A Randomized, Open-Label, Multicenter, Phase 3 Study of Rovalpituzumab Tesirine Compared with Topotecan for Subjects with Advanced or Metastatic DLL3high Small Cell Lung Cancer (SCLC) who have First Disease Progression During or Following Front-Line Platinum-Based Chemotherapy (TAHOE)

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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-OMON49877

Source
ToetsingOnline

Brief title
M16-289

Condition

- Respiratory and mediastinal neoplasms malignant and unspecified

Synonym
advanced or metastatic lung cancer, small cell lung cancer

Research involving
Human

Sponsors and support

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

Intervention

Keyword: Rovalpituzumab Tesirine, SCLC, Topotecan

Outcome measures

Primary outcome

- Overall survival (OS)

Timepoints of evaluation of this endpoint:

- Overall Survival is defined as the time from the date of randomization to the date of death from any cause (i.e., date of subject*s death - date of randomization +1)

Secondary outcome

- Progression-free survival (PFS) based on the CRAC per RECIST v1.1,

- Duration of objective response (DOR) based on the CRAC per RECIST v1.1,

- Patient reported outcomes (PROs)

Timepoint(s) of evaluation of this endpoint

- PFS is based on independent review of tumor assessment, defined as the time from randomization to documented CRAC-assessed disease progression or death

from any cause (whichever occurs earlier).

- DOR is defined as the time between the date of the first response (CR or PR,

whichever is recorded first) to the date of the first documented tumor

progression (per RECIST 1.1) or death due to any cause, whichever comes first.

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 in the US. SCLC can be staged using the Veterans Administration Lung Study Group (VA LG) classification, which distinguishes between limited and extensive stage disease, or the TNM-classification. Approximately two-third of newly diagnosed subjects will have extensive stage SCLC.

Systemic chemotherapy (platinum salt in combination with etoposide or irinotecan) remains the cornerstone of therapy for all stages of SCLC. For subjects with limited stage disease, concurrent or sequential involved-field thoracic radiotherapy is indicated. Response rates to initial therapy are high; ranging from 70 - 90% for limited stage and 60 - 70% for extensive stage. However, responses are typically not durable and recurrence rates are high in the limited stage disease and nearly universal in the extensive stage disease, leading to median survivals of 14 - 20 months and 9 - 11 months, respectively.

For subjects with relapsed/recurrent SCLC, options are limited. The topoisomerase I inhibitor topotecan is currently the only agent with several global regulatory approvals, but its activity is less than impressive and associated toxicity is significant. Therefore, exploration of new therapies in second line SCLC is warranted, with the goals of extending disease control and improving overall survival.

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

Study objective

The primary objective is to assess treatment with rovalpituzumab tesirine improves overall survival rate (OS) compared to topotecan in subjects with DLL3high SCLC who have first disease progression during or following front-line platinum based chemotherapy.

The secondary objectives are:
1. Assess if treatment with rovalpituzumab tesirine improves progression free survival (PFS) compared to topotecan in subjects with advanced or metastatic DLL3high SCLC who have first disease progression during or following front-line platinum based chemotherapy,
2. Compare the duration of response of object response between two arms,
3. To assess the pharmacokinetics (PK) and immunogenicity of rovalpituzumab tesirine,
4. Assess the effect on patient reported outcomes (i.e. health-related quality of life and symptom assessment) due to treatment with rovalpituzumab tesirine compared to topotecan in subjects with DLL3high SCLC who have first disease progression during or following front-line platinum based chemotherapy.
5. To assess if the treatment with rovalpituzumab tesirine improves objective response rate and clinical benefit rate compared to topotecan in subjects with advanced advanced or metastatic DLL3high SCLC who have first disease progression during or following front-line platinum based chemotherapy.
6. To compare the duration of objective response between two arms.

Study design

This is a phase 3 randomized, open-label, multicenter study comparing Rova-T with topotecan in subjects with advanced or metastatic DLL3high SCLC who have first disease progression during or following front-line platinum-based chemotherapy. Subjects will be randomized in a 2:1 ratio to receive Rova-T or topotecan. Subjects receiving Rova-T will also receive 8 mg orally of dexamethasone twice daily on Day -1, Day 1 and Day 2 of each cycle in which Rova-T is administered. 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 prior history of brain metastases (yes versus no), prior PCI (yes vs. no) for subjects with no prior history of brain metastases, sensitivity to first line platinum-based regimen and LDH (> ULN vs. <= ULN) at screening. Approximately 411 subjects will be enrolled worldwide.

Intervention

Subjects in the Rova-T arm will receive Rova-T (IV) on Day 1 of each 42-day cycle, and 8 mg orally of dexamethasone twice daily on Day -1, Day 1 and Day 2 of each cycle in which Rova-T is administered. The regimen of this arm will be administered for 2 cycles unless earlier discontinuation is warranted, or up to 2 additional cycles for subjects who satisfy the criteria as specified in the protocol. Subjects in this arm have clinic visits conducted for Screening, Days 1/22 of each cycle, End of Treatment (EoT) and every 6 weeks during the post-treatment follow-up phase. Subjects will be advised to avoid unprotected sun exposure due to Rova-T related skin photosensitivity.

Subjects in the topotecan arm will receive topotecan (IV) on Days 1 - 5 of each 21-Day cycle (topotecan may be administered at a lower dose if required by the local label). All subjects in this arm will continue to receive topotecan until disease progression, unless earlier discontinuation is warranted due to unacceptable toxicity or any other reason. Subjects in this arm will have clinic visits conducted for Screening, Days 1-5 of each cycle, EoT and every 6 weeks during the post-treatment follow-up phase.

For both arms, disease progression will be assessed every 6 weeks by a CT-scan. An echocardiogram will be done on Day 1 of each cycle and the EoT visit to assess pericardial effusion. Subjects will be asked to monitor their weight via a daily fluid retention questionnaire.

An EoT visit will be conducted once disease progression is identified or when a subject meets other criteria for study treatment discontinuation. The EoT visit is the last visit during the treatment phase before a subject enters the post treatment follow-up (PTFU) phase and/or Survival follow-up phase.

For all subjects without disease progression, PTFU visits will be conducted every 6 weeks after the last dose of investigational product. After disease progression or study discontinuation, the subject enters the survival follow-up period. During this period, the subject will be contacted every 6 weeks for subsequent anti-cancer therapies as well as survival status. These visits 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

The burden for the subjects consists of extra visits to the site, two ECGs, two echocardiograms, additional blood draws on top of the standard lab draws, daily weights, completion of QoL questionnaires and the fluid retention questionnaire, 6-weekly CT-scans and four urinalyses. Subjects will remain in the study until progression of disease is identified or when other discontinuation criteria have been met. While the subject is still on the study, no additional anti-cancer therapies may be started.

The most frequent treatment-emergent adverse events (TEAE) terms considered related to Rova-T have included fatigue (35%), pleural effusion (28%) and peripheral edema (26%), while the most frequent, related TEAE groups of Grade 3 or higher have included thrombocytopenia (10%), serosal effusions (13%), and skin reactions (10%). In addition, preclinical toxicology studies conducted in the rat and the cynomolgus monkey have identified bone marrow, lung, liver and kidney as potential sources of clinical adverse events.

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) Subjects must be an age of 18 years or older, providing written informed consent
2) Histologically or cytologically confirmed advanced or metastatic SCLC with documented first disease progression after or during front-line platinum-based systemic regimen.
3) Tumor must have high DLL3 expression (DLL3high) defined as having > 75% tumor cells staining positive according to the VENTANA DLL3 (SP347) IHC Assay. Archived or fresh tumor material can be used for the DLL3 testing.
4) Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1.
5) Females of childbearing potential must have a negative serum

pregnancy test result at Screening, and a negative urine pregnancy test at randomization. Females of non-childbearing potential (either postmenopausal or permanently surgically sterile) at Screening do not require pregnancy testing.

Exclusion criteria

1) Any significant medical condition that, in the opinion of the investigator or Sponsor, may place the subject at undue risk from the study, including but not necessarily limited to uncontrolled hypertension and/or diabetes, clinically significant pulmonary disease or neurological disorder (e.g., seizure disorder active within 6 months)
2) Documented history of a cerebral vascular event (stroke or transient ischemic attack), unstable angina, myocardial infarction, or cardiac symptoms consistent with New York Heart Association (NYHA) Class III - IV within 6 months prior to their first dose of study drug.
3) Subject has known leptomeningeal metastases
4) Subject has Isolated CNS disease progression with no evidence of progression outside of CNS
5) Subject has more than one prior systemic therapy regimen for SCLC (prior systemic maintenance therapy following front-line platinum based regimen, administered as part of clinical trial is allowed)

Study design

Design

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

Recruitment

NL
Recruitment status: Completed

Start date (anticipated):	30-08-2017
Enrollment:	9
Type:	Actual

Medical products/devices used

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

Ethics review

Approved WMO Date:	21-11-2002
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	06-06-2017
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	19-07-2017
Application type:	First submission
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:	31-01-2018
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	23-10-2018
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	07-11-2018
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	11-12-2018
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	06-02-2019
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	06-03-2019
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	18-06-2019
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	19-07-2019
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	15-10-2019
Application type:	Amendment

Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	11-11-2019
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	14-11-2019
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	12-12-2019
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	EUCTR2016-003726-17-NL
ClinicalTrials.gov	NCT03061812
CCMO	NL60441.042.17

Study results

Date completed:	10-02-2020
Results posted:	26-02-2021

First publication
23-02-2021

URL result
URL
Type
int
Naam
M2.2 Samenvatting voor de leek
URL

Internal documents
File