female participants:

8. A female participant is eligible to participate if she is not pregnant or breastfeeding, and at least one of the following conditions applies:
•is not a WOCBP
OR
- is a WOCBP and using a contraceptive method that is highly effective (with a failure rate of <1% per year), or be abstinent from heterosexual intercourse as their preferred and usual lifestyle (abstinent on a long-term and persistent

basis), as described in Appendix 5 from the Protocol during the intervention period and for at least 120 days after the last dose of pembrolizumab/placebo and 180 days after the last radiotherapy dose. The investigator should evaluate the potential for contraceptive method failure (ie, noncompliance, recently initiated) in relationship to the first dose of study intervention.
- A WOCBP must have a negative highly sensitive pregnancy test (urine or serum as required by local regulations) within 24 hours for urine or within 72 hours for serum before the first dose of study
intervention.
- If a urine test cannot be confirmed as negative (eg, an ambiguous result), a serum
pregnancy test is required. In such cases, the participant must be excluded from participation if the serum pregnancy result is positive.
- Additional requirements for pregnancy testing during and after study intervention are in the protocol.
-The investigator is responsible for review of medical history, menstrual history, and recent sexual activity to decrease the risk for inclusion of a woman with an early undetected pregnancy.
-Contraceptive use by women should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies.

9. The participant (or legally acceptable representative) has provided documented informed consent/assent for the study. The participant may also provide consent/assent for future biomedical research. However, the participant may participate in the study without participating in future biomedical research.

10. Has a radiation therapy plan approved by the central radiation therapy quality assurance vendor.

Exclusion criteria

The participant must be excluded from the study if the participant:

1. Is a WOCBP who has a positive highly sensitive pregnancy test within 24 hours for urine or 72 hours for serum prior to randomization or treatment allocation (see Appendix 5). If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required.
Note: If 24 hours for urine or 72 hours for serum have elapsed between the screening pregnancy test and the first dose of study intervention, another pregnancy test (urine or serum) must be performed and must be negative in order for participant to start receiving study medication.

2. 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).

3. Has received prior radiotherapy to the thorax, including radiotherapy to the esophagus,
mediastinum, or breast. Participants receiving radiotherapy to the contralateral breast at least 5 years prior to randomization may still be eligible.

4. Has received a live vaccine within 30 days prior to the first dose of study intervention. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, varicella/zoster (chicken pox), yellow fever, rabies, Bacillus Calmette-Guérin (BCG), and typhoid vaccine. Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed; however, intranasal influenza vaccines (eg, FluMist®) are live attenuated vaccines and are not allowed. Refer to Section 6.5 for information on COVID-19 vaccine.

5. Has received an investigational agent or has used an investigational device within 4 weeks prior to the first dose of study intervention administration.

6. Has a diagnosis of immunodeficiency or is receiving chronic systemic steroid therapy (in dosing exceeding 10 mg daily of prednisone equivalent) or any other form of immunosuppressive therapy within 7 days prior the first dose of study drug.

7. Has a known additional malignancy that is progressing or has required active treatment within the past 3 years. A prior NSCLC that occurred and was treated curatively at least 2 years prior to the date of the current diagnosis would be considered a separate primary lung cancer, and therefore an additional malignancy.
Note: Participants with basal cell carcinoma of the skin, squamous cell carcinoma of the skin, or carcinoma in situ (eg, breast carcinoma, cervical cancer in situ) that have undergone potentially curative therapy are not excluded.

8. Has a known hypersensitivity (>=Grade 3) to pembrolizumab and/or any of its excipients.

9. Has a history of (non-infectious) pneumonitis that required steroids or has current pneumonitis.

10. Has a known history of Hepatitis B (defined as Hepatitis B surface antigen [HBsAg] reactive) or known active Hepatitis C virus (defined as HCV RNA [qualitative] is detected) infection.
Note: No testing for Hepatitis B and Hepatitis C is required unless mandated by local health authority.

11. Has an active autoimmune disease that has required systemic treatment in past 2 years,except replacement therapy (eg, thyroxine, insulin, or physiologic corticosteroid).

12. Has an active infection requiring systemic therapy.

13. Has a known history of human immunodeficiency virus (HIV) infection. No HIV testing is required unless mandated by local health authority.

14. Has a known history of active tuberculosis (TB; Bacillus tuberculosis). No TB testing is required unless mandated by local health authority.

15. Has a history or current evidence of any condition, therapy, or laboratory abnormality that might confound the results of the study, interfere with the participant*s participation for the full duration of the study, or is not in the best interest of the participant to participate, in the opinion of the treating investigator.

16. Has a known psychiatric or substance abuse disorder that would interfere with the participant*s ability to cooperate with the requirements of the study.

17. Is pregnant or breastfeeding or expecting to conceive within the projected duration of the study, starting with the screening visit through 120 days after the last dose of pembrolizumab/placebo and 180 days after the last radiotherapy dose.

18. Has had an allogenic tissue/solid organ transplant.

19. Participants who have not adequately recovered from major surgery or have ongoing
surgical complications.

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):	23-08-2022
Enrollment:	6
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Keytruda
Generic name:	Pembrolizumab
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO

Date:	29-11-2021
Application type:	First submission
Review commission:	METC Brabant (Tilburg)

Approved WMO

Date:	17-01-2022
Application type:	First submission
Review commission:	METC Brabant (Tilburg)

Approved WMO

Date:	15-02-2022
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)

Approved WMO

Date:	07-03-2022
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)

Approved WMO

Date:	27-07-2022
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	08-08-2022
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
EU-CTR	CTIS2022-500413-11-00
EudraCT	EUCTR2018-004320-11-NL
Other	IND 116.833
CCMO	NL78926.028.21