Randomized phase III trial investigating the survival benefit of adding thoracic radiotherapy to durvalumab (MEDI4736) immunotherapy plus chemotherapy in extensive stage small-cell lung cancer

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This study has been transitioned to CTIS with ID 2023-505514-15-00 check the CTIS register for the current data. Primary Objective:- To investigate whether adding TRT to durvalumab plus chemotherapy improves 1-year survival. Secondary Objectives:-...

Ethical review	Approved WMO
Status	Pending
Health condition type	Respiratory tract neoplasms
Study type	Interventional

Summary

ID

NL-OMON53938

Source
ToetsingOnline

Brief title
TRIPLEX

Condition

- Respiratory tract neoplasms

Synonym
cancer, small-cell lungcancer

Research involving
Human

Sponsors and support

Primary sponsor: Universiteit voor Wetenschap en Technologie
Source(s) of monetary or material Support: het onderzoek wordt gefinancierd door de Universiteit voor Wetenschap en Technologie uit Trondheim in Noorwegen

Intervention

Keyword: chemo-immunotherapy, durvalumab, extensive small-cell lungcancer, radiotherapy

Outcome measures

Primary outcome

The primary endpoint of the study is to compare the 1-year overall survival

patients on reference therapy versus investigational therapy.

Secondary outcome

Secondary endpoints are the 2-year, 3-year, 4-year and 5-year overall survival,

overall response rates, response rates in non-irradiated lesions, PFS, PFS in

non-irradiated lesions, local control rates in the thorax, frequency and

severity of adverse events, and health-related quality of life.

Study description

Background summary

Lung cancer is the most common cause of cancer-related death. Small cell lung cancer (SCLC) is responsible for about 15% of these cases. It is a very aggressive disease that, if left untreated, usually leads to death within 2-4 months. SCLC metastasizes quickly and often.
Chemo-immunotherapy, e.g. chemotherapy plus a PD-L1 inhibitor is considered a new standard of care for first-line treatment of advanced stage small cell lung cancer (ES) but is not yet available/reimbursable in all countries. Durvalumab (anti-PD-L1) plus platinum/etoposide is one of these new standard regimens. However, the survival benefit is limited, especially during the first 6 months, and more effective treatment is needed. Thoracic radiotherapy (TRT) has been shown to improve survival in ES SCLC, and the effect in terms of

progression-free survival (PFS) is immediate. Several studies suggest a synergistic effect of combining RT and immune checkpoint inhibitors and co-administration appears to be the most effective approach.
The main hypothesis is that adding TRT to durvalumab plus chemotherapy provides a survival benefit for patients with ES SCLC.

Study objective

This study has been transitioned to CTIS with ID 2023-505514-15-00 check the CTIS register for the current data.

Primary Objective:
- To investigate whether adding TRT to durvalumab plus chemotherapy improves 1-year survival.

Secondary Objectives:
- To investigate whether adding TRT improves 2-, 3-, 4- and 5-year overall survival.
- To investigate whether adding TRT improves overall response rates, response rates in non-irradiated lesions and PFS.
- To investigate whether TRT improves local control.
- To compare the frequency and severity of adverse events between the treatment arms.
- To compare health related quality of life between treatment arms.

Study design

Open label randomized phase III trial.
Patients will be randomized 1:1 in blocks of various sizes to receive chemo-immunotherapy alone or chemo-immunotherapy plus TRT stratifying for presence of liver metastases and/or presence of brain metastases.

Intervention

Reference therapy: Durvalumab plus carboplatin/etoposide
Investigational therapy: Durvalumab plus carboplatin/etoposide and TRT

Study burden and risks

Risk: Side Effects of the Study Drug

Burden:
Screening (2-4 weeks), 4 courses of chemotherapy, durvalumab adjuvant treatment until progression, 50% of patients: 10 fractions of thoracic radiotherapy

Therapy:

Etoposide: I.V. infusion 500 ml every 3 weeks (30 min per infusion, days 1-3, 4 courses)
Carboplatin: I.V. infusion 1,000 ml every 3 weeks (2 hours per infusion, day 1, 4 courses)
Durvalumab: I.V. infusion 500 ml every 3 weeks (30-60 min per infusion, day 1, 1 year

Study procedures:
Physical examination: (almost) every course; follow up: 2-4 times a year.
Blood test: any course; follow-up: 2-4 times a year, 10-25 ml each time
Brain MRI scan: during screening (in line with standard treatment)
PET CT scan: during screening (in line with standard treatment)
CT scan thorax and abdomen: during screening (in line with standard treatment)
Tumor biopsy: 0-1.
Pregnancy test (if relevant): every month for ..... months
Lung function: 1
Questionnaires EORTC QLQ-C30 and LC13: every 3 months during .... year
Stool sampling:
Optional: tumor biopsy for disease progression

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. Capable of giving signed informed consent which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and in this protocol. Written informed consent and any locally required authorization (e.g. Health Insurance Portability and Accountability Act in the US, European Union [EU] Data Privacy Directive in the EU) obtained from the patient/legal representative prior to performing any protocol-related procedures, including screening evaluations.
2. Age > 18 years at time of study entry.
3. ECOG performance status of 0 or 1.
4. Body weight >30 kg.
5. Adequate normal organ and marrow function as defined below:
• Haemoglobin >=10.0 g/dL.
• Absolute neutrophil count (ANC) >=1.5 × 109 /L
• Platelet count >=100 × 109/L
• Serum bilirubin <=1.5 x institutional upper limit of normal (ULN). This does not apply to patients with confirmed Gilbert*s syndrome (persistent or recurrent hyperbilirubinemia that is predominantly unconjugated in the absence of hemolysis or hepatic pathology).
• ALT (SGPT) <=2.5 x institutional upper limit of normal unless liver metastases are present, in which case it must be <=5 x ULN.
• Measured creatinine clearance (CL) >40 mL/min or Calculated creatinine CL>40 mL/min by the Cockcroft-Gault formula (Cockcroft and Gault 1976) or by 24-hour urine collection for determination of creatinine clearance.
6. Patient is willing and able to comply with the protocol for the duration of the study including undergoing treatment and scheduled visits and examinations including follow-up.
7. Life expectancy of at least 3 months.
8. At least 1 lesion, not previously irradiated, that qualifies as a RECIST 1.1 target lesion (TL) at baseline. Tumor assessment by computed tomography (CT) scan or magnetic resonance imaging (MRI) must be performed within 28 days prior to randomization.
9. At least 1 measurable lesion in the thorax which is possible to irradiate to 30 Gy in 10 fractions.
10. Histologically or cytologically confirmed SCLC.
11. Stage IV disease according to the TNM v8. Patients with stage III disease are eligible if the disease is too widespread to be treated as limited stage SCLC.

12. Pulmonary function: FEV1 >1 L or >30 % of predicted value and DLCO >30 % of predicted value.
13. Female patients of childbearing potential (postmenarcheal, not postmenopausal [>12 continuous months of amenorrhea with no identified cause other than menopause], and no surgical sterilization) should use highly effective contraception and take active measures to avoid pregnancy while undergoing systemic study therapy and for at least 5 months after the last dose.
14. Patients with brain metastases are eligible provided they are asymptomatic or treated and stable on steroids and/or anticonvulsants prior to the start of treatment.

Exclusion criteria

1. Participation in another clinical study with an investigational product during the last 30 days.
2. Concurrent enrolment in another clinical study, unless it is an observational (non-interventional) clinical study or during the follow-up period of an interventional study.
3. Previous chemo- or radiotherapy for SCLC. Patients who have undergone surgery, but no adjuvant therapy are eligible.
4. Any unresolved toxicity NCI CTCAE Grade >=2 from previous anticancer therapy with the exception of alopecia, vitiligo, and the laboratory values defined in the inclusion criteria.
5. Patients with Grade >=2 neuropathy will be evaluated on a case-by-case basis after consultation with the Chief Investigator.
6. Patients with irreversible toxicity not reasonably expected to be exacerbated by treatment with durvalumab may be included only after consultation with the Chief Investigator.
7. Any concurrent chemotherapy, investigational product or biologic cancer therapy.
8. Any prior checkpoint inhibitor therapy, including durvalumab.
9. Radiotherapy treatment to more than 30% of the bone marrow or with a wide field of radiation within 4 weeks of the first dose of study drugs.
10. Immediate need for thoracic radiotherapy or bulky disease outside the thorax, or need for such
radiotherapy before completion of chemo-immunotherapy
11. Major surgical procedure within 28 days prior to the first dose of study drugs. Note: Local surgery of isolated lesions for palliative intent is acceptable.
12. History of allogenic organ transplantation.
13. Active or prior documented autoimmune or inflammatory disorders (including inflammatory bowel disease [e.g., colitis or Crohn's disease], diverticulitis [with the exception of diverticulosis], systemic lupus erythematosus, Sarcoidosis syndrome, or Wegener syndrome [granulomatosis with polyangiitis, Graves' disease, rheumatoid arthritis, hypophysitis, uveitis, etc]). The

following are exceptions to this criterion:
a. Patients with vitiligo or alopecia.
b. Patients with hypothyroidism (e.g., following Hashimoto syndrome) stable on hormone replacement.
c. Any chronic skin condition that does not require systemic therapy.
d. Patients without active disease in the last 5 years may be included but only after consultation with the Chief Investigator.
e. Patients with celiac disease controlled by diet alone.
14. Uncontrolled intercurrent illness, including but not limited to, ongoing or active infection, symptomatic congestive heart failure, uncontrolled hypertension, unstable angina pectoris, cardiac arrhythmia, interstitial lung disease, serious chronic gastrointestinal conditions associated with diarrhea, or psychiatric illness/social situations that would limit compliance with study requirement, substantially increase risk of incurring AEs or compromise the ability of the patient to give written informed consent.
15. History of another primary malignancy except for:
a. Malignancy treated with curative intent and with no known active disease >=5 years before the first dose of IP and of low potential risk for recurrence.
b. Localized breast or prostate cancer treated with hormonal therapy alone.
c. Adequately treated non-melanoma skin cancer or lentigo maligna without evidence of disease.
d. Adequately treated carcinoma in situ without evidence of disease.
16. Leptomeningeal carcinomatosis.
17. Untreated, symptomatic central nervous system (CNS) metastases. Any neurologic symptoms that developed either as a result of the brain metastases or their treatment must have resolved or be stable either, without the use of steroids, or are stable on steroids and/or anticonvulsants prior to the start of treatment.
18. History of active primary immunodeficiency.
19. Active infection including tuberculosis (clinical evaluation that includes clinical history, physical examination and radiographic findings, and TB testing in line with local practice), hepatitis B (known positive HBV surface antigen (HBsAg) result), hepatitis C. Patients with a past or resolved HBV infection (defined as the presence of hepatitis B core antibody [anti-HBc] and absence of HBsAg) are eligible. Patients positive for hepatitis C (HCV) antibody are eligible only if polymerase chain reaction is negative for HCV RNA.
20. Current or prior use of immunosuppressive medication within 14 days before the first dose of durvalumab. The following are exceptions to this criterion:
a. Intranasal, inhaled, topical steroids, or local steroid injections (e.g., intra articular injection).
b. Systemic corticosteroids at physiologic doses not to exceed 10 mg/day of prednisone or its equivalent.
c. Steroids as premedication for hypersensitivity reactions (e.g., CT scan premedication).
21. Receipt of live attenuated vaccine within 30 days prior to the first dose of IP. Note: Patients, if enrolled, should not receive live vaccine whilst receiving IP and up to 30 days after the last dose of IP.

22. Female patients who are pregnant or breastfeeding or male or female patients of reproductive potential who are not willing to employ effective birth control.
23. Known allergy or hypersensitivity to any of the study drugs or any of the study drug excipients.
24. Judgment by the investigator that the patient is unsuitable to participate in the study and the patient
is unlikely to comply with study procedures, restrictions and requirements.

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Crossover
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Pending
Start date (anticipated):	01-01-2023
Enrollment:	155
Type:	Anticipated

Medical products/devices used

Product type:	Medicine
Brand name:	Carboplatin
Generic name:	Carboplatin
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Etoposide

Generic name:	Etoposide
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Imfinzi
Generic name:	Durvalumab
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	01-12-2022
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	04-04-2023
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	29-01-2024
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

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	CTIS2023-505514-15-00
EudraCT	EUCTR2021-001648-91-NL
CCMO	NL80688.078.22