A Phase 1 Dose Escalation and Phase 2 Randomized Double-Blind Study of Veliparib in Combination with Carboplatin and Etoposide as a Therapy of Treatment-Naïve Extensive Stage Disease Small Cell Lung Cancer.

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The objectives of the Phase 1 dose escalation are:Primary Objectives:* To establish the Maximum Tolerated Dose (MTD) and to establish the Recommended Phase 2 Dose (RPTD) for veliparib in combination withcarboplatin and etoposide.* To evaluate the...

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

Summary

ID

NL-OMON44322

Source
ToetsingOnline

Brief title
M14-361

Condition

- Respiratory and mediastinal neoplasms malignant and unspecified

Synonym
extensive stage disease lung cancer, small cell lung cancer

Research involving

Human

Sponsors and support

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

Intervention

Keyword: ED SCLC, PARP inhibitor

Outcome measures

Primary outcome

Objective Response Rate

The proportion of subjects with objective response (CR or PR) as assessed by the investigator

Progression-Free Survival

Progression-Free Survival will be defined as the number of days from the date of randomization to the date of earliest disease progression or death.

Overall Survival

Overall survival will be defined as the number of days from the date of randomization to the date of death.

Duration of Overall Response

Duration of overall response will be defined as the number of days from the date of first response (CR or PR) to the earliest documentation of progressive disease.

Secondary outcome

Not applicable.

Study description

Background summary

Small cell lung cancer (SCLC) is a neuroendocrine carcinoma that exhibits aggressive behavior, rapid growth, and early spread to distant sites. It constitutes approximately 15% of lung carcinomas. SCLC is staged as limited or extensive stage disease (LD and ED SCLC, respectively). At presentation, 60% to 70% of SCLC cases in the United States are diagnosed as extensive-stage disease, for which at present there is no curative treatment. There has been no significant improvement in the clinical outcome for subjects with ED SCLC in the last 2 decades, and
it remains one of the most fatal cancers.

Veliparib is a PARP inhibitor. PARP is a nuclear enzyme that recognizes DNA damage and facilitates DNA repair. Inhibition of PARP results in less efficient DNA repair following a DNA damaging insult. As cancer cells are genetically unstable, these cells are more susceptible than normal tissues to cytotoxicity induced by DNA-damaging agents and PARP-inhibitors. The combination of DNA damaging cytotoxic chemotherapy (cisplatin and etoposide) and a pharmacologic inhibitor of DNA damage repair enzyme, poly (ADP) Ribose polymerase (PARP), may result in greater cytotoxicity and antitumor efficacy of the cytotoxic agents.
It is postulated that that enhanced efficacy may translate into improved disease progression without concomitant increased toxicity in subjects with extensive stage SCLC.

Study objective

The objectives of the Phase 1 dose escalation are:

Primary Objectives:
* To establish the Maximum Tolerated Dose (MTD) and to establish the Recommended Phase 2 Dose (RPTD) for veliparib in combination with carboplatin and etoposide.
* To evaluate the pharmacokinetic interaction between veliparib and etoposide.

Secondary Objective:
* To evaluate the safety of maintenance veliparib monotherapy at 400 mg BID in subjects completing 4 cycles of carboplatin, etoposide and veliparib without evidence of disease progression.

The objectives of Phase 2 are:

Primary Objective:
* To evaluate if veliparib in combination with carboplatin and etoposide followed by veliparib maintenance monotherapy results in improved progression free survival (PFS) versus placebo in combination with carboplatin and etoposide followed by placebo monotherapy in subjects with treatment-naïve ED SCLC.

Secondary Objectives:
* To evaluate if veliparib in combination with carboplatin and etoposide followed by placebo monotherapy results in improved progression free survival (PFS) versus placebo in combination with carboplatin and etoposide followed by placebo monotherapy in subjects with treatment-naïve ED SCLC.
* To evaluate if veliparib in combination with carboplatin and etoposide results in improved objective response rate (ORR) versus placebo in combination with carboplatin and etoposide, at the time of completion of combination therapy.
* To evaluate if veliparib in combination with carboplatin and etoposide followed by veliparib maintenance monotherapy results in improved overall survival (OS) versus placebo in combination with carboplatin and etoposide followed by placebo monotherapy.
* To evaluate if veliparib in combination with carboplatin and etoposide followed by placebo monotherapy results in improved overall survival (OS) versus placebo in combination with carboplatin and etoposide followed by placebo monotherapy.
* To further evaluate the safety of veliparib in combination with carboplatin and etoposide followed by veliparib maintenance monotherapy.

Tertiary Objectives are:
* To evaluate if veliparib in combination with carboplatin and etoposide followed by veliparib maintenance monotherapy results in improved duration of overall response (DOR) versus placebo in combination with carboplatin and etoposide followed by placebo monotherapy.
* To evaluate if veliparib in combination with carboplatin and etoposide followed by placebo monotherapy results in improved duration of overall response (DOR) versus placebo in combination with carboplatin and etoposide followed by placebo monotherapy.
* To compare PFS and OS of subjects treated with veliparib in combination with carboplatin and etoposide followed by veliparib maintenance to PFS and OS of subjects treated with veliparib in combination with carboplatin and etoposide followed by placebo maintenance.
* To evaluate performance status.

Study design

This Phase 1, open-label, dose escalation/Phase 2 randomized double-blind study

of veliparib in combination with carboplatin and etoposide and maintenance veliparib monotherapy. Subjects in Phase 1 will be group sequentially assigned to the ascending dose levels of veliparib in combination of standard carboplatin/etoposide regimen based on the observed toxicities. Subjects in Phase 2 will be randomized in a 1:1:1 ratio to one of the following treatment arms: carboplatin, etoposide, placebo followed by placebo maintenance, or carboplatin, etoposide, veliparib followed by veliparib maintenance, or carboplatin, etoposide, veliparib followed by placebo maintenance.

Approximately 215 adult male or female subjects diagnosed with extensive stage disease SCLC or other advanced/metastatic solid tumors will be selected to participate in the study according to the inclusion/exclusion criteria. The study was designed to enroll approximately 35 subjects in Phase 1 and approximately 180 subjects in Phase 2 to meet scientific and regulatory objectives without enrolling an undue number of subjects in alignment with ethical considerations.

Intervention

Screening procedures should be performed within 28 days prior to Cycle 1 Day -2. If the screening visit is performed greater than 7 days prior to Cycle 1 Day -2, the physical exam, laboratory tests, and pregnancy test (for female subjects of childbearing potential) must be repeated on Cycle Day 2. Vital signs and performance status assessments will be performed on Cycle 1 Day 2 for all subjects. Baseline radiographic tumor assessments per computed tomography (CT)/magnetic resonance imaging (MRI) of the chest, abdomen, and head will be conducted within 14 days prior to Cycle 1 Day -2.

Dosing of oral veliparib/placebo (placebo only in phase 2) will begin 2 days prior to the start of the carboplatin/etoposide infusion on C1D1 and will continue twice a day (BID) through C1D5 (7 consecutive days). Carboplatin (AUC 5 mg/ml/min) will be administered intravenously on Day 1 of every 21-day cycle (except for Cycle 2 which is administered on Day 2 in Phase 1). Etoposide (100 mg/m2) will be administered
intravenously on Days 1, 2 and 3 of every 21-day cycle. Etoposide will be administered prior to carboplatin. On the days of chemotherapy veliparib will be administered after the premedications are given for etoposide, prior to the infusion of etoposide.

Phase 1 subjects with SD, PR, or CR at the completion of all scheduled combination therapy cycles (4 cycles) will receive veliparib (400 mg) monotherapy, BID continuously in 21-day cycles starting on Day 1 of each cycle. Phase 2 subjects with SD, PR or CR at the completion of combination therapy cycles (up to 6 cycles) will receive veliparib (400 mg) or placebo monotherapy, BID continuously in 21-day cycles starting on Day 1 of each cycle.

Tumor assessments will be performed until disease progression for up to 24

months from the first dose of study drugs. Tumor assessment and assessment of response will occur every 6 weeks (± 1 week) for the first 24 weeks after the first dose of study drugs, then every 9 weeks (± 1 week) thereafter.

Post treatment tumor assessments will be collected via EDC at monthly intervals (or as requested by the sponsor to support data analysis) beginning on the date the subject is registered off study and continuing for up to two (2) years on all subjects until the endpoint of death, the subject has become lost-to follow-up, or if AbbVie terminates the study.

All subjects will be followed for survival information (i.e., the date and cause of death or last known alive date if not deceased) unless the subject requests to be withdrawn specifically from study survival follow-up.

Study burden and risks

The burden for the subject consist of extra visits to the site, ECGs, additional blood draws besides the standard safety labs. Tumor assessment and assessment of response will occur every 6 weeks (± 1 week) for the first 24 weeks after the first dose of study drugs, then every 9 weeks (± 1 week) thereafter.

Subjects will receive veliparib/placebo (placebo only in phase 2) in combination with carboplatin/etoposide for up to 4 cycles of treatment (additional 2 cycles of combination therapy may be administered only in phase 2) , followed by veliparib/placebo (placebo only in phase 2) monotherapy.

Risks in this study include toxicity from the addition of veliparib to standard therapy. Preliminary safety data from several Phase 1 and Phase 2 studies indicate that veliparib is tolerated in combination with carboplatin and paclitaxel at doses of up to 120 - 200 mg BID, and with cisplatin and etoposide at the maximum tested dose of 100 mg BID. Standard clinical practices to manage the toxicity of carboplatin + etoposide are well established. Toxicity will be closely monitored at all study visits. Toxicities of veliparib expected to overlap with the toxicity of carboplatin + etoposide regimen include nausea/vomiting and myelosuppression. Other potential risks of veliparib administration, identified in preclinical studies or based on pharmacological mechanism, but not confirmed in clinical studies must also be considered. These risks include seizures, changes in testes/ovaries, toxicity to the developing fetus and secondary malignancies.

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. Subject with histologically or cytologically confirmed extensive stage SCLC which is newly diagnosed and chemotherapy naïve.;2. Phase 1 ONLY: histologically or cytologically confirmed advanced/metastatic solid tumors for which carboplatin/etoposide treatment is considered appropriate.;3. Subject in Phase 2 only: must have measureable disease per RECIST 1.1.;4. Subjects with ED SCLC must consent to provide available archived formalin fixed paraffin embedded (FFPE) tissue sample of SCLC lesion (primary or metastatic) for central review and biomarker analysis.;5. Subject has an Eastern Cooperative Oncology Group (ECOG) performance score of 0 to 1.;6. Subject must be >= 18 years of age.;7. Subject must have adequate hematologic, renal and hepatic function as follows:
• Bone Marrow: Absolute neutrophil count ANC >= 1,500/mm3 (1.5 × 10e9/L); White blood cells >= 3,000/mm3 (3 × 10e9/L); Platelets >= 100,000/mm3 (100 × 10e9/L); Hemoglobin >= 9 g/dL (5.58 mmol/L)

• Renal function: creatinine <= ULN or if creatinine > ULN calculated creatinine clearance via the Cockroft Gault formula of >= 50 mL/min
• Hepatic function:
- Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) <= 2.5 × upper limits of normal (ULN). For subjects with liver metastases, AST and ALT <= 5 × ULN;
- Bilirubin: <= 1.5 × ULN; for subjects with Gilbert's syndrome bilirubin > 1.5 × ULN is allowed if no symptoms of compromised liver function are present.;8. Subject must be able to swallow pills.;9. Female and male patients of fertile age, and/or their partners should use contraception. If male, subject and subject's female partner(s) of childbearing potential should practice at least one of the following methods of birth control. If female, subject must be either postmenopausal for at least 1 year, surgically sterile (bilateral tubal ligation, bilateral oophorectomy or hysterectomy), or the subject and the subject's male partner(s) practicing at least one of the following methods of birth control:
• total abstinence from sexual intercourse (if it is the subject's preferred and usual lifestyle; for minimum one complete menstrual cycle prior to study drug administration and to extend 6 months after treatment);
• vasectomized subject or partner(s);
• hormonal contraceptives (oral, parenteral or transdermal) for at least 90 days prior to study drug administration for the subject or subject's female partner(s);
• intrauterine device (IUD) for the subject or subject's female partner(s); or
• double-barrier method (condoms, contraceptive sponge, diaphragm or vaginal ring with (spermicidal jellies or creams) for the subject or subject's female partner(s). ;If hormonal contraceptives are used, the specific contraceptive must have been used for at least 90 days prior to study drug administration. If the subject or subject's female partner(s) is currently using a hormonal contraceptive, she should also use a barrier method during this study and for 6 months (or per local label) after study completion. ;Female subjects must have negative results for pregnancy tests performed:
• at Screening on a serum specimen obtained within 7 days prior to initial study drug administration, and
• prior to dosing on a urine sample obtained C1D-2 unless the serum pregnancy test was collected within 7 days of C1D-2. ;10. Must voluntarily sign and date each informed consent, approved by an Independent Ethics Committee (IEC)/Institutional Review Board (IRB), prior to the initiation of any screening or study-specific procedures.

Exclusion criteria

1. Phase 1 ONLY: Subject has had any prior anti-cancer therapy other than:
* Hormonal, non-myelosuppressive, biologic, targeted, or immune therapy (must be completed >= 4 weeks prior to Cycle 1 Day -2).
* One line of cytotoxic chemotherapy (must be completed >= 4 weeks prior to Cycle 1 Day -2).
* Adjuvant/neoaduvant radiotherapy (must be completed >= 12 months prior to Cycle 1 Day -2, with field not involving > 10% of bone marrow reserve).;2. Phase 2 ONLY: Subject has had any prior chemotherapy, radiotherapy, investigational anti-cancer agents or biologic therapy for the disease under study. Single non-target lesion irradiation with intent of symptom

palliation is allowed if >= 2 weeks prior Cycle 1 Day -2.;3. Subject has known hypersensitivity to etoposide, platinum compounds or veliparib.;4. Phase 1 ONLY: Subject has received prior myelopoietic growth factors.;5. Subject has current central nervous system (CNS) or leptomeningeal metastases or history of CNS or leptomeningeal metastases. If CNS progression is suspected, a head CT should be performed at screening.;6. Subject has a history of seizures within 12 months of Cycle 1 Day -2 or diagnosed neurological condition placing subject at the increased risk of seizures.;7. Subject has received traditional herbal anti-cancer medicine (e.g. Chinese, Asian, etc) within 14 days prior to Cycle 1 Day -2.;8. Subject has had major surgery within 6 weeks prior to Cycle 1 Day -2 (subjects must have
completely recovered from any previous surgery prior to Cycle 1 Day -2).;9. Subject has clinically significant and uncontrolled major medical condition(s) including but not limited to:
* Uncontrolled nausea/vomiting/diarrhea;
* Active uncontrolled infection;
* History of hepatitis B (HBV) with surface antigen (HBsAg) positivity within 3 months prior to the date of informed consent for this study (if no test has been performed within 3 months, it must be done at screening);
* History of hepatitis C (HCV) with HCV RNA positivity within 3 months prior to the date of informed consent for this study (if no test has been performed within 3 months it must be done
at screening);
* Symptomatic congestive heart failure (New York Heart Association [NYHA] class >= II);
* Unstable angina pectoris or cardiac arrhythmia;
* Psychiatric illness/social situation that would limit compliance with study requirements;
* Any other medical condition, which in the opinion of the Investigator, places the subject at an
unacceptably high risk for toxicities.;10. Subject is pregnant or lactating.;11. The subject has a history of another active cancer within the past 3 years except cervical cancer in situ, in situ carcinoma of the bladder, squamous or basal cell carcinoma of the skin or another in situ cancer that is considered cured by the investigator (e.g., in situ prostate cancer, breast ductal carcinoma in situ [DCIS]).

Study design

Design

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):	24-06-2015
Enrollment:	19
Type:	Actual

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:	Placebo
Generic name:	Placebo
Product type:	Medicine
Brand name:	Veliparib
Generic name:	Veliparib

Ethics review

Approved WMO Date:	30-10-2014
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	30-01-2015
Application type:	Amendment

Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	10-03-2015
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	23-04-2015
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	18-05-2015
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	06-07-2015
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	10-07-2015
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	28-08-2015
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	21-09-2015
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	20-10-2015
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	03-12-2015
Application type:	Amendment

Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	11-02-2016
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	26-07-2016
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	15-08-2016
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	27-10-2016
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	28-10-2016
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	02-02-2017
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	21-03-2017
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	04-09-2017
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	15-09-2017
Application type:	Amendment

Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	27-10-2017
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:	02-08-2018
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	22-08-2018
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	17-12-2018
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	22-08-2019
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	EUCTR2014-001764-35-NL
ClinicalTrials.gov	NCT02289690
CCMO	NL50299.042.14

Study results

Date completed: 04-12-2018

Results posted: 24-04-2020

First publication
02-04-2020

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

Internal documents
File