A Randomized Open-Label Phase III Trial of MK-3475 versus Platinum based Chemotherapy in 1L Subjects with PD-L1 Strong Metastatic Non-Small Cell Lung Cancer

Published: 19-06-2014
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Primary objective:To compare the Progression Free Survival (PFS) per RECIST 1.1 as assessed by blinded independent central radiologists* review in subjects with PD-L1 strong, 1L metastatic NSCLC treated with MK-3475 compared to standard of care (SOC...

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

Summary

ID

NL-OMON44857

Source
ToetsingOnline

Brief title
MK-3475 versus SOC in 1L Subjects with PD-L1 Strong Metastatic NSCLC

Condition

- Respiratory and mediastinal neoplasms malignant and unspecified

Synonym
lung cancer

Research involving
Human

Sponsors and support

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

Intervention

Keyword: Chemotherapy, Lungcancer, Primary therapy

Outcome measures

Primary outcome

Progression free survival is an acceptable measure of clinical benefit for a randomized phase 3 trial that demonstrates superiority of a new antineoplastic therapy, especially if the magnitude of effect is large and the therapy has an acceptable risk-benefit profile. Furthermore, it is an endorsed regulatory endpoint for 1L NSCLC trials with recent FDA and EMA approvals including the EGFR inhibitors afatinib and erlotinib. PFS will be assessed by RECIST 1.1 by an independent central radiologists* review who will be blinded to treatment assignment so as to minimize any bias in the response assessments.

Secondary outcome

Overall survival will be included as it is a standard assessment of clinical benefit in subjects with advanced or metastatic NSCLC. Achieving superiority in overall survival, however, is likely to be limited by dilution of benefit with multiple post-progression therapies as well as disproportionate crossover in the control arm to available PD-1/PD-L1 axis of therapies. ORR by RECIST 1.1 criteria as assessed by blinded independent central radiology review and the duration of response by RECIST 1.1 as assessed by blinded independent central radiologists* review will serve as additional measures of efficacy.

Study description

Background summary

Lung cancer had the highest incidence of malignancies globally in 2008 with more than 1.6 million cases. Mortality from lung cancer in 2008 was similar with over 1.4 million deaths from lung cancer globally. NSCLC accounts for approximately 85% of all lung cancer cases.
Progress has been made in the clinical management of early stage NSCLC by establishing comprehensive, multi-modality treatment regimens; however, the prognosis for advanced disease has not improved substantially. With an overall 5-year survival rate of 9% to 13%, the treatment of NSCLC remains a highly unmet medical need. Cytotoxic chemotherapy as single agents or in combination have served as the mainstay of treatment for decades with platinum containing doublets and maintenance strategies conferring the greatest advances in overall survival gains.

Platinum-based combination chemotherapy prolongs survival, improves quality-of-life, and controls disease related symptoms. Platinum chemotherapy, thus, is the backbone treatment for initial (first line) treatment of patients not candidates for treatment with tyrosine kinase inhibitors (TKIs) and who have an ECOG PS of 0 or 1. Single agent cytotoxic agents such as gemcitabine or docetaxel are considered SOC for patients with an ECOG PS of 2. Approved therapies for EGFR wt and EML4-ALK fusion negative NSCLC in previously untreated patients with advanced or metastatic settings in Europe include paclitaxel, gemcitabine, docetaxel, pemetrexed and bevacizumab, all in combination with platinum based chemotherapy. While ECOG 1594 demonstrated that the four platinum-doublets tested (cisplatin combined with either paclitaxel, gemcitabine, or docetaxel, and carboplatin and paclitaxel) have equivalent activity in the first-line setting, neither pemetrexed nor bevacizumab is appropriate for patients with squamous histology.

Recently, targeted therapies for specific tumor genetic alterations have resulted in higher response rates in specific subpopulations of NSCLC patients. Examples include inhibitors against the epidermal growth factor receptor (EGFR) family and the anaplastic lymphoma kinase (ALK). Because of the highly significant demonstration of clinical benefit in these molecularly defined sub-populations, ESMO and NCCN guidelines indicate that first-line treatment with an approved TKI, should be prescribed to patients with tumors bearing an activating (sensitizing) epidermal growth factor receptor (EGFR) mutation because of significantly higher response rate (RR), longer PFS, and better quality of life (QoL) (ESMO) when compared with first-line chemotherapy.
Patients with NSCLC harboring an anaplastic lymphoma kinase (ALK) translocation should be considered for crizotinib (Xalkori) for the treatment of ALK translocated, previously treated non-small cell lung cancer.

Despite the development of these targeted therapies, most patients relapse and die from their lung cancer; therefore, advanced and metastatic NSCLC remain a major unmet medical need.

Study objective

Primary objective:

To compare the Progression Free Survival (PFS) per RECIST 1.1 as assessed by blinded independent central radiologists* review in subjects with PD-L1 strong, 1L metastatic NSCLC treated with MK-3475 compared to standard of care (SOC) chemotherapies.

Secondary objectives:

1. Evaluate the safety and tolerability profile of MK-3475 in subjects with 1L metastatic PD-L1 strong NSCLC.

2. Evaluate the overall survival (OS) in subjects with 1L metastatic PD-L1 strong NSCLC treated with MK-3475 compared to SOC chemotherapies.

3. Evaluate the ORR (overall response rate) as assessed by RECIST 1.1 by blinded independent central radiology review in subjects with 1L metastatic PD-L1 strong NSCLC treated with MK-3475 compared to standard of care (SOC) chemotherapies.

Study design

This is a multicenter, international, randomized, open label, controlled trial of intravenous (IV) MK-3475 monotherapy versus the choice of five different standard of care platinum based chemotherapies in subjects previously untreated for their stage IV, PD-L1 strong, non-small cell lung cancer.

Intervention

One group will receive MK-3475 200 mg IV Q3W;

The second group will receive one if the following Standard of Care therapies:

- Gemcitabine 1250 mg/m2 & Cisplatin 75 mg/m2 Q3W for 4-6 cycles
- Gemcitabine 1250 mg/m2 & Carboplatin AUC 5-6 Q3W for 4-6 cycles
- Pemetrexed 500 mg/m2 & Carboplatin AUC 5-6 Q3W for 4-6 cycles followed by optional pemetrexed 500 mg/m2 Q3W (permitted for nonsquamous histologies only)
- Pemetrexed 500 mg/m2 & Cisplatin 75 mg/m2 Q3W for 4-6 cycles followed by optional pemetrexed 500 mg/m2 Q3W (permitted for nonsquamous histologies only)
- Paclitaxel 200 mg/m2 & Carboplatin AUC 5-6 Q3W for 4-6 cycles followed by

optional pemetrexed maintenance (pemetrexed maintenance is permitted for nonsquamous histologies only)

Study burden and risks

Blood samples: drawing blood from the arm may cause pain, bruising, lightheadedness, and rarely, infection.

IV line for infusion of the study drug may cause: discomfort, irritation, mild bruising, bleeding, leakage of drug solution, and rarely infection, nausea, and lightheadedness.

The electrocardiogram (ECG) procedure may cause minimal discomforts during the attachment and removal of the ECG leads to and from the skin.

CT Scan: High dose radiation is known to produce cancer cells. The effect of exposure to radiation adds up over a lifetime. The amount of radiation exposure involved in this trial will not be significantly greater than for subjects who do not take part in the trial. The contrast solution that may be given for a CT scan may cause an allergic reaction (rare). Severe allergic reactions can be life threatening. CT contrast solution can cause kidney damage, especially when subject is diabetic, dehydrated (lost body water) or elderly.

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.

Contacts

Public
Merck Sharp & Dohme (MSD)

Waarderweg 39
Haarlem 2031 BN
NL
Scientific
Merck Sharp & Dohme (MSD)

Waarderweg 39
Haarlem 2031 BN
NL

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

1. Have a histologically or cytologically confirmed diagnosis of stage IV, EGFR wt and EML4/ALK fusion negative NCSLC and have received no prior systemic chemotherapy treatment for their metastatic NSCLC. Completion of treatment with chemotherapy as part of neoadjuvant/adjuvant therapy is allowed as long as therapy was completed at least 6 months prior to the diagnosis of metastatic disease. ;2. Subject must have at least one radiographically measurable lesion per RECIST 1.1 as determined by blinded independent central radiology review; eligibility will be determined by central review of the screening CT images.;3. Be *18 years of age on day of signing informed consent.;4. Have a life expectancy of at least 3 months;5. Have a performance status of 0 or 1 on the Eastern Cooperative Oncology Group (ECOG) Performance Status;6. Have adequate organ function;7. Subject has no 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, or has undergone potentially curative therapy with no evidence of that disease recurrence for 5 years since initiation of that therapy.;8. Have provided newly obtained formalin fixed tumor tissue from a biopsy of a tumor lesion AFTER the diagnosis of metastatic disease has been made AND from a site not previously irradiated. Biopsies obtained PRIOR to the administration of any systemic therapy administered for the treatment of a subject*s tumor (such as neoadjuvant/adjuvant therapy) will not permitted for analysis. The tissue sample must be received by the central vendor prior to randomization. Fine needle aspirates are not acceptable. Needle or excisional biopsies, or resected tissue is required. ;- Investigators must be able to produce the source documentation of the EGFR, ALK or KRAS mutation status in all subjects with non-squamous histologies AND for subjects in whom testing is clinically recommended. If any of the three (KRAS, EGFR or ALK) are documented as mutated or rearranged, additional information regarding the mutation status of the other molecules is not required as these mutations/rearrangements are mutually exclusive. If unable to test for these molecular changes, formalin fixed paraffin embedded tumor tissue of any age should be submitted to a central laboratory designated by the Sponsor for such testing. Subjects with non-squamous histologies will not be randomized until EGFR mutation, ALK translocation

status and/or KRAS mutation status is available in source documentation at the site.;9. Have a PD-L1 strong tumor as determined by IHC at a central laboratory; only PD-L1 strong subjects will be randomized.

Exclusion criteria

1. Has an EGFR sensitizing mutation and/or an EML4/ALK translocation.;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. Tumor specimen is not evaluable for PD-L1 expression by the central laboratory. If an additional tumor specimen is submitted AND evaluable for PD-L1 expression, the subject will be eligible to participate if PD-L1 expression is assessed as *strong* by the central laboratory. ;4. Is receiving systemic steroid therapy > 3 days prior to the first dose of trial treatment or receiving any other form of immunosuppressive medication (corticosteroid use on study for management of ECIs is allowed or as a pre-medication for the control chemotherapies is allowed). Subjects who are receiving daily steroid replacement therapy serve as an exception to this rule. Daily prednisone at doses of 5-7.5 mg is an example of replacement therapy. Equivalent hydrocortisone doses are also permitted if administered as a replacement therapy. ;5. Is expected to require any other form of systemic or localized antineoplastic therapy while on trial (including maintenance therapy with another agent for NSCLC, radiation therapy, and/or surgical resection).;6. Has received prior systemic cytotoxic chemotherapy, biological therapy, 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 palliative radiotherapy of 30Gy or less within 7 days of the first dose of trial treatment.;7. Has received prior therapy with an anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CD137, or anti-Cytotoxic 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).;8. Has known symptomatic 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. Subjects with brain metastases for whom complete surgical resection would be clinically appropriate are excluded from the study. ;9. Has an active autoimmune disease, or a syndrome that requires systemic steroids or immunosuppressive agents. Subjects that require inhaled corticosteroids would not be excluded from the study. Subjects with a history of autoimmune disease who have not required systemic steroids or immunosuppressive agents for 2 years prior to signing informed consent would not be excluded from this study, however subjects with any history of autoimmune induced thyroid dysfunction WILL be excluded from this study. Subjects with vitiligo or resolved childhood asthma/atopy would not be excluded from the study. Subjects that require local steroid injections would not be excluded from the study. Subjects with hypothyroidism stable on hormone replacement would not be excluded from the study. ;10. Has had an allogeneic tissue/solid organ transplant.;11. Has had a history of pneumonitis that has required oral or IV steroids. Subjects whose pneumonitis was solely a result of radiation therapy for their

NSCLC would not be excluded from the study unless they received oral/IV steroids to manage the pneumonitis. ;12. Has received or will receive a live vaccine within 30 days prior to the first administration of study medication.;13. Has an active infection requiring intravenous systemic therapy.;14. Has known history of Human Immunodeficiency Virus (HIV) (HIV 1/2 antibodies).;15. Has known active Hepatitis B or C.

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:	Recruitment stopped
Start date (anticipated):	20-08-2014
Enrollment:	9
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Abraxane, Taxol
Generic name:	Paclitaxel
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Alimta
Generic name:	Pemetrexed
Registration:	Yes - NL intended use
Product type:	Medicine

Brand name:	NA
Generic name:	Carboplatin
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	NA
Generic name:	Cisplatine
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	19-06-2014
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	20-08-2014
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	21-11-2014
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	05-12-2014
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	19-02-2015
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO	

Date:	25-03-2015
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	28-05-2015
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	19-06-2015
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:	05-04-2016
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	06-09-2016
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:	10-02-2017
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	01-03-2017
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
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:	18-01-2018
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	02-08-2018
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	EUCTR2014-000323-25-NL
CCMO	NL49036.056.14