Randomized, Double-Blind, Multicenter, Phase 3 Study Comparing Veliparib Plus Carboplatin and Paclitaxel Versus Placebo Plus Carboplatin and Paclitaxel in Previously Untreated Advanced or Metastatic Squamous Non-Small Cell Lung Cancer (NSCLC)

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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-OMON44246

Source
ToetsingOnline

Brief title
M11-089

Condition

- Respiratory and mediastinal neoplasms malignant and unspecified

Synonym
advanced or metastatic lung cancer, squamous non-small cell lung cancer

Research involving
Human

Sponsors and support

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

Intervention

Keyword: PARP inhibitor, squamous NSCLC

Outcome measures

Primary outcome

Overall Survival (OS) in the group of current smokers; Time to death starting

on randomization.

Secondary outcome

Progression-free Survival (PFS) in the group of current smokers and PFS in the

whole population: number of days randomization till Progressive Disease or

death.

Objective Response Rate (ORR) in the group of current smokers and ORR in the

whole population: proportion of subjects with complete or partial response.

Study description

Background summary

Most NSCLC patients are diagnosed at an advanced stage, conferring a poor prognosis. Current standard therapy for NSCLC provides time-to-progression of 4 to 6 months and overall survival of 10 to 12 months.

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.
Preliminary data of a phase 2 study showed an improvement in median progression-free survival of approximately 2 months and an improvement in overall survival of > 2 months among 76 squamous NSCLC subjects treated with veliparib. This suggest the addition of veliparib to carboplatin and paclitaxel may improve outcome of patients with advanced or metastatic squamous NSCLC.

Study objective

The primary objective of the study is to assess whether the addition of oral veliparib to carboplatin and paclitaxel will improve overall survival (OS) in current smokers when compared to the addition of placebo to carboplatin and paclitaxel, in subjects with previously untreated locally advanced and metastatic squamous NSCLC.

The secondary objectives of the study are to assess the effects of veliparib combination therapy on: progression-free survival (PFS) in current smokers, PFS in the whole population, Objective Reponse Rate (ORR) in current smokers and ORR in the whole population.

The tertiary objectives are to assess duration of overall response (DOR), Quality of Life (as assessed by the European Quality of Life-5 Dimensions [EQ-5D-5L], EORTC-QLQ-C30, and EORTC-LC13 questionnaires), and ECOG performance status.

Study design

This is a Phase 3, randomized, double-blind, multicenter study evaluating the efficacy, safety, and tolerability of veliparib plus carboplatin and paclitaxel versus placebo plus carboplatin and paclitaxel in previously untreated subjects with metastatic or advanced squamous NSCLC. Approximately 975 subjects will be enrolled at approximately 250 sites. Subjects will be randomized in a 1:1 ratio to veliparib 120 mg BID or placebo BID. Subject randomization will be stratified by tumor stage (locally advanced versus metastatic), smoking history (current smoker versus never smoked versus past smoker), ECOG performance status (0 versus 1) and region (Western Europe/Australia/Americas versus Eastern Europe/Russia).

Intervention

Screening procedures, quality of life assessment within 21 days, and baseline

radiographic tumor assessments within 28 days will be performed prior to starting treatment on C1D-2 (i.e., the first day veliparib/placebo is administered).

Dosing of oral veliparib/placebo will begin 2 days prior to the start of the carboplatin/paclitaxel infusion on C1D-2 and will continue twice a day (BID) through C1D5 (7 consecutive days). All subjects will receive carboplatin (AUC 6 mg/mL/min) and paclitaxel (200 mg/m2) IV infusion starting on Day 1 of each cycle. Subjects will continue to receive veliparib/placebo in combination with carboplatin/paclitaxel for up to a maximum 6 cycles of treatment, until unacceptable toxicity occurs, or until radiographic progression.

Subjects who complete 6 cycles of treatment will be followed by assessments every 6 weeks until 1 year after beginning treatment (C1D-2), then every 12 weeks. Assessments will continue until radiographic progression, discontinuation from study for additional cancer treatment, or death. Radiographic tumor assessments will be conducted at baseline, prior to C3D1, prior to C5D1, every 6 weeks until 1 year after beginning treatment (C1D-2), and then every 12 weeks.

All subjects who have a Final Visit < 30 days after the last dose of study drug will have a Follow-up Visit approximately 30 days after the Final Visit.

Survival information will be collected via the eCRF at 2 month intervals beginning on the date of progression and continuing until the endpoint of death, the subject has become lost to follow-up, or AbbVie terminates the study.

Study burden and risks

The burden for the subject consist of extra visits to the site, two times an ECG, additional blood draws besides the standard safety labs. Next to this the subject will complete 3 questionnaires at most visits. Progression of disease will be measured every 6 weeks until 1 year after beginning treatment (C1D-2), and then every 12 weeks.

Subjects will receive veliparib/placebo in combination with carboplatin/paclitaxel for up to a maximum 6 cycles of treatment, until unacceptable toxicity occurs, or until radiographic progression. After that, subjects will go into the post-treatment phase with assessments every 6 weeks until 1 year and then every 12 weeks.

Risks in this study include toxicity from the addition of veliparib to standard therapy. Preliminary safety data from a blinded, randomized Phase 2 study of the proposed combination therapy in subjects with advanced NSCLC suggest low rates of additional toxicities (frequency leukopenia increased < 15% and neutropenia increased < 10%) and no compromise to the delivery of carboplatin

and paclitaxel. Standard clinical practices to manage the toxicity of carboplatin + paclitaxel are well established.
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

Public
AbbVie

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Scientific
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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 must be >= 18 years of age.
2. Life expectancy > 12 weeks (as per Investigator's clinical assessment).
3. Subject must have cytologically or histologically confirmed squamous NSCLC. Subjects with mixed histology tumors will be eligible if the tumor is predominantly squamous histology and

does not include tumor cells with small cell histology. If cytology is used for diagnosis, the sample must be unequivocally and predominantly squamous NSCLC. Subjects must have a pathologist's report confirming squamous NSCLC available for collection by the sponsor.
4. Subject must have advanced or metastatic squamous NSCLC that is not amenable to surgical resection or radiation with curative intent at time of study Screening. Subjects with recurrent squamous NSCLC after surgical treatment that is not amenable to surgical resection or radiation with curative intent are eligible.
5. Subject must have at least 1 unidimensional measurable NSCLC lesion on a CT scan as defined by RECIST (version 1.1).
6. Subject must consent to provide archived sample of squamous NSCLC lesion (primary or metastatic) biomarker analysis.
7. Subject must have no history of brain metastases or evidence of CNS tumors at screening assessment. Subjects with signs or symptoms of CNS involvement will undergo imaging to confirm absence of CNS metastases.
8. Subject must have an Eastern Cooperative Oncology Group (ECOG) Performance Score of 0-1.
9. Subject must be able to take oral medication (PO).
10. Subjects with fluid retention, including ascites or pleural effusion, may be allowed at the discretion of the Investigator.
11. Subject must have adequate bone marrow, renal and hepatic function as follows:
• Bone Marrow: Absolute neutrophil count (ANC) >= 1,500/mm3 (1.5 × 109/L); Platelets >= 100,000/mm3 (100 × 109/L); Hemoglobin >= 9.0 g/dL (5.6 mmol/L);
• Renal function: serum calculated creatinine clearance > 50 mL/min according to the Cockcroft and Gault equation or urine creatinine clearance >50 mL/min;
• Hepatic function: AST and ALT <= 2.5 × ULN unless liver metastases are present, then AST and ALT < 5.0 × ULN; bilirubin <= 1.5 × ULN; or subjects with Gilbert's Syndrome may have a bilirubin >= 1.5 × ULN.
Female and male patients of fertile age, and/or theirs partners should use contraception for at least 6 months after treatment with paclitaxel. 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 labels) after study drug completion.
Female subjects must have negative results for pregnancy tests performed at Screening on a serum specimen obtained within 21 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.
13. Subject must be capable of understanding and complying with parameters as outlined in the protocol and able to consent to participate prior to the initiation of any screening or study-specific procedures.

Exclusion criteria

1. Subject has a known hypersensitivity to paclitaxel or to other drugs formulated with polyethoxylated castor oil (Cremophor).
2. Subject has a known hypersensitivity to platinum compounds.
3. Subject has peripheral neuropathy >= grade 2.
4. Subject has non-squamous NSCLC, or a known EGFR mutation of exon 19 deletion or L858R mutation in exon 21, or a known ALK gene rearrangement. According to NCCN guidelines, EGFR and ALK testing should be performed in subjects with squamous NSCLC who have never smoked or in case of small biopsy specimens (as judged by the investigator) or mixed histology. Such subjects should be tested to confirm absence of EGFR mutation or ALK gene rearrangement according to local standard of care prior to study entry.
5. A history of seizure within 12 months prior to study entry.
6. Subject has received prior cytotoxic chemotherapy (including definitive chemoradiotherapy) for NSCLC, except for adjuvant or neoadjuvant therapy.
7. Subject has received adjuvant or neoadjuvant chemotherapy <= 12 months prior to randomization.
8. Subject has received herbal remedies or non-prescription anti-cancer supplements for cancer treatment <= 2 weeks prior to randomization.
9. Subject has undergone focal External Beam Radiation Therapy (EBRT) <= 2 weeks prior to randomization. EBRT to larger fields (i.e., 100 cm2) should be excluded if < 4 weeks prior to randomization. Radiated lesions may not be considered target lesions.
10. Clinically significant and uncontrolled major medical condition(s) including but not limited to:
* Uncontrolled nausea/vomiting/diarrhea;
* Active uncontrolled infection;
* Symptomatic congestive heart failure;
* Unstable angina pectoris or cardiac arrhythmia;
* Psychiatric illness/social situation that would limit compliance with study requirements;
* History of gross hemoptysis;
* Any medical condition, which in the opinion of the Investigator, places the subject at an unacceptably high risk for toxicities.
11. Subject is pregnant or lactating.

12. Subject has previously been treated with a known PARP inhibitor.
13. The subject has a history of another 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).
14. Any subjects will be excluded if prohibited from participation according to local law.

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):	12-01-2015
Enrollment:	32
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:	Paclitaxel
Generic name:	Paclitaxel
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:	13-06-2014
Application type:	First submission
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	31-07-2014
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	24-09-2014
Application type:	First submission
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	21-10-2014
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	24-10-2014
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	18-12-2014

Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	22-12-2014
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	21-01-2015
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	28-01-2015
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	19-02-2015
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	02-03-2015
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	17-08-2015
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	21-08-2015
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)

Approved WMO Date:	01-03-2016
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	21-03-2016
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	16-08-2016
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	15-09-2016
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	17-08-2017
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	12-10-2017
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	03-11-2017
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	17-07-2018
Application type:	Amendment

Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	06-12-2018
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	18-12-2018
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)

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	EUCTR2013-005020-42-NL
CCMO	NL47784.060.14

Study results

Date completed:	19-07-2019
Results posted:	18-11-2020

URL result
URL
Type

int
Naam
M2.2 Samenvatting voor de leek
URL

Internal documents
File