A Phase III, Randomized, Placebo-controlled, Double-blind, Multi-center, International Study of Durvalumab with Stereotactic Body Radiation Therapy (SBRT) for the Treatment of Patients with unresected Stage I/II, lymph-node negative Non-small Cell Lung Cancer (PACIFIC-4/RTOG-3515)

Published: 15-04-2019
Last updated: 19-09-2024

This study has been transitioned to CTIS with ID 2024-512667-31-00 check the CTIS register for the current data. Primary objective:- To assess the efficacy of durvalumab with SoC SBRT compared to placebo with SoC SBRT in terms of PFS in patients…

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

Summary

ID

NL-OMON54495

Source
ToetsingOnline

Brief title
PACIFIC-4/RTOG-3515

Condition

- Respiratory and mediastinal neoplasms malignant and unspecified

Synonym
non small-cell lung cancer; lung cancer

Research involving
Human

Sponsors and support

Primary sponsor: Astra Zeneca
Source(s) of monetary or material Support: Opdrachtgever/sponsor: AstraZeneca

Intervention

Keyword: Durvalumab, Non Small Cell Lung Cancer, Osimertinib, Stereotactic Body Radiation Therapy

Outcome measures

Primary outcome

- To assess the efficacy of durvalumab with SoC SBRT compared to placebo with

SoC SBRT in terms of PFS in patients with subset of T1 to T3N0 NSCLC using BICR

assessments according to RECIST 1.1

Osimertinib cohort:

- To assess the efficacy of osimertinib following SoC SBRT in terms of 4-year

PFS in patients with T1 to T3N0 NSCLC using BICR assessments according to

RECIST 1.1

Secondary outcome

- To assess the efficacy of durvalumab with SoC SBRT compared to placebo with

SoC SBRT in terms of PFS in patients with T1 to T3N0 NSCLC using BICR

assessments according to RECIST 1.1

- To assess the efficacy of durvalumab with SoC SBRT compared to placebo with

SoC SBRT in terms of OS in patients with subset of T1 to T3N0 NSCLC and in

patients with Stage I/II NSCLC

- To further assess the efficacy of durvalumab with SoC SBRT compared to placebo with SoC SBRT in terms of PFS24, TTP, TTDM using BICR assessments according to RECIST 1.1, and PFS2 using local assessment

- To assess the PK of durvalumab

- To investigate the immunogenicity of durvalumab

- To assess symptoms and health-related quality of life in patients treated with durvalumab with SoC SBRT compared to placebo with SoC SBRT using the EORTC QLQ-C30

Osimertinib cohort:

- To assess the safety, tolerability, and compliance of a maximum of 3 years of osimertinib following SoC SBRT

- To further assess other parameters of the efficacy of osimertinib following SoC SBRT

- To assess the events following disease progression for these medically inoperable patients treated by osimertinib following SoC SBRT

Study description

Background summary

Lung cancer has been the most common cancer in the world for several decades, and by 2012, there were an estimated 1.8 million new cases, representing 12.9% of all new cancers. It was also the most common cause of death from cancer, with 1.59 million deaths (19.4% of the total). NSCLC represents approximately 80% to 85% of all lung cancers and approximately 19% present with localized (lung only) disease.

With increasing evidence that screening with CT can detect lung cancers at an earlier stage, the number of patients diagnosed with early stage NSCLC is expected to rise significantly as screening program implementation increases. The SoC for patients who have medically operable NSCLC is surgery. However, many patients cannot tolerate surgery due to comorbidities. When receiving no active cancer treatment, the median survival of patients with Stage I NSCLC is only about 9 months.
In the past, conventional radiation therapy has been used in early stage NSCLC patients who are considered medically inoperable. However, conventional radiation therapy is generally toxic in this population and outcomes are poor. SBRT is a technique that allows for the delivery of very high doses of radiation, administered in several large fractions (hypofractionation). Compared to conventional RT, toxicity is reduced by minimizing the radiation exposure to normal tissue. SBRT has become a de facto SoC for patients with medically inoperable early stage (T1a to T3N0M0) NSCLC due to excellent patient tolerance, short overall treatment time, and infrequent clinically significant toxicity with high rates of primary tumor control. Although modern SBRT shows primary tumor control rates of >90%, 30% of which will succumb to PD after SBRT. Furthermore, even in this relatively frail patient population with competing risks of death, lung cancer-specific mortality remains a key determinant of OS. Chemotherapy administered after SBRT may decrease relapse rates and improve survival; however, the majority of patients are unfit to receive cytotoxic chemotherapy. As such, early stage NSCLC patients who receive SBRT as definitive therapy are in need of an effective and tolerable systemic adjuvant therapy to both reduce recurrence rates and improve survival.

Study objective

This study has been transitioned to CTIS with ID 2024-512667-31-00 check the CTIS register for the current data.

Primary objective:
- To assess the efficacy of durvalumab with SoC SBRT compared to placebo with SoC SBRT in terms of PFS in patients with subset of T1 to T3N0 NSCLC

Osimertinib cohort:
- To assess the efficacy of osimertinib following SoC SBRT by 4 year PFS in T1 to T3N0M0 (Stage I/II) EGFRm NSCLC

Study design

A Phase III, Randomized, Placebo-controlled, Double-blind, Multi-center study randomization 1:1 to:
- durvalumab and SBRT (only during first cycle of durvalumab)
- placebo and SBRT (only during first cycle of durvalumab)
Stratification factors:

- tumor size (T1 versus T2/3)
- tumor location (central versus peripheral).

Osimertinib cohort (EGFRm subset of patients):
- single arm Osimertinib monotherapy after SBRT

Intervention

Durvalumab monotherapy:
- Durvalumab (1500 mg IV infusion) q4w

Placebo:
- Placebo (saline IV infusion) q4w.

Osimertinib monotherapy:
- Osimertinib (80 mg PO) QD

Study burden and risks

On several days during the study, the patients will undergo the following assessments:
- anamnesis (at screening also medical history)
- physical examination
- ECOG performance status
- vital signs (blood pressure, pulse, temperature, respiration rate)
- body weight
- length measurement
- CT and/or MRI scan
- Administration of Stereotactic Body Radiation Therapy
- ECG
- Pulmonary function testing
- blood and urine assessments
- questionnaires: EORTC QLQ-C30, PRO-CTCAE, EQ-5D-5L
- pregnancy test if applicable
- AE/SAE assessment
- Administration durvalumab/placebo

Osimertinib cohort:
- anamnesis (at screening also medical history)
- physical examination
- ECOG performance status
- vital signs (blood pressure, pulse, temperature, respiration rate)
- body weight
- length measurement
- CT and/or MRI scan
- Administration of Stereotactic Body Radiation Therapy

- ECG
- Longfunction test
- blood and urine assessments
- pregnancy test if applicable
- AE/SAE assessment
- ECHO/MUGA
- Eye exams

Contacts

Public
Astra Zeneca

Prinses Beatrixlaan 582
Den Haag 2595BM
NL
Scientific
Astra Zeneca

Prinses Beatrixlaan 582
Den Haag 2595BM
NL

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

Main cohort:
1. Age >=18 years
2. Histologically or cytologically documented Stage I to II NSCLC, with

clinical Stage I/II lymph node-negative (T1 to T3N0M0) disease and planned to receive definitive treatment with SBRT. Patients may be medically inoperable or are medically operable and refusing surgery or choosing to have SBRT (Stereotactic Body Radiation Therapy) as definitive therapy
3. Planned SoC SBRT as definitive treatment
4. World Health Organization (WHO)/Eastern Cooperative Oncology Group (ECOG) PS of 0, 1, or 2
5. Life expectancy of at least 12 weeks
6. Body weight > 30 kg
7. Submission of available tumor sample
8. Adequate organ and marrow function required
9. Patients with central or peripheral lesions are eligible
10. Staging must be done within 10 weeks before randomization (PET)
11. Pulmonary Function Testing within 12 weeks of randomization
12. Patients with a history of metachronus stage I/II (T1-T3N0M0) NSCLC treated definitely with surgery only or SBRT only > 1 yr prior to enrolment are eligible
Osimertinib cohort:
1. Age >=18 years
2. Histologically or cytologically documented Stage I to II NSCLC, with clinical Stage I/II lymph node-negative (T1 to T3N0M0) disease and planned to receive definitive treatment with SBRT. Patients may be medically inoperable or are medically operable and refusing surgery or choosing to have SBRT (Stereotactic Body Radiation Therapy) as definitive therapy
3. Planned SoC SBRT as definitive treatment
4. World Health Organization (WHO)/Eastern Cooperative Oncology Group (ECOG) PS of 0, 1, or 2
5. Life expectancy of at least 12 weeks
6. Body weight > 30 kg
7. Submission of available tumor sample
8. Adequate organ and marrow function required
9. Patients with central or peripheral lesions are eligible
10. Staging must be done within 10 weeks before randomization (PET)
11. Pulmonary Function Testing within 12 weeks of randomization
12. Patients with a history of metachronus stage I/II (T1-T3N0M0) NSCLC treated definitely with
13. Local confirmation of EGFR mutation (Ex19del and/or L858R)

Exclusion criteria

Main cohort:
1. Mixed small cell and non-small cell cancer histology
2. History of allogeneic organ transplantation
3. History of another primary malignancy with exceptions
4. History of active primary immunodeficiency
5. Uncontrolled intercurrent illness (patients with controlled chronic

obstructive pulmonary disease are allowed)
6. Known allergy or hypersensitivity to any of the drugs or any of the study drug excipients
7. Prior exposure to immune-mediated therapy including, but not limited to, other anti-CTLA-4, anti-PD-1, anti-PD-L1, and anti-programmed cell death ligand 2
antibodies, excluding therapeutic anticancer vaccines
8. Any concurrent chemotherapy, IP, biologic, or hormonal therapy for cancer treatment. Concurrent use of hormonal therapy for non-cancer-related conditions (eg, hormone replacement therapy) is acceptable. If patient has been on adjuvant hormonal treatment for early stage breast cancer for more than 5 years, and there is no evidence of recurrence, then patient is eligible with study physician discussion.
9. Major surgical procedure within 28 days prior to first dose of IP
10. Current or prior use of immunosuppressive medication within 14 days before the first dose of IP.
11. Positive pregnancy test for pre-menopausal women
12. local confirmation of EGFR mutation (Ex19del and/or L858R)

Osimertinib cohort:
1. Mixed small cell and non-small cell cancer histology
2. Treatment with any of the following:
- Preoperative (neoadjuvant) or adjuvant platinum-based or other chemotherapy for
the disease under investigation;
- Any prior anticancer or immunological therapy, including investigational therapy,
for treatment of NSCLC for the disease under investigation;
- Prior treatment with neoadjuvant or adjuvant EGFR-TKI;
3. History of another primary malignancy with exceptions
4. Sever or uncontrolled systemic disease.
5. Refractory nausea and vomiting, chronic GI diseases, inability to swallow the formulated product, or previous significant bowel resection that would preclude adequate absorption of osimertinib;
6. Any of the following cardiac criteria:
- Mean resting QTc > 470 msec obtained from 3 electrocardiograms (ECGs), using the screening clinic ECG machine-derived QTcF value;
- Any clinically important abnormalities in rhythm, conduction, or morphology of resting ECG
- Patient with any factors that increase the risk of QTc prolongation or risk of arrhythmic events, such as electrolyte abnormalities
7. Past medical history of ILD, drug-induced ILD, or any evidence of clinically active ILD;

8. History of hypersensitivity to active or inactive excipients of osimertinib or drugs withva similar chemical structure or class to osimertinib;

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):	14-01-2020
Enrollment:	8
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	NA
Generic name:	Durvalumab
Registration:	Yes - NL outside intended use
Product type:	Medicine
Brand name:	Tagrisso
Generic name:	Osimertinib
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO

Date:	15-04-2019
Application type:	First submission

Review commission:	METC Amsterdam UMC
Approved WMO Date:	17-10-2019
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	23-03-2020
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	09-06-2020
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	19-03-2021
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	26-03-2021
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	28-01-2022
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	24-03-2022
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	07-04-2022
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	25-07-2022
Application type:	Amendment

Review commission:	METC Amsterdam UMC
Approved WMO Date:	28-01-2023
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	24-03-2023
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	02-08-2023
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	05-10-2023
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	22-01-2024
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	08-02-2024
Application type:	Amendment
Review commission:	METC Amsterdam UMC

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	CTIS2024-512667-31-00
EudraCT	EUCTR2018-002572-41-NL
ClinicalTrials.gov	NCT03833154
CCMO	NL68648.029.19