A Phase 3, Randomized, Double-Blind Study of MK-7684A in Combination with Etoposide and Platinum Followed by MK-7684A vs Atezolizumab in Combination with Etoposide and Platinum Followed by Atezolizumab for the First-Line Treatment of Participants with Extensive-Stage Small Cell Lung Cancer

Published: 16-02-2022
Last updated: 14-09-2024

This study has been transitioned to CTIS with ID 2023-503517-30-00 check the CTIS register for the current data. Primary objectivesTo compare overall survival for MK-7684A in combination with the background therapy of etoposide/platinum followed by...

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Respiratory and mediastinal neoplasms malignant and unspecified
Study type	Interventional

Summary

ID

NL-OMON53681

Source
ToetsingOnline

Brief title
MK7684A-008

Condition

- Respiratory and mediastinal neoplasms malignant and unspecified

Synonym
ES-SCLC, small cell lung cancer

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: Double-Blind, First-Line Treatment, Phase 3, Small Cell Lung Cancer

Outcome measures

Primary outcome

1. Overall Survival (OS)

Secondary outcome

1. Progression-Free Survival (PFS)

2. Objective Response Rate (ORR)

3. Duration of Response (DOR)

4. Percentage of Participants Who Experienced an Adverse Event (AE)

5. Percentage of Participants Who Discontinued Study Treatment Due to an AE

6. Change from Baseline in the Global Health Status/Quality of Life (Items 29

and 30) Combined Score on the European Organization for

Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC

QLQ-C30)

7. Change from Baseline in Physical Functioning (Items 1-5) Combined Score on

the EORTC QLQ-C30

8.Change from Baseline in Dyspnea Score (Item 8) on the EORTC QLQC30

9. Change from Baseline in Cough Score (Item 31) on the European Organization

for Research and Treatment of Cancer Quality of Life

Questionnaire Lung Cancer 13 (EORTC QLQ-LC13)

10. Change from Baseline in Chest Pain Score (Item 40) on the EORTC QLQ-LC13

11. Time to True Deterioration (TTD) in the Global Health Status/Quality of

Life (Items 29 and 30) Combined Score on the EORTC QLQ-C30

12. TTD in Physical Functioning (Items 1-5) Combined Score on the EORTC QLQ-C30

13. TTD in Dyspnea Score (Item 8) on the EORTC QLQ-C30

14. TTD in Cough Score (Item 31) on the EORTC QLQ-LC13

15. TTD in Chest Pain Score (Item 40) on the EORTC QLQ-LC13

Study description

Background summary

SCLC is an aggressive neuroendocrine malignancy of the lung, which remains a worldwide public health problem as it is a major cause of cancer mortality. This malignancy accounts for approximately 13% to 17% of all lung cancer cases, with approximately 30,000 patients diagnosed annually in the US [American Cancer Society 2020] [National Cancer Institute 2014] [Zhao, H., et al 2018]. Worldwide, approximately 275,000 patients are diagnosed with SCLC annually [Majem, M. 2017]. This malignancy is strongly linked to tobacco use, with only 2% to 3% of cases occurring in never-smokers [Varghese, A. M., et al 2014] [Thomas,A., et al 2020].

SCLC is characterized by a short doubling time, high growth fraction, and early development of widespread metastases [Gazdar, A. F., et al 2017]. The overwhelming majority of patients with SCLC present with ES-SCLC, with advanced, bulky nodal disease or with tumors that have spread beyond a single tolerable radiation field in the chest. Therefore, SCLC is not considered a surgical disease and chemotherapy is the foundation of treatment [Gaspar, L.

E., et al 2012]. The fundamental approach of first-line treatment of SCLC had not changed in nearly 4 decades since the introduction of an etoposide/platinum doublet, which is administered to both patients with LS-SCLC (cancer confined to the chest in a single tolerable radiation field) and patients with ES-SCLC. Although first-line treatment for SCLC yields high tumor response rates, essentially all patients with ES-SCLC, and most with LSSCLC, develop chemoresistance and relapse within months of completing initial therapy. Once patients develop recurrent or progressive, advanced or metastatic disease, treatment options are limited, which is in stark contrast to the progress that has been made in NSCLC. Correspondingly, there has been very little improvement in survival rates; the overall 5-year survival rate of SCLC patients from diagnosis is <7% [National Cancer Institute 2014] [Gazdar, A. F., et al 2017] [American Cancer Society 2020].

Study objective

This study has been transitioned to CTIS with ID 2023-503517-30-00 check the CTIS register for the current data.

Primary objectives
To compare overall survival for MK-7684A in combination with the background therapy of etoposide/platinum followed by MK-7684A to atezolizumab in combination with the background therapy of etoposide/platinum followed by atezolizumab.
Hypothesis (H1): MK-7684A in combination with the background therapy of etoposide/platinum followed by MK-7684A is superior to atezolizumab in combination with the background therapy of etoposide/platinum followed by atezolizumab with respect to overall survival.

Secondary objectives
1. To compare progression-free survival per RECIST 1.1 by blinded independent central review (BICR) for MK-7684A plus etoposide/platinum followed by MK-7684A to atezolizumab plus etoposide/platinum followed by atezolizumab.

2. To evaluate objective response rate per RECIST 1.1 by BICR for MK-7684A plus etoposide/platinum followed by MK-7684A compared to atezolizumab plus etoposide/platinum followed by atezolizumab.

3. To evaluate duration of response per RECIST 1.1 by BICR for MK-7684A plus etoposide/platinum followed by MK-7684A compared to atezolizumab plus etoposide/platinum followed by atezolizumab.

4. To evaluate safety and tolerability based on proportion of adverse events.

5. To evaluate change from baseline and time to true deterioration in global health status/quality of life, physical functioning, dyspnea, cough, chest pain for MK-7684A plus etoposide/platinum followed by MK-7684A compared

to atezolizumab plus etoposide/platinum followed by atezolizumab.

Study design

This is a Phase 3, randomized, double-blind, active-controlled, multisite study of MK-7684A combined with etoposide/platinum chemotherapy followed by MK-7684A compared to atezolizumab combined with etoposide/platinum chemotherapy followed by atezolizumab in the first-line treatment of ES-SCLC.

Following a screening period of up to 28 days, approximately 450 eligible participants will be randomized 1:1 into 2 intervention groups:
Group A - Participants will receive 4 cycles of etoposide/platinum chemotherapy in combination with MK-7684A followed by MK-7684A until any of the conditions for discontinuation are met.
Group B - Participants will receive 4 cycles of etoposide/platinum chemotherapy in combination with atezolizumab followed by atezolizumab until any of the conditions for discontinuation are met. For example, an important criteria for discontinuation is radiographically confirmed disease progression.

Crossover will not be allowed between the intervention groups. A double-blinding technique will be used for atezolizumab and MK-7684A assignment. The chemotherapy agents will be open-label. The choice of platinum (cisplatin or carboplatin) in both arms is selected by the investigators before randomization.

Treatment randomization will be stratified according to ECOG performance status (0 or 1), LDH (<=ULN or >ULN), presence of liver metastases (yes or no), and presence of brain metastases (yes or no).

Specific procedures to be performed during the study, including prescribed times and associated visit windows, are outlined in Section 1.3 of the SoA. Details of each procedure are provided in Section 8 from the Study Protocol. Tumor response will be evaluated per RECIST 1.1 and participants 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.

Adverse events will be monitored throughout the study and graded in severity according to the guidelines outlined in the NCI CTCAE v5.0. Each participant will be monitored for AEs and SAEs (refer to Section 8.4.1 for details). If study intervention is discontinued for toxicity, neither pembrolizumab nor MK-7684 will be offered as a single agent.

Intervention

Intervention Group A:
- MK-7684A - 200 mg/200 mg; Q3W; IV infusion; until discontinuation criteria are met
- Saline placebo - at Cycle 1 (and Q3W as needed beyond Cycle 1); IV infusion; as needed beyond Cycle 1
- Etoposide - 100 mg (may vary according to supplier/country); Q3W; IV infusion; up to 4 cycles
- Cisplatin - 50 mg (may vary according to supplier/country); Q3W; IV infusion; up to 4 cycles
OF
- Carboplatin - 600 mg (may vary according to supplier/country); Q3W; IV infusion; up to 4 cycles

Intervention Group B:
- Atezolizumab - 1200 mg; Q3W; IV infusion; until discontinuation criteria are met
- Saline placebo - at Cycle 1 (and Q3W as needed beyond Cycle 1); IV infusion; as needed beyond Cycle 1
- Etoposide - 100 mg (may vary according to supplier/country); Q3W; IV infusion; up to 4 cycles
- Cisplatin - 50 mg (may vary according to supplier/country); Q3W; IV infusion; up to 4 cycles
OF
- Carboplatin - 600 mg (may vary according to supplier/country); Q3W; IV infusion; up to 4 cycles

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 combination therapies, during three-week cycles. 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.
Available clinical safety data indicated that vibostolimab is tolerable at doses up to and including 700 mg, both when used as monotherapy and in combination with pembrolizumab. No DLTs were observed at any of the vibostolimab doses tested either as monotherapy or in combination with pembrolizumab during the dose escalation and confirmation portion of Study

MK-7684-001, and the MTD was not reached.

Contacts

Public
Merck Sharp & Dohme (MSD)

Waarderweg 39
Haarlem 2031 BN
NL
Scientific
Merck Sharp & Dohme (MSD)

Waarderweg 39
Haarlem 2031 BN
NL

Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

1. Has histologically or cytologically confirmed diagnosis of ES-SCLC in need of first-line therapy.
2. Has ES-SCLC defined as Stage IV (T any, N any, M1a/b/c) by the American Joint Committee on Cancer, Eighth Edition or T3-T4 due to multiple lung nodules that are too extensive or have tumor/nodal volume that is too large to be encompassed in a tolerable radiation plan.
3. Is male or female, at least 18 years of age at the time of providing documented informed consent.
4. Male participants are eligible to participate if they agree to the following

during the intervention period and for at least the time needed to eliminate each study intervention after the last dose of study intervention. The length of time required to continue contraception for each study intervention after the last dose of the intervention is as follows:
- Etoposide, cisplatin, or carboplatin: 95 days
- Blinded study intervention: no contraception measures
• 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 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 who is not currently pregnant.
- 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.
5. 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 low user dependency, or be abstinent from heterosexual intercourse as their preferred and usual lifestyle (abstinent on a longterm and persistent basis) during the intervention period and for at least the time needed to eliminate each study intervention after the last dose of study intervention and agrees not to donate eggs (ova, oocytes) to others or freeze/store for her own use for the purpose of reproduction
during this period. The length of time required to continue contraception for each study intervention after the last dose of the intervention is as follows:
- Etoposide, cisplatin, or carboplatin: 180 days
- Blinded study intervention: 5 months
The investigator should evaluate the potential for contraceptive method failure in relationship to the first dose of study intervention.
- A WOCBP must have a negative highly sensitive pregnancy test within 24 hours before the first dose of study intervention.
- If a urine test cannot be confirmed as negative, 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 Section 8.3.6 of 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. 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.
6. The participant (or legally acceptable representative) has provided documented informed consent/assent for the study. The participant may also provide consent/assent for FBR. However, the participant may participate in the study without participating in FBR.
7. Has measurable disease per RECIST 1.1 as assessed by the local site investigator/radiology. Lesions situated in a previously irradiated area are considered measurable if progression has been shown in such lesions. At least 1 lesion that meets the criteria for being measurable, as
defined by RECIST 1.1, must be appropriate for selection as a target lesion.
8. Submits a pretreatment archival tumor tissue sample or newly obtained core, incisional, or excisional biopsy of a tumor lesion not previously irradiated where such sample exists. Biopsy/tissue is preferred, but cytology sample by fine needle aspiration is allowed. The
sample may be submitted after enrollment but must be submitted within 4 weeks after randomization.
9. Has an ECOG performance status of 0 to 1 assessed within 7 days before allocation/ randomization.
10. Has adequate organ function.
11. Has a predicted life expectancy of >3 months.

Exclusion criteria

1. Is considered a poor medical risk due to a serious, uncontrolled medical disorder or nonmalignant systemic disease. Examples include, but are not limited to, uncontrolled major seizure disorder, unstable spinal cord compression, or severe or life-threatening superior vena cava syndrome.
2. Has received prior treatment (systemic therapy including investigational agents, curativeintent radiotherapy, or curative-intent surgical resection) for SCLC.
3. Is expected to require any other form of antineoplastic therapy for SCLC while on study.
4. Has received a live or live-attenuated vaccine within 30 days before the first dose of study intervention. Administration of killed vaccines are allowed.
5. Has received an investigational agent or has used an investigational device within 4 weeks prior to the first dose of study 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 medication.
7. Has a known additional malignancy that is progressing or has required active treatment within the past 3 years.
8. Has known active CNS metastases and/or carcinomatous meningitis. Participants with brain metastases may participate only if they satisfy all of the following:
• Completed treatment (eg, whole brain radiation treatment, stereotactic radiosurgery, or equivalent) at least 14 days before the first dose of study intervention
• Have no evidence of new or enlarging brain metastases confirmed by posttreatment repeat brain imaging (preferably using the same modality) performed at least 4 weeks after treatment and within the screening period, and
• Are neurologically stable without the need for steroids at least 7 days before the first dose of study intervention as per local site assessment.
9. Has a history of severe hypersensitivity reaction (>=Grade 3) to any study intervention and/or any of its excipients (refer to the IB and/or approved product label(s) for a list of excipients).
10. Has an active autoimmune disease that has required systemic treatment in past 2 years (ie, with use of disease modifying agents, corticosteroids or immunosuppressive drugs). Replacement therapy (eg, thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency) is not considered a form of systemic treatment and is allowed.
11. Has a history of (noninfectious) pneumonitis/interstitial lung disease that required steroids or has current pneumonitis/interstitial lung disease.
12. Has a known history of, or active, neurologic paraneoplastic syndrome.
13. Has an active infection requiring systemic therapy.
14. Has a known history of HIV infection. No HIV testing is required unless mandated by local health authority.
15. Has a known history of Hepatitis B (defined as HBsAg reactive) or known active Hepatitis C virus (defined as HCV RNA [qualitative] is detected) infection.
16. 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.
17. Has a known psychiatric or substance abuse disorder that would interfere with the participant's ability to cooperate with the requirements of the study.
18. Has had an allogenic tissue/solid organ transplant.
19. Has had major surgery within 3 weeks before receiving the first dose of study intervention or has not recovered adequately from toxicity and/or complications from an intervention prior to receiving the first dose of study intervention.
20. Has symptomatic ascites or pleural effusion. A participant who is clinically stable following treatment for these conditions (including

therapeutic thoraco- or paracentesis) is eligible.

Study design

Design

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

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	21-06-2022
Enrollment:	28
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Carboplatine
Generic name:	carboplatine
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Cisplatine
Generic name:	cisplatine
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Etoposide, Eposin, Toposin, Vepesid
Generic name:	etoposide
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:	Vibostolimab
Generic name:	Vibostolimab

Ethics review

Approved WMO Date:	16-02-2022
Application type:	First submission
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	17-03-2022
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	11-04-2022
Application type:	First submission
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	02-06-2022
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	14-06-2022
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	13-08-2022
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO	

Date:	23-08-2022
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	07-02-2023
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	21-04-2023
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	13-05-2023
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	26-05-2023
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	CTIS2023-503517-30-00
EudraCT	EUCTR2021-005034-42-NL

Register	ID
Other	IND: 157492
CCMO	NL80150.028.22