A Phase II clinical trial of MK-3475 (pembrolizumab) in subjects with relapsed or refractory (R/R) classical Hodgkin Lymphoma (cHL)

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Primary objectives:(1) To determine the safety and tolerability of pembrolizumab. (2) To evaluate the Overall Response Rate (ORR) of pembrolizumab by independent central review according to the International Working Group (IWG) response criteria (...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Lymphomas Hodgkin's disease
Study type	Interventional

Summary

ID

NL-OMON42797

Source
ToetsingOnline

Brief title
MK3475-087

Condition

- Lymphomas Hodgkin's disease

Synonym
Hodgkin lymphoma; Hodgkin's disease

Research involving
Human

Sponsors and support

Primary sponsor: Merck Sharp & Dohme (MSD)

Source(s) of monetary or material Support: Industrie

Intervention

Keyword: Hodgkin lymphoma, Pembrolizumab

Outcome measures

Primary outcome

- Safety and tolerability of pembrolizumab

- Overall Response Rate (independent central review)

Secondary outcome

- Overall Response Rate (investigator assessment)

- Complete Remission Rate

- Progression Free Survival

- Duration of Response

- Overall Survival

Study description

Background summary

Hodgkin lymphoma (HL) accounts for approximately 10 percent of all lymphomas and approximately 0.6 percent of all cancers diagnosed in the developed world annually. Although, HL is curable in 80% of patients diagnosed, new therapies are needed, especially for patients who present with advanced disease. The standard of care for patients with relapsed or refractory HL is salvage chemotherapy and anti-CD-30 therapy followed by autologous stem-cell transplantation (auto-SCT), which can induce long-term remissions in approximately 50% of patients. For patients who experience relapse or progressive HL within 1 year after auto-SCT, the prognosis is exceedingly poor with a median survival time of approximately 1.2 years. The median PFS after brentuximab is only 5.6 months requiring the development of additional therapies that will improve PFS in this patient population. Patients who have also progressed after brentuximab vedotin (anti-CD-30) have no currently available standard of care and represent an urgent unmet medical need.

This study aims to characterize the safety and tolerability of pembrolizumab in subjects with relapsed or refractory Hodgkin Lymphoma.

Study objective

Primary objectives:
(1) To determine the safety and tolerability of pembrolizumab.
(2) To evaluate the Overall Response Rate (ORR) of pembrolizumab by independent central review according to the International Working Group (IWG) response criteria (Cheson, 2007).

Secondary objectives:
(1) Evaluate ORR of pembrolizumab by investigator assessment according to the IWG response criteria; and additionally by independent central review using the 5-point scale according to the Lugano Classification.
(2) Evaluate Complete Remission Rate (CRR) of pembrolizumab by independent central review and by investigator assessment according to the IWG response criteria;and additionally by independent central review using the 5-point scale according to the Lugano Classification.
(3) Evaluate Progression Free Survival (PFS) and Duration of Response (DOR) of pembrolizumab by independent central review and by investigator assessment according to the IWG response criteria.
(4) Evaluate the Overall Survival (OS) of pembrolizumab.

Study design

This is a multicenter, single arm, multi-cohort, nonrandomized trial of pembrolizumab (MK-3475) in subjects with relapsed or refractory classical Hodgkin lymphoma: that have failed to achieve a response or progressed after auto-SCT and have relapsed after treatment with or failed to respond to brentuximab vedotin post auto-SCT (Cohort 1); that are ineligible for a stem cell transplant (unable to achieve a CR or PR to salvage chemotherapy) and have relapsed after treatment with or failed to respond to brentuximab vedotin post auto-SCT (Cohort 2); and subjects that have failed to respond to or progressed after auto-SCT and have not received brentuximab vedotin post auto-SCT. These patients could have received brentuximab vedotin as part of primary or salvage treatment (Cohort 3).

Intervention

All enrolled patients: pembrolizumab 200mg IV every three weeks

Study burden and risks

Patients will receive the study drug every 3 weeks for up to 24 months. After achieving complete response and subsequent discontinuation of the initial

treatment periode, additional treatment is possible (under certain conditions) for up to 1 year for patients who experience disease progression.

The patient will visit the doctor every 3 weeks. The first visit, a tumor biopsy (if needed) and a bone marrow biopsy will be taken. Every other visit a physical examination will be performed and every visit blood samples will be taken (volume range 2-41 ml per visit). Patients will also electronically complete EuroQol EQ-5D and EORTC QLQ-C30 questionnaires at all visits except 6, 7 and 8.

The patient may experience physical and/or psychological discomfort with the procedures performed during the visits, such as blood sampling, biopsies, IV line, ECG, CT/PET scan, pulmonary function test.

The main side effect reported with the use of MK3475 are fatigue, itching, rash, frequent or excessive bowel movements, joint pain and nausea.

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

See protocol section 5.1.2 for a complete overview of the inclusion criteria.;1. Be willing and able to provide written informed consent/assent for the trial. The subject may also provide consent/assent for Future Biomedical Research. However, the subject may participate in the main trial without participating in Future Biomedical Research.
2. Be at least 18 years of age on day of signing informed consent.
3. Have relapsed* or refractory* de novo classical Hodgkin lymphoma and meet one of the following cohort inclusions:
*Relapsed: disease progression after most recent therapy
*Refractory: failure to achieve CR or PR to most recent therapy
a. Cohort 1: Have failed to achieve a response or progressed after auto-SCT. Subjects must have relapsed after treatment with or failed to respond to brentuximab vedotin post auto-SCT.
b. Cohort 2: Are ineligible (unable to achieve a complete or a partial response to salvage chemotherapy) for auto-SCT. Subjects must have relapsed after treatment with or failed to respond to brentuximab vedotin post auto-SCT.
c. Cohort 3: Have failed to achieve a response or progressed after auto-SCT and have not have received brentuximab vedotin post auto-SCT. Note: These subjects could have received brentuximab vedotin as part of primary treatment, or salvage treatment.
4. Have measureable disease defined as at least one lesion that can be accurately measured in at least two dimensions with spiral CT scan. Minimum measurement must be > 15 mm in the longest diameter by > 10 mm in the short axis.
5. Be able to provide an evaluable core or excisional lymph node biopsy for biomarker analysis from an archival or newly obtained biopsy at Screening. In addition subjects may provide additional biopsy at Week 12 and at the time of discontinuation due to progression. If submitting unstained cut slides, freshly cut slides should be submitted to the testing laboratory within 14 days from when the slides are cut. See Section 7.1.2.6.8 for an explanation.
6. Must have a performance status of 0 or 1 on the ECOG Performance Scale.
7. Must demonstrate adequate organ function as defined in Table 1; all screening labs should be performed within 7 days of treatment initiation.
8. Female subject of childbearing potential should have a negative urine or serum pregnancy within 72 hours prior to receiving the first dose of study medication. If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required.
9. Female subjects of childbearing potential should be willing to use 2 methods of birth control or be surgically sterile, or abstain from heterosexual activity for the course of the study through 120 days after the last dose of study medication (Reference Section 5.7.2). Subjects of child bearing potential are those who have not been surgically sterilized or have not been free from menses for > 1 year.
Note: Abstinence is acceptable if this is the established and preferred contraception for the subject.

10. Male subjects should agree to use an adequate method of contraception starting with the first dose of study therapy through 120 days after the last dose of study therapy.

Exclusion criteria

See protocol section 5.1.3 for a complete overview of the exclusion criteria.;1. Is currently participating and receiving study therapy or has participated in a study of an investigational agent and received study therapy or used an investigation device within 4 weeks of the first dose of treatment.
2. Has a diagnosis of immunosuppression or is receiving systemic steroid therapy or any other form of immunosuppressive therapy within 7 days prior to the first dose of trial treatment. The use of physiologic doses of corticosteroids may be approved after consultation with the Sponsor
3. Has had a prior monoclonal antibody within 4 weeks prior to study Day 1 or who has not recovered (i.e. <= Grade 1 or at baseline) from adverse events due to agents administered more than 4 weeks earlier.
-Note: Subjects with <= Grade 2 neuropathy are an exception to this criterion and may qualify for the study.
4. Has had prior chemotherapy, targeted small molecule therapy, or radiation therapy within 2 weeks prior to study Day 1 or who has not recovered (i.e. <= Grade 1 or at baseline) from adverse events due to a previously administered agent.
-Note: Subjects with <= Grade 2 neuropathy are an exception to this criterion and may qualify for the study.
-Note: If subject received major surgery, they must have recovered adequately from the toxicity and/or complications from the intervention prior to starting therapy.
-Note: Toxicity that has not recovered to <= Grade 1 is allowed if it meets the inclusion requirements for laboratory parameters defined in Table 1.
5. Has undergone prior allogeneic hematopoetic stem cell transplantation within the last 5 years. (Subjects who have had a transplant greater than 5 years ago are eligible as long as there are no symptoms of GVHD.)
6. Has a known additional malignancy that is progressing or requires active treatment. Exceptions include basal cell carcinoma of the skin, squamous cell carcinoma of the skin, or in situ cervical cancer that has undergone potentially curative therapy.
7. Has known clinically active CNS involvement.
8. Has active autoimmune disease that has required systemic treatment in past 2 years (i.e. with use of disease modifying agents, corticosteroids or immunosuppressive drugs). Replacement therapy (e.g., thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency, etc.) is not considered a form of systemic treatment
9. Has evidence of active, non-infectious pneumonitis.
10. Has an active infection requiring intravenous systemic therapy.
11. Has known psychiatric or substance abuse disorders that would interfere with cooperation with the requirements of the trial.
12. Is pregnant or breastfeeding, or expecting to conceive or father children within the projected duration of the trial, starting with the pre-screening or screening visit through 120

days after the last dose of trial treatment.
13. 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).
14. Has a known Human Immunodeficiency Virus (HIV), Hepatitis B (HBV), or Hepatitis C (HCV) infection.
15. Has received a live vaccine within 30 days prior to first dose.
16. Is or has an immediate family member (e.g., spouse, parent/legal guardian, sibling or child) who is investigational site or sponsor staff directly involved with this trial, unless prospective IRB approval (by chair or designee) is given allowing exception to this criterion for a specific subject.

Study design

Design

Study phase:	2
Study type:	Interventional
Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	07-08-2015
Enrollment:	9
Type:	Anticipated

Medical products/devices used

Product type:	Medicine
Brand name:	Pembrolizumab
Generic name:	Pembrolizumab

Ethics review

Approved WMO Date:	13-05-2015
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	21-07-2015
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	22-07-2015
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:	09-02-2016
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	12-02-2016
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	EUCTR2014-004482-24-NL
CCMO	NL53010.056.15