A Phase II/III Randomized Trial of Two Doses of MK-3475 (SCH900475) versus Docetaxel in Previously Treated Subjects with Non-Small Cell Lung Cancer

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1) Objective: To compare the overall survival (OS) of previously-treated subjects with NSCLC in the strongly positive PD-L1 stratum treated with MK-3475 compared to docetaxel.2) Objective: To compare progression-free survival (PFS) per RECIST 1.1 by...

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

Summary

ID

NL-OMON47020

Source
ToetsingOnline

Brief title
MK3475-010

Condition

- Respiratory and mediastinal neoplasms malignant and unspecified
- Respiratory tract neoplasms

Synonym
lung cancer

Research involving
Human

Sponsors and support

Primary sponsor: Merck Sharp & Dohme (MSD)
Source(s) of monetary or material Support: Merck;Sharp & Dohme (MSD)

Intervention

Keyword: Docetaxel, lung cancer, non-small cell

Outcome measures

Primary outcome

Overall Survival, (OS)

Progression Free Survival, (FPS)

Secondary outcome

Overall Response Rate (ORR)

response duration per RECIST 1.1 based on blinded independent radiologists*

review.

Study description

Background summary

While docetaxel is an accepted second-line standard of care for patients with NSCLC, the objective response rate is about 5-10%, median progression-free survival is about 3 months, and the median overall survival is about 7.5 months [62, 63, 64]. Improvements in OS are needed since no one with progressive NSCLC is cured. A large surgical series of resected NSCLC specimens revealed that about 25% of squamous and adenocarcinoma have tumor infiltrating lymphocytes (TILs) present [68]. These TILs often contain CD8+ T cells [68]. The presence of increased CD8+ cells in the tumor sets the stage for an immune-based response against the tumor if inhibition of the immune system can be abrogated. Indeed, in a study of ipilimumab, an anti-CTLA4 monoclonal antibody, combined with first-line carboplatin and paclitaxel, a post-hoc subset analysis identified an improvement in OS that favored patients with squamous histology compared to placebo plus carboplatin and paclitaxel (HR 0.48 [95% CI 0.22-1.03]). Results were not as favorable for patients with nonsquamous histology (HR 1.17 [95% CI 0.74-1.86]). These findings have led to

the initiation of a Phase III trial in the same population with ipilimumab.
The Phase I trial of nivolumab demonstrated that patients with tumors expressing PD-L1 using a 5% cut point for the 5H1 anti-PD-L1 mAb for IHC were more likely to respond to anti-PD-1 therapy (9/25 patients) than patients with tumors that did not express PD-L1 (0/17 patients). Specifically, of the ten lung tumors for which tumor tissue was available, five expressed PD-L1, and only one of those five was a responder; none of the patients with PD-L1 negative tumors experienced an objective response per RECIST [65]. The activity of anti-PD-1 monoclonal antibodies in previously treated patients with NSCLC seems promising.
Therefore, this study will compare monotherapy MK-3475 with standard of care docetaxel in patients with NSCLC. Overall survival and PFS are the primary endpoints of the trial, and are accepted regulatory endpoints for this disease.
Details regarding specific benefits and risks for subjects participating in this clinical trial may be found in the accompanying Investigators Brochure (IB) and Informed Consent documents.

Study objective

1) Objective: To compare the overall survival (OS) of previously-treated subjects with NSCLC in the strongly positive PD-L1 stratum treated with MK-3475 compared to docetaxel.
2) Objective: To compare progression-free survival (PFS) per RECIST 1.1 by independent radiologists* review of previously-treated subjects with NSCLC in the strongly positive PD-L1 stratum treated with MK-3475 compared to docetaxel.
3) Objective: Evaluate safety and tolerability profile of MK-3475 in previously-treated subjects with NSCLC in the strongly positive PD-L1 stratum.

Study design

This is a multi-center, worldwide, randomized, adaptively designed Phase II/III trial of intravenous (IV) MK-3475 at two dosing schedules versus docetaxel in subjects with non-small cell lung cancer (NSCLC) with PD-L1 positive tumors who have experienced disease progression after platinum-containing systemic therapy. Approximately 520-920 subjects will be enrolled in this trial to examine the efficacy compared to docetaxel in an enriched population. Subjects will be randomized in a 1:1:1 ratio to receive MK-3475 at 10 mg/kg every 3 weeks (Q3W), 2 mg/kg Q3W, or docetaxel at 75 mg/m2 Q3W (Figure 1). Because this is an adaptively designed trial, the total number of patients randomized will depend upon demonstration of sufficient objective responses at interim analysis 1 in an MK-3475 arm in the stratum of subjects whose tumors test strongly positive for PD-L1. Assignment to MK-3475 or docetaxel will be unblinded. Subjects will be stratified by Eastern Cooperative Oncology Group (ECOG) Performance Scale (0 vs. 1), and geographic region of the enrolling site (East Asia vs. non-East Asia) prior to randomization.

Subjects will be evaluated every 9 weeks (63 ± 7 days) with radiographic imaging to assess response to treatment. Investigators will make all treatment-based decisions using the Immune-Related Response Criteria (irRC). All imaging obtained on study will be submitted for independent radiologists* review; they will assess the images using Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 for determination of overall response rate (ORR) and progression-free survival (PFS). Adverse events will be monitored throughout the trial and graded in severity according to the guidelines outlined in the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0. Treatment with MK-3475 or docetaxel will continue until two years of therapy have been administered, documented disease progression, unacceptable adverse event(s), intercurrent illness that prevents further administration of treatment, investigator*s decision to withdraw the subject, subject withdraws consent, pregnancy of the subject, noncompliance with trial treatment or procedure requirements, or administrative reasons. MK-3475 treated subjects who attain an investigator-determined confirmed complete response (CR) per irRC may consider stopping trial treatment. These subjects will be eligible for re-treatment for up to one year with MK-3475 after they have experienced radiographic disease progression at the discretion of the investigator according to the criteria in Section 7.1.5.4; this re-treatment will be the Second Course Phase. Response or progression in the Second Course Phase will not count towards the ORR and PFS of the primary endpoint in this trial.
After the end of treatment, each subject will be followed for a minimum of 30 days for adverse event monitoring (serious adverse events will be collected for up to 90 days after the end of treatment). Subjects will have post-treatment follow-up for disease status, including initiating a non-study cancer treatment and experiencing disease progression, until death, withdrawing consent, or becoming lost to follow-up. The primary objectives of the trial include overall survival (OS), PFS per RECIST 1.1 by independent radiologists* review, and safety as assessed by a variety of parameters of adverse events (AEs), including incidence and time to first Grade 3-5 AE in the strongly positive PD-L1 stratum. Pre-specified adverse events of clinical interest include the following events:1) Grade * 3 diarrhea 2) Grade * 2 colitis, 3) Grade * 2 pneumonitis, 4) Grade * 3 hypo- or hyperthyroidism. Secondary objectives include OS, and PFS and ORR per RECIST 1.1 by independent radiologists* review in subjects whose tumors express PD-L1. Additional secondary objectives include the analysis of ORR per RECIST 1.1 by independent radiologists* review and per irRC by investigators* review, PFS per irRC by investigators* review, and response duration per RECIST 1.1 by independent radiologists* review and per irRC by investigators* review in subjects whose tumors strongly express PD-L1. Change in tumor volume and health-related quality-of-life assessments in subjects whose tumors strongly express PD-L1 will be pursued as exploratory objectives.
Participation in this trial will be dependent upon supplying tumor tissue from either a newly obtained formalin-fixed specimen, or an older formalin-fixed, paraffin-embedded specimen from locations not radiated prior to biopsy; newly obtained formalin-fixed specimens are strongly encouraged. If new scientific

data emerge that indicate that an existing biopsy or surgical specimen is suboptimal for identification of patients, only new biopsies will be acceptable for determination of PD-L1 status. The specimen will be evaluated at a central laboratory facility for expression status of PD-L1 in a prospective manner. Only subjects whose tumors express PD-L1 as determined by the central laboratory facility will be eligible for randomization in this study.
This trial will use an adaptive design based on pre-specified criteria, using an independent, external Data Monitoring Committee (DMC) to monitor safety and efficacy. Subjects enrolled to the weakly positive PD-L1 stratum will not be included in the populations for primary efficacy and safety analyses. Two formal interim analyses based on the data from the randomized cohort will occur during the conduct of this trial. The first interim analysis will be triggered after 120 subjects in the strongly positive PD-L1 stratum have completed a minimum of 3 months of follow-up. The primary objective of this analysis is to stop the study for futility or to discontinue the MK-3475 at 2 mg/kg Q3W dose if it is less effective than MK-3475 at 10 mg/kg Q3W in the strongly positive PD-L1 stratum.

The second interim analysis is expected to occur around 1 month after all trial subjects have been randomized. It will be conducted when 174 events of progression per RECIST 1.1 by independent radiologists* review have occurred in the MK-3475 at 10 mg/kg Q3W and docetaxel arms in the strongly positive PD-L1 stratum. The purpose of the second interim analysis is to demonstrate superiority of MK-3475 in PFS in the strongly positive PD-L1 stratum and whether the trial should be stopped for overwhelming efficacy based on OS in the strongly positive PD-L1 stratum. In addition, the trial may be stopped early at the recommendation of the DMC if the risk/benefit ratio to the trial population as a whole is unacceptable. Details are described in Section 8.0 * Statistical Analysis Plan.

If the 2 mg/kg dose arm is dropped due to lack of efficacy , per the Investigator*s discretion the subjects can continue to be treated with MK-3475 on the 10 mg/kg dose. The efficacy and safety data from these patients will not be used in the primary analysis, but will be used in supportive analyses.

Study burden and risks

Blood samples: drawing blood from your arm may cause pain, bruising, lightheadedness, and rarely, infection.
IV line: may cause discomfort, irritation, mild bruising, bleeding, leakage of drug solution, and rarely, infection, nausea, and lightheadedness.
ECG: the procedure may cause minimal discomfort during the attachment and removal of the ECG leads to and from the skin.
CT Scan: A *Computerized Tomography* or CT scan provides multiple detailed pictures of the inside of the body, like an MRI scan, but the CT scan uses radiation, similar to an x-ray. CT scans may be done with or without oral or intravenous contrast. The scan may take between 30-90 minutes to complete

depending on the areas of the body being scanned and the type of scanner.
Magnetic Resonance Imaging (MRI): Risks of MRI include claustrophobia, discomfort due to lying still for a prolonged period of time, and other factors which will be described to you and discussed with you at the MRI center.
Tumor Biopsy: Having biopsies performed may cause pain, bruising, bleeding, redness, low blood pressure, swelling, and/or infection at the site of the biopsy. An allergic reaction to the anesthetic may occur. A scar may form at the biopsy site.
Pulmonary Function Test: A brief light-headed feeling.

Contacts

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NL

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

1) Be willing and able to provide written informed consent/assent for the trial.

2) Be *18 years of age on day of signing informed consent.
3) Have a life expectancy of at least 3 months.
4) Have a histologically or cytologically confirmed diagnosis of nonsmall cell lung cancer (NSCLC) and have at least one measurable lesion as defined by RECIST 1.1.
5) Have experienced investigator determined radiographic progression per RECIST 1.1 of NSCLC after treatment with at least two cycles of a platinum-containing doublet for stage IIIB/IV or recurrent disease.
a. Subjects with an EGFR mutation must also be able to demonstrate progression of disease on the EGFR tyrosine kinase inhibitor (either erlotinib or gefitinib or afatinib).
b. Subjects with an ALK translocation must also be able to demonstrate progression of disease on crizotinib in a similar manner to that above for the platinum-containing doublet.
6) Have a performance status of 0 or 1 on the ECOG Performance Scale.
7) Have provided tissue for PD-L1 biomarker analysis from a newly obtained formalin fixed tumor tissue from a recent biopsy of a tumor lesion not previously irradiated; no systemic antineoplastic therapy may be administered between the PD-L1 biopsy and initiating study medication.
8) Have resolution of toxic effect(s) of the most recent prior chemotherapy to Grade 1 or less (except alopecia). If subject received major surgery or radiation therapy of > 30 Gy, they must have recovered from the toxicity and/or complications from the intervention.
9) Have a PD-L1 positive (either strongly or weakly) tumor as determined by IHC at a central laboratory (either in the neoplastic cells themselves or in mononuclear inflammatory cells infiltrating the tumor).;Inclusion Criteria for Optional Crossover from docetaxel to MK-3475 2mg/kg arm In order to be eligible for participation in the crossover phase, the subject must:
1. Be willing and able to provide written informed consent/assent for the trial.
2. Have been randomized into the docetaxel arm of MK-3475 PN010 study and taken at least one dose of study medication
3. Have experienced disease progression (either clinical or radiographic, as assessed by the investigator) from docetaxel or other subsequent anti-cancer therapies.
4. Have a performance status of 0 or 1 on the ECOG Performance Scale.
5. Subjects with known and treated brain metastasis are eligible provided they are clinically stable, and brain metastases have been treated. Steroid use for symptom control is allowed but the total daily dose should be < or <= 10 mg of prednisone or its equivalent.
6. Have baseline imaging scan done within 30 days of the first dose of MK-3475
7. Have adequately recovered from adverse events of previous anticancer therapy.

Exclusion criteria

1) Has received prior therapy with docetaxel for NSCLC.
2) Is currently participating or has participated in a study of an investigational agent or using an investigational device within 30 days of the first dose of trial treatment.
3) Is receiving systemic steroid therapy within three days prior to the first dose of trial treatment or receiving any other form of immunosuppressive medication (corticosteroid use on study for
management of ECI-ies or as a pre-medication for docetaxel is allowed).
4) Is expected to require any other form of systemic or localized antineoplastic therapy while

on trial (including maintenance therapy with another agent for NSCLC or radiation therapy).
5) Has received prior systemic cytotoxic chemotherapy, biological therapy (e.g., cetuximab), major surgery within 3 weeks of the first dose of trial treatment; received radiation therapy of > 30 Gy within 6 months of the first dose of trial treatment; received prior tyrosine kinase inhibitor therapy or palliative radiotherapy of 30Gy or less within 7 days of the first dose of trial treatment.
6) Has received prior therapy with an anti-PD-1, anti-PD-L1, anti-PDL2, anti-CD137, or anti-Cytotxic T-lymphocyte-associated antigen-4 (CTLA-4) antibody (including ipilimumab or any other antibody or drug specifically targeting T-cell co-stimulation or checkpoint pathways).
7) Has a known history of prior malignancy, with the exception of basal cell carcinoma of the skin, superficial bladder cancer, squamous cell carcinoma of the skin, or in situ cervical cancer, and has undergone potentially curative therapy with no evidence of that disease recurrence for 5 years since initiation of that therapy.
8) Has known active central nervous system (CNS) metastases and/or carcinomatous meningitis. Subjects with previously treated brain metastases may participate provided they are stable (without evidence of progression by MRI for at least four weeks prior to the first dose of trial treatment and any neurologic symptoms have returned to baseline), have no evidence of new or enlarging brain metastases, and are using no steroids for at least three days prior to study medication.
9) Has an active autoimmune disease, or a documented history of autoimmune disease, or a syndrome that requires systemic steroids or immunosuppressive agents.
10) Has interstitial lung disease or a history of pneumonitis.
11) Has interstitial lung disease or a history of pneumonitis that required oral or intravenous glucocorticoids to assist with management. Lymphangitic spread of the NSCLC is not exclusionary.
12) Has had an allogeneic tissue/solid organ transplant.;Exclusion Criteria for Optional Crossover from docetaxel to MK-3475 2mg/kg arm
The subject must be excluded from participating in the trial if the subject:
1. Has withdrawn consent from study (MK-3475 PN010).
2. Have active pneumonitis of Grade 2 or greater or history of pneumonitis requiring systemic steroid therapy.
3. Has received thoracic radiation therapy of > 30 Gy within 6 months
4. have active and untreated brain metastasis.

Study design

Design

Study phase:	2
Study type:	Observational invasive
Intervention model:	Crossover
Allocation:	Randomized controlled trial

Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	15-10-2013
Enrollment:	15
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	KEYTRUDA
Generic name:	Pembrolizumab
Product type:	Medicine
Brand name:	Taxotere
Generic name:	Docetaxel
Registration:	Yes - NL intended use

Ethics review

Approved WMO

Date:	10-04-2013
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)

Approved WMO

Date:	26-04-2013
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)

Approved WMO

Date:	02-08-2013
Application type:	Amendment

Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	23-08-2013
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	29-11-2013
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	13-03-2014
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	28-05-2014
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	16-01-2015
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	30-01-2015
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	06-03-2015
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO	

Date:	06-07-2015
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	31-07-2015
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	21-08-2015
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	19-11-2015
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	12-01-2016
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	21-01-2016
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	21-11-2016
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	01-12-2016
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek

	(Assen)
Approved WMO Date:	06-12-2016
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Approved WMO Date:	01-03-2017
Application type:	Amendment
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Approved WMO Date:	24-03-2017
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	29-06-2017
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	18-10-2017
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	16-03-2018
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Approved WMO Date:	19-03-2018
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Approved WMO Date:	17-12-2018
Application type:	Amendment
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Approved WMO Date:	04-09-2019
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	06-11-2019
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	17-04-2020
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	04-11-2020
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)

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	EUCTR2012-004391-19-NL
CCMO	NL43092.056.13
Other	nog niet bekend