A Randomized, Double-Blind, Placebo-Controlled Phase 3 Study of Rovalpituzumab Tesirine as Maintenance Therapy Following First-Line Platinum-Based Chemotherapy in Subjects with Extensive Stage Small Cell Lung Cancer (MERU)

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

Summary

ID

NL-OMON50134

Source
ToetsingOnline

Brief title
M16-298

Condition

- Respiratory and mediastinal neoplasms malignant and unspecified

Synonym
extensive-stage lung cancer, small cell lung cancer

Research involving
Human

Sponsors and support

Primary sponsor: AbbVie B.V.
Source(s) of monetary or material Support: Farmaceutische industrie

Intervention

Keyword: maintenance therapy, Rovalpituzumab Tesirine, SCLC

Outcome measures

Primary outcome

Progression-free survival (PFS) determined by a Central Radiographic Assessment

Committee (CRAC) and overall survival (OS).

Timepoints of evaluation:

PFS - From randomization to disease progression, or death of any cause,

whichever occurs first.

OS - From randomization to death of any cause

Secondary outcome

- Progression-free survival (PFS) based on investigator assessment

- Objective response rate (ORR) per the CRAC and investigator assessment,

respectively

- Clinical benefit rate (CBR) per the CRAC and investigator assessment,

respectively

- Duration of response (DOR) per the CRAC and investigator assessment,

respectively

Response assessment will be based on RECIST v1.1.

- Changes in patient reported outcomes (PROs) as measured by European

Organization for Research and Treatment of Cancer (EORTC) Quality of Life

Questionnaire (QLQ-C30) and Lung Cancer Module (QLQ-LC13)

- Safety endpoints will be summarized using data from the Safety set.

Timepoints of evaluation:

Disease progression will be defined as radiographic progression of disease by

RECIST version 1.1.

PFS, ORR, CBR, DOR - From randomization to disease progression, or death of any

cause, whichever occurs first.

Changes in PROs - From baseline (the assessment prior to first dose) to disease

progression, or death of any cause, whichever occurs first.

Safety endpoints - From baseline to specified time points throughout the study.

Study description

Background summary

Small cell lung cancer (SCLC) is an important unmet medical need, representing 15-20% of the 220,000 annual new cases of lung cancer. SCLC has been staged using the Veterans Administration (VA) staging system as limited versus extensive stage disease. Approximately one-third of newly diagnosed patients have limited stage disease while the rest has extensive stage.

Standard initial chemotherapy for all patients with a suitable performance status consists of a platinum salt (carboplatin or cisplatin) in combination with a second agent (usually etoposide or irinotecan). Response rates to initial therapy are high, ranging from 60 - 70% (for extensive stage). However,

responses are typically not durable and recurrence rates are high, leading to median survival of approximately 9 - 11 months.
Extensive stage disease subjects achieving SD or better during first-line platinum-based therapy have median progression-free survival (PFS) of approximately 2.1 - 2.3 months and median OS of approximately 6.9 - 8.9 months from the completion of first-line therapy. Exploration of clinical benefit maintenance strategies in extensive disease SCLC with the goal of prolonging PFS and OS after completion of first-line standard therapies is therefore warranted.

The positive results of a phase 1 trial support the further clinical development of Rova-T.

Study objective

The primary objective of the study is to evaluate if rovalpituzumab tesirine improves progression-free and overall survival in subjects with extensive-stage SCLC who have ongoing clinical benefit (SD, PR, or CR) following the completion of 4 cycles of first-line, platinum-based chemotherapy (cisplatin or carboplatin plus irinotecan or etoposide) compared to placebo.

The secondary objectives of the study are to evaluate rovalpituzumab tesirine anti-tumor activity by determining objective response rate (ORR), clinical benefit rate (CBR), duration of response (DOR), and to assess change in patient reported outcomes (PRO) with EORTC QLCC30/LC13 questionnaires.

Study design

This is the first randomized, double-blind, multicenter, Phase 3 study comparing Rova-T versus placebo as maintenance therapy following first-line platinum-based therapy in subjects with extensive-stage SCLC.

Upon completion of first-line chemotherapy, eligible subjects must be offered prophylactic cranial irradiation (PCI), if offering this procedure is not contradictory to country or institutional guidelines. Subjects receiving PCI must complete it prior to randomization into the study.

Subjects will be assigned in a 1:1 ratio to receive Rova-T or placebo in combination with dexamethasone or placebo on day 1 of a 6-week cycle, omitting every third cycle until disease progression. Survival Follow-up will continue until the endpoint of death, the subject becomes lost to follow-up or withdraws consent or termination of the study by AbbVie, whichever occurs first.

Randomization will be stratified by best response to first-line platinum-based chemotherapy (SD vs. PR/CR), DLL3 expression, history of central nervous system (CNS) metastases (Yes vs. No), and for subjects with no history of CNS

metastases, PCI vs. no PCI.

Intervention

Subjects will receive one of the following treatments: 0.3 mg/kg Rova-T or placebo IV infusion. Subjects will receive their assigned therapy on Day 1 of each 6-week cycle, omitting every third cycle. Furthermore, subjects will also receive 8 mg orally (PO) of dexamethasone or placebo twice daily on Day -1, Day 1 (the day of dosing), and Day 2 of each 6-week cycle, also omitting every third cycle.

Disease progression will be assessed by study-specific CT every 6 weeks. An echocardiogram will be done before every cycle. Subject will be asked to monitor their weight via a daily fluid retention questionnaire. Furthermore, subjects will be advised to protect themselves from sunlight for this might induce skin reactions.

An end of treatment visit will be conducted when disease progression occurs. For all subjects who discontinue study treatment for reasons other than disease progression, the first follow-up visit will occur at 6 weeks (± 1 week) after the last Disease Response/Assessment, then every 6 weeks (± 1 week) until disease progression or initiation of new anti-cancer therapy, whichever occurs first. At disease progression an optional collection of fresh tumor tissue may be conducted.

After disease progression or if subjects stop treatment and decline further study radiographic assessments prior to the endpoint of disease progression, subjects will be followed for subsequent anti-cancer therapies (dates and responses), as well as survival status. This will occur every 6 weeks (± 1 week) until the endpoint of death, the subject becomes lost to follow-up or withdraws consent, or termination of the study by AbbVie, whichever occurs first.

Study burden and risks

Although response rates to first-line platinum-based chemotherapy in ED SCLC is high, SCLC nearly invariably recurs, which may be attributed to the relative resistance of cancer stem cells (CSCs)/ tumor-initiating cells (TICs) to conventional chemotherapy. By targeting this resistant, residual cell population, Rova-T has a unique mechanistic rationale for benefit in post-chemotherapy maintenance setting.

The most frequent treatment-emergent adverse event (TEAE) terms considered related to Rova-T have included fatigue, pleural effusion and peripheral edema, while the most frequent, related TEAE groups of Grade 3 or higher have included thrombocytopenia, serosal effusions, and skin reactions. Safety assessments

will include regular assessments at protocol-specified time points of routine physical examination, laboratory and imaging tests, echocardiograms, a fluid retention questionnaire, daily weights, and spot urine protein testing. This concludes that subjects participating in the study will have a higher burden because of participation in the trial. This burden consists of extra visits to the site, an Echocardiogram, additional blood draws besides the standard safety labs. In addition, the subjects will complete daily fluid retention questionnaires. Furthermore, every 6 weeks a CT will be performed.

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

• Histologically or cytologically confirmed extensive-stage disease small cell lung cancer (ED SCLC at initial diagnosis) with ongoing clinical benefit (stable disease [SD], partial response

[PR], or complete response [CR] per RECIST v1.1) following completion of 4 cycles of first-line platinum-based therapy
• Subject is eligble to be randomized at least 3 but no more than 9 weeks from day 1 of the fourth cycle platinum-based chemotherapy.
• Participants with a history of central nervous system (CNS) metastases prior to the initiation of first-line platinum-based chemotherapy must have received definitive local treatment and have
documentation of stable or improved CNS disease status
• Eastern Cooperative Oncology Group (ECOG) performance score of 0 or 1
• Participants must have adequate bone marrow, renal and hepatic function

Exclusion criteria

• Any prior systemic chemotherapy, small molecule inhibitors, immune checkpoint inhibitors, other monoclonal antibodies, antibody-drug conjugates, radioimmunoconjugates, T-cell or other cell-based or biologic therapies, or any other anti-cancer therapy than that described in inclusion criteria 3-5 for SCLC
• Any disease-directed radiotherapy (except prophylactic cranial irradiation, palliative radiotherapy to a radiographically documented non-progressing lesion for symptom control, or pre-planned radiotherapy for CNS metastases present prior to start of first-line therapy and non-progressing) after last dose of first-line chemotherapy.
• Prior exposure to a pyrrolobenzodiazepine (PBD)- or indolinobenzodiazepine-based drug, prior participation in a rovalpituzumab tesirine clinical trial, or known hypersensitivity or other contraindications to rovalpituzumab tesirine or excipient contained in the drug formulation.

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:	Completed
Start date (anticipated):	30-01-2018
Enrollment:	21
Type:	Actual

Medical products/devices used

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

Ethics review

Approved WMO Date:	02-05-2017
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	29-05-2017
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	03-08-2017
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	22-08-2017
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	12-10-2017
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)

Approved WMO Date:	28-11-2017
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	02-01-2018
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	08-02-2018
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	24-10-2018
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	29-11-2018
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	20-02-2019
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	14-05-2019
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	25-06-2019
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	16-08-2019
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO	

Date:	23-12-2019
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	20-01-2020
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)

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
EudraCT	EUCTR2016-003503-64-NL
ClinicalTrials.gov	NCT03033511
CCMO	NL60055.042.17

Study results

Date completed:	03-09-2019
Results posted:	16-12-2020

First publication
01-01-1900