A Phase III, Randomized, Double-blind, Placebo-controlled, Multi-center, International Study of Durvalumab or Durvalumab and Tremelimumab as Consolidation Treatment for Patients with Limited Stage Small-Cell Lung Cancer Who Have Not Progressed Following Concurrent Chemoradiation Therapy

Published: 29-11-2018
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This study has been transitioned to CTIS with ID 2023-509602-29-00 check the CTIS register for the current data. Primary objectives:- To assess the efficacy of durvalumab monotherapy compared to placebo in terms of PFS- To assess the efficacy of...

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

Summary

ID

NL-OMON54567

Source
ToetsingOnline

Brief title
ADRIATIC

Condition

- Respiratory and mediastinal neoplasms malignant and unspecified

Synonym
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: chemoradiation therapy, durvalumab, small-cell lung cancer, tremelimumab

Outcome measures

Primary outcome

- To assess the efficacy of durvalumab monotherapy compared to placebo in terms

of PFS using BICR assessments according to RECIST 1.1

- To assess the efficacy of durvalumab monotherapy compared to placebo in terms

of OS

Secondary outcome

- To assess the efficacy of durvalumab and tremelimumab combination therapy

compared to placebo in terms of PFS and OS

- To further assess the efficacy of durvalumab monotherapy and durvalumab and

tremelimumab combination therapy compared to placebo in terms of ORR, PFS18,

PFS24, TTDM, OS24, OS36, and PFS2

- To assess the efficacy of durvalumab and tremelimumab combination therapy compared to durvalumab monotherapy in terms of PFS, OS, and ORR

- To assess disease-related symptoms and HRQoL in patients treated with durvalumab monotherapy and durvalumab and tremelimumab combination therapy compared to placebo using the EORTC QLQ-C30 v3 and QLQ-LC13

- To assess the PK of durvalumab monotherapy and durvalumab and tremelimumab combination therapy

- To investigate the immunogenicity of durvalumab monotherapy and durvalumab and tremelimumab combination therapy

- To investigate the relationship between PD-L1 expression and spatial distribution within the tumor microenvironment and clinical outcomes with durvalumab monotherapy or durvalumab and tremelimumab combination therapy

Study description

Background summary

Lung cancer has been the most common cancer in the world for several decades, with an estimated 1.8 million new cases in 2012 (12.9% of all new cancers), and was also the most common cause of death from cancer in 2012, with 1.59 million deaths (19.4% of the total cancer deaths).

SCLC represents approximately 13% of all newly diagnosed lung cancers. SCLC is perhaps the most aggressive form of the disease and is distinguishable from NSCLC by its rapid doubling time, high growth fraction, and early

dissemination. A 2-stage system divides patients into limited and extensive-stage disease. Limited disease is defined as tumor tissue that can be encompassed in a single radiation port, and at present, is identified in ~30% of SCLC patients.

The standard-of-care treatment for LD-SCLC is thoracic radiotherapy (once daily with a total dose of 60 to 66 Gy or twice daily with a total dose of 45 Gy) combined with 4 cycles of either cisplatin or carboplatin and etoposide chemotherapy. In addition, data suggest that prophylactic cranial irradiation (PCI; for patients that respond to initial therapy) may increase the OS and PFS in LD-SCLC patients. Response rates for concurrent CRT in LD-SCLC are approximately 90%, but the majority of patients eventually progress, with median PFS of 10 to 15 months and median OS of 15 to 30 months. Therefore, there is still a significant unmet medical need for additional treatment options for use in this patient population to improve on PFS and OS.

Study objective

This study has been transitioned to CTIS with ID 2023-509602-29-00 check the CTIS register for the current data.

Primary objectives:

- To assess the efficacy of durvalumab monotherapy compared to placebo in terms of PFS
- To assess the efficacy of durvalumab monotherapy compared to placebo in terms of OS

Study design

Phase III, randomized, double-blind, placebo-controlled, multi-center study

For the first 600 randomised patients:

Randomisation 1:1:1 to:

- Durvalumab + Tremelimumab
- Durvalumab
- Placebo

For patients 601 until 724:

Randomisation 1:1 to:

- Durvalumab
- Placebo

Stratification factors:
- TNM Classification of Malignant Tumors: stage I/II vs III (TNM Stage III disease will be limited to up to 85% of the targeted global population)
- Prophylactic Cranial Irradiation: yes vs no

Intervention

For the first 600 patients randomised:

Durvalumab + Tremelimumab combination therapy:
- Durvalumab (1500 mg IV) q4w in combination with tremelimumab (75 mg IV) q4w for up to 4 doses/cycles each, followed by durvalumab 1500 mg q4w.

Durvalumab monotherapy:
- Durvalumab (1500 mg intravenous [IV]) q4w in combination with placebo saline solution (IV) q4w for up to 4 doses/cycles each, followed by durvalumab 1500 mg q4w.

Placebo:
- Placebo saline solution (IV) q4w in combination with a second placebo saline solution (IV) q4w for up to 4 doses/cycles each, followed by a single placebo saline solution q4w.

For patients 601 until 724:

Durvalumab monotherapy:
- Durvalumab (1500 mg intravenous [IV]) q4w

Placebo:
- Placebo saline solution (IV) q4w

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
- ECG
- blood and urine assessments
- questionnaires: EQ-5D-5L, EORTC QLQ-C30, QLQ-LC13, PRO-CTCAE, PGIS
- pregnancy test if applicable

- AE/SAE assessment
- Collection of stool samples (voluntary participation)

Contacts

Public
Astra Zeneca

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

- 18 years or older at the time of screening,
- Histologically or cytologically documented limited-stage SCLC (Stage I-III SCLC [T any, N any, M0] according to the American Joint Committee on Cancer Staging Manual [AJCC Cancer Staging Manual, 8th Edition] or the International Association for the Study of Lung Cancer Staging Manual in Thoracic Oncology [IASLC Staging Manual in Thoracic Oncology 2016]), ie, patients whose disease can be encompassed within a radical radiation portal. Patients who are Stage I or II must be medically inoperable

- World Health Organization (WHO)/Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0 or 1 at enrollment and randomization
- Received an appropriate first line concurrent chemoradiotherapy regimen as defined below, unless after consultation with the global study medical team an alternative is acceptable
* Received 4 cycles of platinum-based chemotherapy concurrent with RT, which must be completed within 1 to 42 days prior to randomization and the first dose of IP.
* The chemotherapy regimen must contain platinum and IV etoposide, administered as per local standard-of-care regimens.
* Received a total dose of radiation of 60 to 66 Gy over 6 weeks for standard QD radiation schedules or 45 Gy over 3 weeks for hyperfractionated BID radiation schedules.
* Radiotherapy must have commenced no later than the end of Cycle 2 of chemotherapy.
* Receipt of 3 cycles of platinum-based chemotherapy concurrent with RT will be permitted if the patient has achieved disease control and in the opinion of the Investigator, no additional benefit will be expected with additional cycle of chemotherapy.,
- Patients must have achieved CR, PR, or SD and not have progressed following definitive, platinum-based chemotherapy, concurrent with radiotherapy.
- PCI may be delivered at the discretion of investigator and local standard of care and must be conducted after the end of cCRT and completed between 1 to 42 days to first dose of IP.
- Tumor sample requirements:
* Mandatory availability of tumor sample, which may include a core needle biopsy, newly cut unstained slides, or fine needle aspirate (FNA) cell block samples.
* A newly acquired tumor biopsy is optional, provided that a biopsy procedure is technically feasible and the procedure is not associated with unacceptable clinical risk.
- Adequate organ and marrow function independent of transfusion, infusion, or growth factor support for at least 14 days prior to obtaining screening labs,
- Must have a life expectancy of at least 12 weeks, - Body weight >30 kg

Exclusion criteria

- Mixed SCLC and NSCLC histology,
- Extensive-stage SCLC,
- Any history of Grade >=2 pneumonitis,
- History of allogeneic organ transplantation,
- Active or prior documented autoimmune or inflammatory disorders (including inflammatory bowel disease [eg, 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:
* Patients with vitiligo or alopecia
* Patients with hypothyroidism (eg, following Hashimoto syndrome) stable on hormone replacement
* Any chronic skin condition that does not require systemic therapy
* Patients without active disease in the last 5 years may be included but only after consultation with the Study Physician
* Patients with celiac disease controlled by diet alone,
- Uncontrolled intercurrent illness, including but not limited to, ongoing or active infection, symptomatic congestive heart failure, uncontrolled hypertension, unstable angina pectoris, uncontrolled cardiac arrhythmia, active ILD, serious chronic GI conditions associated with diarrhea, or psychiatric illness/social situations that would limit compliance with study requirements, substantially increase risk of incurring AEs or compromise the ability of the patient to give written informed consent,
- History of another primary malignancy except for:
* 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
* Adequately treated non-melanoma skin cancer or lentigo maligna without evidence of disease
* Adequately treated carcinoma in situ without evidence of disease,
- History of leptomeningeal carcinomatosis,
- History of active primary immunodeficiency, - Active infection including tuberculosis (clinical evaluation that includes clinical history, physical examination and radiographic findings, and tuberculosis testing in line with local practice), hepatitis B (known positive HBV surface antigen [HBsAg] result), hepatitis C (HCV), or human immunodeficiency virus (positive HIV 1/2 antibodies). Patients with a past or resolved HBV infection (defined as the presence of hepatitis B core antibody and absence of HBsAg) are eligible. Patients positive for HCV antibody are eligible only if polymerase chain reaction is negative for HCV RNA.,
- Any unresolved toxicity NCI Common Terminology Criteria for Adverse Events (CTCAE) Grade >=2 from previous CRT with the exception of alopecia, vitiligo, and the laboratory values defined in the inclusion criteria
* Patients with Grade >=2 neuropathy will be evaluated on a case-by-case basis after consultation with the Study Physician.
* Patients with irreversible toxicity not reasonably expected to be exacerbated by treatment with durvalumab or tremelimumab may be included only after consultation with the Study Physician.,
- Brain metastases or spinal cord compression. All patients will have an MRI (preferred) or CT, preferably with IV contrast of the brain, prior to study entry.,
- Mean QT interval corrected for heart rate using Fridericia's formula (QTcF) >=470 ms calculated from 3 ECGs (within 15 minutes at 5 minutes apart), - Known allergy or hypersensitivity to any of the study drugs or any of the study drug excipients,

- Patients who received sequential CRT for LD-SCLC (no overlap of RT with chemotherapy), - Patients whose conditions have progressed while on concurrent CRT,
- Receipt of chemotherapy that exceeds 4 cycles in total. Chemotherapy regimens other than etoposide and platinum are not permitted.,
- 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 (anti-PD-L2) antibodies, excluding therapeutic anticancer vaccines.,
- 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.,
- Receipt of live attenuated vaccine within 30 days prior to the first dose of IP. Note: Patients, if randomized, should not receive live vaccine while receiving IP and up to 30 days after the last dose of IP.,
- Major surgical procedure (as defined by the Investigator) within 42 days prior to the first dose of IP.,
- Current or prior use of immunosuppressive medication within 14 days before the first dose of durvalumab or tremelimumab. The following are exceptions to this criterion:
* Intranasal, inhaled, topical steroids, or local steroid injections (eg, intra articular injection)
* Systemic corticosteroids at physiologic doses not to exceed 10 mg/day of prednisone or its equivalent
* Steroids as premedication for hypersensitivity reactions (eg, CT scan premedication),
- Female patients who are pregnant or breastfeeding and male or female patients of reproductive potential who are not willing to employ effective birth control from screening to 180 days after the last dose of IP.

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):	06-01-2020
Enrollment:	20
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	NA
Generic name:	Durvalumab
Product type:	Medicine
Brand name:	NA
Generic name:	Tremelimumab

Ethics review

Approved WMO Date:	29-11-2018
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	11-03-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	11-04-2019
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	21-06-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	02-07-2019

Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	25-03-2020
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	22-04-2020
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	18-01-2021
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	01-03-2021
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	09-05-2021
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	24-08-2021
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	15-12-2021
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	31-03-2022
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	25-02-2023

Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	20-07-2023
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	15-11-2023
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	27-03-2024
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	CTIS2023-509602-29-00
EudraCT	EUCTR2018-000867-10-NL
ClinicalTrials.gov	NCT03703297
CCMO	NL67090.029.18