A Randomized, Open-Label, Multicenter, Phase 3 Trial Comparing Veliparib Plus Carboplatin and Paclitaxel Versus Investigator's Choice of Standard Chemotherapy in Subjects Receiving First Cytotoxic Chemotherapy for Metastatic or Advanced Non-Squamous Non-Small Cell Lung Cancer (NSCLC) and Who Are Current or Former Smokers

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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-OMON47385

Source
ToetsingOnline

Brief title
M14-359

Condition

- Respiratory and mediastinal neoplasms malignant and unspecified

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

Research involving
Human

Sponsors and support

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

Intervention

Keyword: current and former smokers, non-squamous NSCLC, PARP inhibitor

Outcome measures

Primary outcome

The primary efficacy endpoint is overall survival (OS) in LSP positive

subgroup.

Secondary outcome

The secondary efficacy endpoints are

- overall survival in all subjects and in the LSP positive subgroup

- progression-free survival (PFS) in the LSP positive subgroup

- objective response rate (ORR) in the LSP positive subgroup

Study description

Background summary

Lung cancer is the leading cause of cancer-related mortality in both men and women throughout the world. The incidence of non-small cell lung cancer (NSCLC) increases with age; 60% occur in subjects aged 60 years and older, and 30% to

40% occur in subjects aged 70 years and older. Non-small cell lung cancer is divided further into adenocarcinoma (40%), squamous cell carcinoma (40%), and large cell carcinoma histologies. Most NSCLC subjects 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 1227 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.

Data of a double-blind, randomized Phase 2 study of carboplatin and paclitaxel with veliparib or placebo for subjects with advanced NSCLC showed an improvement in median progression-free survival of 1.3 months and an improvement in overall survival of 7.1 months in 95 current smokers with non-squamous NSCLC. This suggests that the addition of veliparib to carboplatin and paclitaxel may improve outcome of current-smokers with advanced or metastatic squamous NSCLC.

Study objective

The primary objective of the study is to assess if treatment with veliparib plus carboplatin and paclitaxel results in improved survival compared to Investigator's choice of standard chemotherapy in Lung Subtype Panel (LSP) positive subjects with metastatic or advanced NSCLC.

The secondary objectives of the study are to assess if treatment with veliparib plus carboplatin and paclitaxel results in improved survival compared to Investigator's choice of standard chemotherapy in the entire study population; to compare progression-free survival (PFS) and to compare objective response rate (ORR) between the two treatment arms in LSP positive subjects or in entire study population.

The tertiary objectives are to compare duration of overall response (DOR), ECOG performance status and Quality of Life (QoL) between the two treatment arms in current smokers or in current plus former smokers.

Study design

This is a Phase 3, randomized, open-label, multi-center study evaluating the efficacy, safety, and tolerability of veliparib plus carboplatin and paclitaxel versus Investigator's choice of standard chemotherapy in subjects receiving first cytotoxic chemotherapy for advanced or metastatic non-squamous NSCLC who are current or former smokers. Subjects will be randomized in a 1:1 ratio to 6

cycles of carboplatin/paclitaxel plus 120 mg BID of veliparib or 6 cycles of Investigator's choice of platinum doublet chemotherapy (carboplatin/paclitaxel, cisplatin/pemetrexed, or carboplatin/pemetrexed). Investigators may elect to administer maintenance pemetrexed regardless of which therapy their subjects are randomized to receive. Following completion of platinum doublet therapy, maintenance pemetrexed is strongly encouraged for all subjects who are suitable candidates.

Subject randomization will be stratified by smoking status (current versus former), by the Investigators' preferred platinum doublet therapy (carboplatin/paclitaxel, carboplatin/pemetrexed or cisplatin/pemetrexed), by gender (male versus female) and by ECOG performance status (0 versus 1).

Intervention

Screening procedures, and quality of life assessments within 28 days, and baseline radiographic tumor assessments within 28 days will be performed prior to randomization.

Subjects randomized to receive carboplatin/paclitaxel/veliparib will begin oral veliparib dosing twice a day on Day -2, 2 days prior to the carboplatin/paclitaxel infusion on Day 1. Veliparib dosing will continue through C1D5 (7 consecutive days). Subjects will receive carboplatin (AUC 6 mg/mL/min) and paclitaxel (200 mg/m2) IV infusion on Day 1 of each cycle. Subjects randomized to receive Investigator's choice of platinum doublet therapy will receive therapy on Day 1 of each cycle.
For both arms, subjects will receive 6 cycles of treatment, unless toxicity requires cessation of therapy, or radiographic progression occurs prior to completing 6 cycles.

Subjects in either arm may receive pemetrexed maintenance therapy or observation after completion of platinum doublet chemotherapy regimen. Maintenance pemetrexed will be administered on Day 1 of each 21-day cycle. Subjects will continue to receive maintenance therapy until toxicity requires cessation of therapy, or radiographic progression occurs.

Subjects will have physician visits q3 weeks while receiving platinum doublet and maintenance therapy. After cessation of therapy, physician visits and quality of life measures will be performed every 9 weeks until one year after randomization, then every 12 weeks until radiographic progression or death. Tumor assessments will be performed at baseline, prior to Cycle 3 Day 1, and prior to Cycle 5 Day 1, every 9 weeks until1 year after randomization, and then every 12 weeks until radiographic progression or death.

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 last dose of study drug.

Subjects no longer undergoing clinical assessments will have survival information reported via the eCRF at two month intervals (or as requested by sponsor to support data analysis) beginning at the last clinical assessment 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 2 questionnaires on baseline, Cycle 3 Day 1, Cycle 5 Day 1, every 9 weeks until1 year after randomization, and then every 12 weeks. Progression of disease will be measured every 9 weeks after treatment until1 year after randomization, and then every 12 weeks.

In one arm, subjects will receive veliparib in combination with carboplatin/paclitaxel for up to a maximum 6 cycles of treatment, unless toxicity requires cessation of therapy, or radiographic progression occurs prior to completing 6 cycles. After that, subjects will go into the post-treatment phase with assessments every 9 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 3 study of the proposed combination therapy in subjects with advanced NSCLC suggest low rates of additional toxicities and no compromise to the delivery of carboplatin and paclitaxel.
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. Standard clinical practices to manage the toxicity of carboplatin + paclitaxel and the Investigator's choice of standard chemotherapy are well established.

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 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 advanced or metastatic non-squamous NSCLC. Subjects with mixed histology tumors will be eligible if the tumor is predominant non-squamous histology and does not include tumor with small cell histology. Subjects must have a pathologist's report confirming non-squamous NSCLC available for collection by the sponsor. Subjects with EGFR mutation (exon 19 deletion or L858R mutation in exon 21) and/or ALK gene rearrangement must have progressed after first line monotherapy treatment with targeted therapy.
4. Subject must have NSCLC that is not amenable to surgical resection or radiation with curative
intent at time of study Screening.
5. Subjects must be current smokers (defined as having > 100 smoking events lifetime and having
smoked within the past year) or former smokers (defined as having > 100 smoking events lifetime
and having not smoked within the past year).
6. Subject must have at least 1 unidimensional measurable NSCLC lesion on a CT scan as defined
by RECIST (version 1.1).
7. Subject must consent to provide archived tissue or cytology sample of NSCLC lesion (primary or
metastatic) for analysis if available.
8. 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 MRI (or CT scan
if MRI is contraindicated) to confirm absence of CNS metastases.
9. Subject must have an Eastern Cooperative Oncology Group (ECOG) Performance Score of 0 - 1.
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;
• Renal function: serum calculated creatinine clearance > 50 mL/min according to the Cockroft-Gault formula; confirmation of creatinine clearance/GFR may be done by a local direct measurement method (e.g., 24 hour urine collection or radioisotope) at the investigator's discretion;
• Hepatic function: AST and ALT <= 2.5 × ULN unless liver metastases are present, then AST and ALT < 5.0 × ULN; bilirubin <= 1.5 × ULN unless Gilbert's Syndrome is present, then bilirubin >= 1.5 × ULN.
12. Female subjects of childbearing potential (i.e., those who are not postmenopausal for at least
1 year or surgically sterile by bilateral tubal ligation, bilateral oophorectomy or hysterectomy) and
their male partners should practice at least one of the methods of birth control listed below during
study and for at least 6 months after treatment with paclitaxel chemotherapy. Male subjects and
their female partners of childbearing potential should practice at least one of the methods of birth
control listed below during study and for at least 6 months after treatment with chemotherapy:
• • total abstinence from sexual intercourse (if it is the subject's preferred and usual lifestyle; for
• beginning a minimum one complete menstrual cycle prior to study drug administration and
• to extend 6 months after treatment):
• • vasectomized subject or partner(s); vasectomy (males);
• • intrauterine device (females);
• • double-barrier method (condoms, contraceptive sponge, diaphragm or vaginal ring with
• spermicidal jellies or creams; both males and females);
• • hormonal contraceptives (oral, parenteral or transdermal) for at least 90 days prior to study
• drug administration (females). If hormonal contraceptives are used, the subject and her
• partner should also use a single-barrier method.
13. Subject must be capable of understanding and complying with parameters as outlined in the
protocol and able to sign and date the 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. 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. Subjects with peripheral neuropathy >= grade 2.
4. Subjects with squamous NSCLC, or those with an untreated EGFR mutation (exon 19 deletion or L858R mutation in exon 21) and/or ALK gene rearrangement. Subjects' EGFR mutation and ALK gene rearrangement status must be known prior to study entry.
5. A history of seizure within 12 months prior to study entry.
6. Subject has received prior cytotoxic chemotherapy or chemoradiotherapy for NSCLC, except adjuvant or neoadjuvant therapy > 12 months prior to C1D-2 or subject has received targeted small molecule monotherapy for EGFR and/or ALK-positive disease <= 14 days prior to C1D-2 or biologic therapy <= 21 days prior to C1D-2.
7. Subject has received anti-cancer Chinese medicine or anti-cancer herbal remedies within 14 days prior to C1D-2.
8. Subject has undergone focal External Beam Radiation Therapy (EBRT) to bone <= 2 weeks prior
to C1D-2; or subject has undergone EBRT to larger fields (i.e., 100 cm2 to thorax) <= 4 weeks
prior to C1D-2.
9. Any medical condition, which in the opinion of the Investigator, places the subject at an unacceptably high risk for toxicities, or any subject circumstance which prohibits trial participation according to local law.
10. Subject is pregnant or lactating.
11. Subject has previously been treated with a PARP inhibitor.
12. 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).

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):	09-07-2015
Enrollment:	22
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Alimta
Generic name:	Pemetrexed
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Carboplatin
Generic name:	Carboplatin
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Cisplatin
Generic name:	Cisplatin
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Paclitaxel
Generic name:	Paclitaxel
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Veliparib
Generic name:	Veliparib

Ethics review

Approved WMO

Date:	18-11-2014

Application type:	First submission
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	22-01-2015
Application type:	First submission
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	15-02-2015
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:	04-03-2015
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	20-05-2015
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	22-05-2015
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	07-08-2015
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:	19-08-2015
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	26-10-2015
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	23-11-2015
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	19-07-2016
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:	03-11-2016
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	29-11-2016
Application type:	Amendment

Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	04-09-2017
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	14-09-2017
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:	14-06-2018
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	04-07-2018
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	01-08-2018
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	08-10-2018
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)
Approved WMO Date:	02-01-2019
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	11-06-2019
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	01-07-2019
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	EUCTR2014-002565-30-NL
CCMO	NL50469.060.14

Internal documents

File