Randomized, Multicenter, Double-Blind, Phase 3 Trial Comparing the Efficacy of Ipilimumab plus Etoposide/Platinum versus Etoposide/Platinum in Subjects with Newly Diagnosed Extensive-Stage Disease Small Cell Lung Cancer (ED-SCLC)

Published: 09-05-2012
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Primary Objective: To compare overall survival (OS) of subjects randomized to ipilimumab in addition toplatinum and etoposide (Arm A) to that of subjects randomized to placebo in addition to platinum andetoposide (Arm B) in subjects with newly...

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

Summary

ID

NL-OMON41684

Source
ToetsingOnline

Brief title
CA184156 (078/508)

Condition

- Respiratory and mediastinal neoplasms malignant and unspecified

Synonym
lung cancer, Small cell lung carcinoma

Research involving
Human

Sponsors and support

Primary sponsor: Bristol-Myers Squibb
Source(s) of monetary or material Support: Bristol-Myers Squibb

Intervention

Keyword: Ipilimumab, Overall survival, Small Cell Lung Cancer

Outcome measures

Primary outcome

Primary Endpoint: The primary endpoint will be overall survival among randomized subjects who received at least one dose of blinded study therapy. Overall survival in the population of randomized subjects who received at least one dose of blinded study therapy will be defined as the time from the date of randomization until the date of death. For those subjects who have not died, OS will be censored on the last date the subject was known to be alive.

Secondary outcome

The secondary endpoints are overall survival (OS) for all randomized subjects and progression-free survival (PFS) per mWHO criteria for randomized subjects who received at least one dose of blinded study therapy. In addition to OS, mWHO PFS will be analyzed as a secondary endpoint in this study, and will be calculated based on TA data recorded in the eCRF. Tumor assessments are required until mWHO PD, or until the end of treatment for subjects who continue to be treated beyond mWHO PD per section 4.3.2.1, or until the start of subsequent therapy for lung cancer for subjects who have discontinued study

therapy.

Study description

Background summary

The dose and schedule of ipilimumab (4 induction doses every 3 weeks and maintenance dosing every 12 weeks) that subjects will receive up to the time they experience PD has shown activity, with an acceptable safety profile, in 3 Phase 2 studies performed in subjects with metastatic melanoma and in a prior Phase 2 study in lung cancer.
The efficacy and safety profile of ipilimumab combined with carboplatin and paclitaxel versus subjects treated with carboplatin and paclitaxel alone have been explored in CA184041 in SCLC subjects. Two administration schedules were explored. The phased schedule resulted in the better efficacy, with a statistically significant prolongation of irPFS, and a trend towards prolonged OS, and an acceptable safety profile.
Preclinical data showed better synergy of ipilimumab with etoposide than with paclitaxel. Etoposide/platinum is standard of care in the treatment of first-line extensive stage SCLC.
Based on the above, this Phase 3 study is designed to demonstrate that overall survival in subjects assigned to treatment with etoposide/platinum/phased ipilimumab will be superior to those assigned to etoposide/platinum/placebo for subjects with extensive stage SCLC.

Study objective

Primary Objective: To compare overall survival (OS) of subjects randomized to ipilimumab in addition to
platinum and etoposide (Arm A) to that of subjects randomized to placebo in addition to platinum and
etoposide (Arm B) in subjects with newly diagnosed extensive stage SCLC, among subjects who received at least one dose of blinded study therapy.

Secondary Objectives:
* To compare OS of all randomized subjects between Arm A and Arm B
* To compare Progression Free Survival (mWHO) in subjects who received at least one dose of blinded study therapy between Arm A and Arm B

Study design

Study Design: This is a randomized, multicenter, double-blind Phase 3 study in chemotherapy-naïve subjects with extensive stage (according to VALG staging) SCLC. Subjects will be randomized to receive etoposide and either cisplatin or

carboplatin (investigator*s choice) plus ipilimumab in a phased induction schedule, followed by ipilimumab maintenance, or etoposide and either cisplatin or carboplatin
(investigator*s choice) plus placebo, followed by placebo maintenance.
The study will randomize approximately 1100 SCLC subjects at a 1:1 ratio to 1 of 2 treatment arms, stratified by ECOG performance status, LDH, choice of platinum and region.
This study is divided into the following phases: Screening, Induction, Maintenance, Toxicity/Progression Follow-up, and Survival Follow-up.

Intervention

Combination chemotherapy etoposide/platinum(carboplatin or cisplatin)/ipilimumab versus etoposide/platinum(carboplatin or cisplatin)/placebo.

Study burden and risks

Risks Associated with Etoposide
Very common:
- low white blood cell count
- low platelet count
- nausea and vomiting
- hair loss

Risks associated with Cisplatin
Very common:
- low white blood cell count
- anemia
- nausea and vomiting

Risks Associated with Carboplatin
Very common:
- bruising or bleeding. Platelets help blood to clot. If the platelet count is low, the subject may bruise or bleed more easily then usual.
- signs of infection/ fever, chills,
- low white blood cell count
- nausea and vomiting can be common side effects with chemotherapy
- tiredness or weakness

Common side effects related to ipilimumab: infusion reaction
-Side Effects considered to be Related to Ipilimumab and advanced melanoma: diarrhea, skin rash, skin itchiness, fatique, nausea, fever, decreased appetite, vomiting, inflammation of the colon, abdominal pain, weight loss, headache, dehydration.
-Side Effects considered to be Related to Ipilimumab + chemo therapy and

advanced melanoma:
Nausea, Fatigue, Diarrhea, Fever, Increase in liver enzyme ALT, Increase in liver enzyme AST, Skin itchiness, Vomiting, Skin rash, Decreased appetite, Constipation, Chills
-Side Effects considered to be Related to Ipilimumab and advanced lung cancer:
Hair loss, Joint Pain, Nausea, Decreased red blood cells, Diarrhea, Fatigue, Numbness or muscle , weakness, Vomiting, Tingling in hands and feet, Decreased white blood cells, Decreased platelets
Serious Side Effects:
Diarrhea, Inflammation of the colon, Increase in liver enzymes, Vomiting, Dehydration, Abdominal pain, Fever, Decrease in hormones of pituitary gland, Inflammation of the liver, Inflammation of the pituitary gland, Decreased red blood cells.

Risks Associated with Study Procedures
Risks associated with the drawing of blood or putting a needle in the vein might include pain from the puncture, bruising, bleeding, infection, or fainting.
The risks associated with x-ray, CT, MRI, and bone scans include the rare occurrence of allergic reactions to the contrast dyes injected into a vein during the scan. Such allergic reactions can involve itching, rash, or in severe cases, difficulty in breathing and dangerous lowering of the blood pressure or other general symptoms.

An extensive list of side effects (also those occuring less frequently) is provided in Appendix 3 of the patient information.

Contacts

Public
Bristol-Myers Squibb

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BE
Scientific
Bristol-Myers Squibb

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Brussel 1170
BE

Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

1) Signed Written Informed Consent
a) Willing and able to provide informed consent.;2) Target Population
a) Subjects with SCLC documented by histology or cytology from brushing, washing or needle aspiration of a defined lesion but not from sputum cytology alone.
b) Subjects must present with extensive stage disease (VALG classification) and defined as disease beyond ipsilateral hemithorax which may include malignant pleural effusion or pericardial effusion or hematogenous metastases.
c) Eastern Cooperative Oncology Group (ECOG) performance status * 1.
d) Accessible for treatment and follow-up. Subjects enrolled in this trial must be treated at the participating centers.
e) Re-enrollment: permitted for a subject who has discontinued the
study as a pretreatment failure (i.e., subject has not been randomized/has not been treated). If re-enrolled, the subject must be re-consented.;3) Age and Reproductive Status
a) Men and Women * 18 years of age.
b) Women of childbearing potential (WOCBP) must use method(s) of contraception as indicated in the Informed Consent Form. For a teratogenic study drug, and/or when there is insufficient information to
assess teratogenicity (preclinical studies have not been done), a highly effective method(s) of contraception (failure rate of less than 1% per year) is required. The individual methods of contraception and duration should be determined in consultation with the investigator. WOCBP must agree to follow instructions for method(s) of contraception for the duration of treatment with blinded study drug plus 5 half-lives (75 days) plus 30 days (duration of ovulatory cycle) for a total of 105 days post completion of blinded study therapy.
c) Women must not be breastfeeding.
d) Sexually active fertile men must use effective birth control if their partners are WOCBP. Men that are sexually active with WOCBP must follow instructions for birth control for the entire duration of treatment
with blinded study therapy, plus 5 half-lives of ipilimumab (75 days) plus 90 days (duration of sperm turnover) for a total of 165 days post completion of blinded study therapy.

e) Not applicable per Protocol Amendment 10.

Exclusion criteria

1) Target Disease Exceptions
a) CNS metastases, unless non-symptomatic (ie, no neurological deficit, epilepsy or other signs and symptoms typical of CNS metastases), and not requiring treatment with steroids or anticonvulsant medications. In addition, if treated with radiation therapy, CNS metastases must be stable with no evidence of progression on scans for at least 30 days from initial radiologic diagnosis of CNS metastases.
b) Pleural effusion which cannot be controlled with appropriate interventions.
2) Medical History and Concurrent Diseases
a) Documented history of severe autoimmune or immune mediated symptomatic disease that required prolonged (more than 2 months) systemic immunosuppressive (ie, steroids) treatment such as: i) Ulcerative colitis and Crohn*s disease, ii) Rheumatoid arthritis, systemic progressive sclerosis (scleroderma),
iii) Systemic Lupus Erythematosus, iv) Autoimmune vasculitis (eg, Wegener*s Granulomatosis).
b) Subjects with history of motor neuropathy considered of autoimmune origin (eg, Guillain-Barré Syndrome).
c) Subjects with a history of toxic epidermal necrolysis (TEN).
d) Interstitial pneumonia or pulmonary fibrosis.
e) Paraneoplastic autoimmune syndrome
f) Dementia, altered mental status, or any psychiatric condition that would prohibit the understanding or rendering of informed consent or completing questionnaires.
g) Serious uncontrolled medical disorder that, in the opinion of the investigator, would impair the ability of the subject to receive protocol therapy.
h) Prior malignancy, active within 5 years, except for locally curable cancers that have been apparently cured and need no subsequent therapy, such as basal or squamous cell skin cancer, superficial bladder cancer or carcinoma in situ of the cervix or breast.
i) HIV, active Hepatitis B, or active Hepatitis C infection, based on testing performed during the CA184156 screening period. In the event of a positive HIV or anti-HCV antibody test, results of confirmatory testing must be awaited before randomization.
j) Prior systemic therapy for lung cancer, including vaccines and other targeted therapies.
i) Prior radiation therapy or loco-regional surgeries are allowed.
k) Subjects with * Grade 2 peripheral neuropathy.;3) Physical and Laboratory Test Findings
a) Inadequate hematologic function defined by:
i) Absolute neutrophil count (ANC) < 1,500/mm3, or
ii) Platelet count < 100,000/mm3; or
iii) Hemoglobin level < 9 g/dL.
b) Inadequate hepatic function as defined by either:
i) Total bilirubin level * 2.5 times the ULN;
ii) AST and ALT levels * 2.5 times the ULN or * 5 times the ULN if livermetastases are present.
c) Inadequate renal function defined as calculated creatinine clearance < 50 ml/min based on the standard Cockroft and Gault formula.

d) Sodium (Na) < 130 mmol/l.;4) Prohibited Treatments and/or Therapies
a) Chronic use of immuno-suppressive drugs (ie, corticosteroids used in the management of cancer or non-cancer related illnesses). Use of corticosteroids are allowed if used as premedication for chemotherapy administration or on-study management of an AE.
b) Any immunotherapy for the treatment of cancer.
c) Prior treatment with any inhibitor or agonist of T-cell co-stimulation.;5) Other Exclusion Criteria
a) Prisoners or subjects who are involuntarily incarcerated.
b) Subjects who are compulsorily detained for treatment of either a psychiatric or physical (eg, infectious disease) illness.

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:	Recruitment stopped
Start date (anticipated):	29-01-2013
Enrollment:	20
Type:	Actual

Medical products/devices used

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

Brand name:	Eposin
Generic name:	Etoposide
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	MDX010
Generic name:	Ipilimumab
Product type:	Medicine
Brand name:	Paraplatin
Generic name:	carboplatin
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	09-05-2012
Application type:	First submission
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	26-07-2012
Application type:	First submission
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	17-09-2012
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	28-09-2012
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	12-11-2012
Application type:	Amendment

Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	29-01-2013
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	21-02-2013
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	19-04-2013
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	16-05-2013
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	11-07-2013
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	29-07-2013
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	05-09-2013
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO	

Date:	18-09-2013
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	14-02-2014
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	27-02-2014
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	16-05-2014
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	06-06-2014
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	28-08-2014
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	23-09-2014
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	09-10-2014
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United

	(Nieuwegein)
Approved WMO Date:	05-12-2014
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	24-07-2015
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	03-08-2015
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	EUCTR2011-000850-48-NL
ClinicalTrials.gov	NCT01450761
CCMO	NL39045.060.12