A Multicenter, Randomized, Controlled, Three-Arm, Phase III Study to Evaluate the Safety and Efficacy of Two Dosing Schedules of Pembrolizumab (MK-3475) Compared to Ipilimumab in Patients with Advanced Melanoma

Published: 13-08-2013
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1. To evaluate progression-free-survival (PFS) in patients with advanced MEL receiving either Pembrolizumab or IPI.2. To evaluate overall survival (OS) in patients with advanced MEL receiving either Pembrolizumab or IPI.

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

Summary

ID

NL-OMON44956

Source
ToetsingOnline

Brief title
MK3475-006

Condition

- Skin neoplasms malignant and unspecified

Synonym
Cancer, Melanoma

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: Advanced, Ipilimumab, Melanoma, MK3475

Outcome measures

Primary outcome

The following evaluations will be performed throughout the course of the study

(see flowchart, 1.7 of protocol for more details):

- Tumor resonse assessments by physical examination, and tumor imaging by CT or

MRI

- Anti-MK3475 antibodies (MK3475 patients only)

- PK measurements (PK peak/trough)

- ECOG performance status

- Tumor biopsies

- EORTC QLQ-C30 / EuroQol EQ-5D

- Health Economic Assessment

Secondary outcome

N/A

Study description

Background summary

The programmed cell death 1 (PD-1) pathway represents a major immune control switch which may be engaged by tumor cells to overcome active T-cell immune surveillance. The ligands for PD-1 (PD-L1 and PD-L2) are constitutively expressed or can be induced in various tumors. High expression of PD-L1 on tumor cells (and to a lesser extent of PD-L2) has been found to correlate with poor prognosis and survival in various cancer types, including renal cell carcinoma (RCC), pancreatic carcinoma, hepatocellular carcinoma, ovarian carcinoma and non-small cell lung cancer (NSCLC).
Furthermore, PD-1 has been suggested to regulate tumor-specific T-cell expansion in patients with malignant MEL.

Preclinical in vitro and in vivo experiments have shown that PD-1 and/or PD-L1 blockade using monoclonal antibodies (mAb) enhances tumor-cell specific T-cell activation, cytokine production, anti-tumor effector mechanisms, and clearance of tumor cells by the immune system. Recent data with nivolumab (BMS-936558), an IgG4 antibody against PD-1, have validated PD-1 as an attractive target for clinical therapeutic intervention. In a recent report of the clinical trial data with nivolumab a total of 296 patients with advanced melanoma, NSCLC, castration -resistant prostate cancer, renal-cell carcinoma or colorectal cancer were treated at a dose of 0.1, 0.3, 1, 3, or 10 mg/kg every 2 weeks. Among 236 evaluable patients, cumulative response rates (all doses and defined by the Response Evaluation Criteria in Solid Tumors [RECIST] were 18% among patients with NSCLC, 28% among patients with melanoma, and 27% among patients with renal-cell cancer. Responses were reported to be durable: 20 of 31 responses lasted 1 year or more in patients with 1 year or more of follow-up. Grade 3 or 4 adverse events were observed in 49% of patients, while 14% of patients had treatmentrelated Grade 3 or 4 adverse events. Drug-related adverse events of special interest (e.g.,
those with potential immune-related causes) occurred in 41% of patients and included pneumonitis, vitiligo, colitis, hepatitis, hypophysitis, and thyroiditis.

MK-3475 (previously known as SCH 900475) is a potent and highly-selective humanized mAb of the IgG4/kappa isotype designed to directly block the interaction between PD-1 and its ligands, PD-L1 and PD-L2. MK-3475 strongly enhances T lymphocyte immune responses in cultured blood cells from healthy human donors, cancer patients, and primates. In T-cell activation assays using human donor blood cells, the EC50 was in the range of 0.1 to 0.3 nM. MK-3475 also modulates the level of interleukin-2 (IL-2), tumor necrosis factor alpha, interferon gamma, and other cytokines. The antibody potentiates existing immune responses only in the presence of antigen and does not nonspecifically activate T-cells.

An open-label Phase I study (PN001) is being conducted to evaluate the safety and clinical activity of single agent MK-3475. The dose escalation portion of this study found the dose levels, 1 mg/kg, 3 mg/kg, and 10 mg/kg, well tolerated and no doselimiting toxicities were observed at doses of up to 10

mg/kg given every 2 weeks. Preliminary evidence of antitumor activity was observed in MEL. The ongoing expansion cohort in Protocol 001 is enrolling metastatic MEL patients and promising preliminary anti-cancer activity was observed with objective responses in 26 of 62 MEL patients (42%; 95% CI: 30%, 55%) after centrally reviewed assessment by the Response Evaluation Criteria in Solid Tumors (RECIST 1.1). Among the IPI naive (n=45) and IPI treated (n=17) patients the observed response rates were 42% (95% CI: 28%, 58%) and 41% (95% CI: 18%, 67 %), respectively. The adverse events (AE) analysis suggested a safety profile which resembles that of nivolumab, with fatigue, rash, and diarrhea as the most common drug-related AEs (mostly grade 1-2). This early anti-tumor activity warrants further evaluation of MK-3475 in advanced MEL patients.

Ipilimumab (Yervoy) was recently approved and regarded as the standard of care treatment for patients with unresectable and metastatic melanoma that are either previously untreated (approved with a first line indication in USA) or treated with other therapies (approved with a second line indication in EU). Ipilimumab is a monoclonal antibody that blocks CTLA-4, a negative regulator of T-cells, and thereby augments Tcell activation and proliferation. Two pivotal trials of IPI have shown an overall survival benefit (median overall survival of 10-11 months) with overall tumor response rates of 11or 15% in MEL patients treated with IPI. In MEL patients who received IPI alone, grade 3/4 AEs occurred in 46% of the patients while 15% of the overall patients experienced grade 3/4 immune-related AEs.

Despite the recent advances in the treatment of MEL patients, overall outlook for patients with metastatic MEL remains dismal and the development of new effective therapy is still needed. Anti-PD1 mAb nivolumab has reported a response rate of 28% in MEL patients. MK-3475 has shown a very promising early response rate of 42% in patients who have not received prior IPI treatment, which is much higher than the 11 or 15% response rate observed in IPI registration trials. Taken all of the above together, the existing data support the evaluation of the safety and efficacy of MK-3475 in patients with unresectable or metastatic MEL who have not received IPI treatment, for whom additional treatment options are needed. The current study will examine the efficacy of MK-3475 versus IPI in patients with unresectable or metastatic MEL who are IPI naive.

Study objective

1. To evaluate progression-free-survival (PFS) in patients with advanced MEL receiving either Pembrolizumab or IPI.

2. To evaluate overall survival (OS) in patients with advanced MEL receiving either Pembrolizumab or IPI.

Study design

This is a randomized, controlled, open-label, three-arm pivotal study of two dosing regimens of intravenous (IV) pembroliozumab versus IPI in patients with unresectable or metastatic MEL who have not received IPI treatment. The study will enroll approximately 645 patients randomized to one of two pembrolizumab arms or IPI in a 1:1:1 ratio, stratified by line of therapy, PD-L1 expression and ECOG performance status. The sample size was based on a target of 286-309 PFS events between an MK arm and the IPI arm at the second interim analysis (final analysis of PFS) and a target of 300 OS events between an MK arm and the IPI arm at the final analysis of OS. The primary endpoint of the study will be progression free survival (PFS) and overall survival (OS). Other endpoints include response rate, response duration, Health Related Quality of Life (HRQoL), and safety. The primary objective of the study is to evaluate for superiority of pembrolizumab to IPI in PFS or OS. The overall type I error rate for this study is strictly controlled at 2.5% (one-sided) with 0.5% allocated to PFS and 2.0% allocated to the overall OS hypothesis. The study is consider to be positive if at least one pembrolizumab arm is superior to IPI in PFS at the interim analysis OR at least one pembrolizumab arm is superior to IPI in OS at either an interim analysis or the final analysis of OS.

Patients randomized to one of the pembrolizumab arms will receive pembrolizumab as IV infusion at a dose of 10 mg/kg given once every 2 weeks or once every 3 weeks, until disease progression, intolerable toxicity, confirmed complete response, withdrawal of consent, or they require another form of antineoplastic therapy as determined by the Investigator. Patients randomized to the IPI arm will receive IPI at 3 mg/kg as IV infusion once every 3 weeks for a total of 4 doses. In order to best evaluate the overall survival objective of this study, patients who progress during the study will not be allowed to cross-over from one arm to the other as part of study therapy, and patients who progress on the IPI arm will be excluded from participation in other pembrolizumab trials unless the DMC or the SPONSOR determine that the study has achieved its efficacy objective(s).

After the baseline tumor evaluation, tumor assessment during the study will be performed by radiological scans every 6 weeks starting from Week 12 until Week 48. At the discretion of investigators, patients who remain on study after 48 weeks and are clinically stable may decrease imaging frequency to every 12 weeks. Patients will be evaluated for tumor response and patient management by sites based on the Immune Related Response Criteria [irRC] (Appendix 6.6) by the investigator with site radiology reading. Copies of tumor images will be collected and provided to a central imaging vendor, and subjected to independent central review. Independent central review will utilize RECIST 1.1 criteria for response assessment. During the course of the study, the Data Monitoring committee (DMC) will monitor all safety information to ensure patient safety in accordance with a separate charter. The DMC will also

evaluate the data at the planned interim analyses and make recommendations of stopping or continuing the study according to a separate charter. There are two planned interim efficacy analyses. The primary objective for the first interim analysis is a futility analysis based on ORR or PFS. The primary objective of the second interim analysis is to demonstrate clinical benefit in PFS. In addition to the IAs, the study will also take into account data external to the study from PN001, which also has an ongoing cohort of advanced melanoma patients who are being randomized to 10 mg/kg every 2 weeks or 10 mg/kg every 3 weeks. As data from PN001 may become available prior to the first IA for PN006, if there is sufficient evidence of superiority or futility for one of the two dosing regimens of MK-3475 from data external to the study, the SPONSOR may elect to discontinue one of the two MK-3475 arms in PN006 prior to the first interim analysis via a protocol amendment.

All patients will be required to submit a tumor tissue sample for PD-L1 expression
evaluation. A pre-defined subgroup analysis will be performed in patients with high PDL1
expression level.

Statistical significance was established for PFS at the first and second interim analyses and OS statistical significance was established at the second interim analysis, as specified by the protocol. The final analysis is supportive and was carried out per protocol. With amendment 05, ongoing Second Course subjects will be treated with a fixed dose of pembrolizumab 200 mg every 3 weeks (not weight-based).

Intervention

Completion of questionnaires, physical examination, ECG, blood draw, CT or MRI scan, intravenous administration of MK3475.

Study burden and risks

- 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.
- Blood samples: drawing blood from the arm may cause pain, bruising, lightheadedness, and rarely, infection.
- CT Scan: CT scans are used to create images of internal bones and organs using radiation. 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 with the disease 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 if diabetic, dehydrated (lost body water) or elderly.
- 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 and discussed 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. Other potential risks will be described to you and discussed with you by physicians who conduct these biopsies.

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)
Patient must have a histologically confirmed diagnosis of unresectable stage III or metastatic MEL not amenable to local therapy.
* Patient may not have a diagnosis of uveal or ocular melanoma.;* Patients who have not received prior systemic treatment (excluding adjuvant or neoadjuvant therapy) for MEL (first line) or who have received one prior systemic treatment (excluding adjuvant or neoadjuvant therapy) for MEL (second line) are both eligible. However, the enrollment of either first line or second line patients will be limited to approximately 387 patients (60% of the total patients). After this limit is reached for either of the groups, only patients from the other group will be enrolled.;* Patients must have testing for a BRAF mutation prior to study entry. Patients with BRAF V600E mutant melanoma may have received prior BRAF inhibitor therapy as first-line systemic therapy and be eligible for this study as second line treatment. At the discretion of the investigator, patients with BRAF V600E mutant melanoma who have NOT received a BRAF inhibitor are also eligible for this study as first line treatment if they meet the following additional criteria:
* LDH < local ULN
* No clinically significant tumor related symptoms in the judgment of the investigator
* Absence of rapidly progressing metastatic melanoma in the judgment of the investigator;2) Patient is male or female and *18 years of age on day of signing informed consent, either by the patient or a parent or legal guardian.;3)
Patient must have a performance status of 0 or 1 on the Eastern Cooperative Oncology Group (ECOG) Performance Scale (Appendix 6.4).;4)
Patient must have adequate organ function as indicated by the protocol.;5)
Patient has a tumor sample (archival or newly obtained biopsy) that is adequate for PD-L1 assessment prior to randomization. Patients must submit the tumor sample during screening for PD-L1 expression testing at a central pathology laboratory. Patients will be eligible to participate regardless of the level of PD-L1 expression, but will be stratified by PD-L1 expression level (high or low PD-L1 expression level) at the time of randomization. Patients who do not submit a sample adequate for PD-L1 determination will not be randomized. Patients with an inadequate archival sample may obtain a new biopsy and patients with an inadequate newly obtained biopsy may undergo re biopsy at the discretion of the investigator.;6)
Female patient of childbearing potential has a negative urine or serum pregnancy test. If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required. The serum pregnancy test must be negative for the patient to be eligible.;7)
Female patients enrolled in the study, who are not free from menses for >18 months, post hysterectomy/oophorectomy, or surgically sterilized, must be willing to use either 2 adequate barrier methods or a barrier method plus a hormonal method of contraception to prevent pregnancy or to abstain from heterosexual activity throughout the study, starting with Visit 1 through 120 days after the last dose of study therapy. Approved contraceptive methods include 2 of the following barrier methods or one barrier method combined with a hormonal contraceptive: intra uterine

device, diaphragm with spermicide, cervical cap with spermicide, male condoms, or female condom with spermicide. Spermicides or condoms alone are not an acceptable method of contraception.
Male patients must agree to use an adequate method of contraception starting with the first dose of study drug through 120 days after the last dose of study therapy.

Exclusion criteria

1)
Patient had prior treatment with IPI or other anti-CTLA-4 agent, any anti-PD-1, anti-PD-L1, or anti- PD-L2 agent.;2)
Patient who has had chemotherapy, radioactive, or biological cancer therapy within four weeks prior to the first dose of study drug, or who has not recovered to CTCAE Grade 1 or better from the AEs due to cancer therapeutics administered more than four weeks earlier.;3)
Patient 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 study drug.;4)
Patient is expected to require any other form of systemic or localized antineoplastic therapy while on study.;5)
Patient is on any systemic corticosteroid therapy within one week before the planned date for first dose of randomized treatment or on any other form of immunosuppressive medication.;6)
Patient has a history of a malignancy (other than the disease under treatment in the study) within 5 years prior to first study drug administration. This should exclude adequately treated Stage 1 or Stage 2 basal/squamous cell carcinoma of the skin, carcinoma in situ of the cervix or breast, or other in situ cancers. Shorter intervals can be considered after discussion with Sponsor.;7)
Patient has known active central nervous system (CNS) metastases and/or carcinomatous meningitis. Patients 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 study drug), have no evidence of new or enlarging brain metastases and are off systemic steroids for at least two weeks.;8)
Patient previously had a severe hypersensitivity reaction to treatment with another mAb.

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):	11-12-2013
Enrollment:	18
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	KEYTRUDA
Generic name:	Pembrolizumab
Product type:	Medicine
Brand name:	Yervoy
Generic name:	Ipilimumab
Registration:	Yes - NL intended use

Ethics review

Approved WMO

Date:	13-08-2013
Application type:	First submission
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)

Approved WMO

Date:	14-11-2013
Application type:	First submission
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)

Approved WMO Date:	29-11-2013
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	05-12-2013
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	10-04-2014
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	16-05-2014
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	15-09-2014
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	30-09-2014
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	05-12-2014
Application type:	Amendment
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Application type:	Amendment

Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	19-02-2015
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
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Approved WMO	

Date:	12-01-2016
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Approved WMO Date:	15-01-2016
Application type:	Amendment
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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	EUCTR2012-004907-10-NL
CCMO	NL45963.031.13
Other	Nog niet bekend