An Open-label, Uncontrolled, Multicenter Phase II Trial of MK-3475 (Pembrolizumab) in Children and Young Adults with Newly Diagnosed Classical Hodgkin Lymphoma with Inadequate (Slow Early) Response to Frontline Chemotherapy (KEYNOTE 667).

Published: 05-08-2020
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This study has been transitioned to CTIS with ID 2023-504821-38-00 check the CTIS register for the current data. Goal of this study is to determine the optimal balance between maintaining high rates of OS in this group and avoiding the long-term...

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

Summary

ID

NL-OMON52677

Source
ToetsingOnline

Brief title
MK3475-667

Condition

- Lymphomas Hodgkin's disease

Synonym
Hodgkin's Lymphoma

Research involving
Human

Sponsors and support

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

Intervention

Keyword: Classic hodgkin, Pediatric, pembrolizumab, Phase 2

Outcome measures

Primary outcome

Objective: To evaluate the objective response rate (ORR) by International

Working Group (IWG) criteria as assessed by blinded independent central review

(BICR) [Cheson, B. D., et al 2007] of pembrolizumab in combination with

chemotherapy in slow early responders (SERs) by risk group (low, high)

Objective response: Complete response (CR) or partial response (PR)

Secondary outcome

(1)

Objective: To evaluate the rate of PET-negativity, 2-year event-free survival

(EFS) from study enrollment, and overall survival (OS) of pembrolizumab in

combination with chemotherapy in SERs by risk group.

Objective reponse:

- PET negativity: Deauville score (1, 2 or 3) after 2 cycles of AVD or 4 cycles

of COPDAC-28, in combination with pembrolizumab.

- EFS: Time from study enrollment to the first documented disease progression

or recurrence, or death due to any cause, whichever occurs first.

- OS: Time from study enrollment to death due to any cause

(2)

Objective: To evaluate the exposure to radiation therapy (RT) and its

associated toxicity in SERs by risk group

Objective response:

- Exposure to RT: Frequency and details of RT

(3)

Objective: To evaluate of the 3-year EFS per investigator assessment and OS in

rapid early responders (RERs) by risk group.

Objective response:

- EFS: Time from study enrollment to the first documented disease progression

or recurrence, or death due to any cause, whichever occurs first.

- OS: Time from study enrolment to death due to any cause

(4)

Objective: To evaluate serum thymus and activation-regulated chemokine (TARC)

as a potential biomarker in SERs by risk group.

Objective reponse:

- Serum TARC levels at screening, early and late response assessments.

(5)

Objective: To evaluate the safety of pembrolizumab in combination with

chemotherapy in SERs by risk group.

Objective reponse:

- Participants experiencing adverse events (AEs)

- Participants discontinuing study treatment due to AEs

Study description

Background summary

Although current treatment for Hodgkin Lymphoma patients results in high 5 years survival rates, a subgroup of cHL patients remains from which initial cure rates are suboptimal. For both adults and children, this group is identified as slow early responders to chemotherapy. As a result, many cooperative groups have used the strategy of dose intensification with chemotherapy and/or radiation to achieve comparable survival rates, however an increase of (longterm) toxicity occured in these patients.
In the Pediatric Oncology Group (POG) 9425 and 9426 trials, a more intense chemotherapy was used for those who sustained an inadequate response to frontline chemotherapy. The French Society of Pediatric Oncology added an extra dose of of radiotherapy (RT) and/or chemotherapy based on early response to their chemotherapy backbone. In POG 9425, comparable results were found upon tailoring therapy to the response, with no statistical difference in 3-year event-free survival (EFS) for 3 versus 5 cycles of chemotherapy.
In AHOD0831, additional chemotherapy, 2 cycles of ifosfamide plus vinorelbine, were associated with increased exposure to alkylating agents and associated toxicity.
It was increasingly apparent that the comparable cure rates were bought at a high price and that this dose intensification was associated with significant risk of premature second malignancies, cardiovascular disease, pulmonary toxicity, gonadal and nongonadal toxicity and early mortality [Castellino, S. M., et al 2011].

Study objective

This study has been transitioned to CTIS with ID 2023-504821-38-00 check the CTIS register for the current data.

Goal of this study is to determine the optimal balance between maintaining high rates of OS in this group and avoiding the long-term toxicity associated with therapy intensificiation. The addition of pembrolizumab to standard care is expected to overcome resistance to the initial agens and to prevent long term complications associated with the initial agents.

Study design

This is a nonrandomized, open-label study with two groups of patients at a single center to evaluate the effect and longterm toxicity after therapy with pembrolizumab combined with 4 cycles of COPDAC-28 chemotherapy, followed by RT, with or without pembrolizumab, in cHL patients with a slow, early response to first-line chemotherapy.

Intervention

Patients complete 2 cycles of OEPA induction chemotherapy to determine the Deauville score, as asessed by PET. Patients with score 4 or 5 (ie, SERs) will receive pembrolizumab in combination with 4 cycles of COPDAC-28. The patients will have a their PET scores assessed again after completing COPDAC-28 chemotherapy; patients with a positive PET-score will then receive RT while continuing their pembro treatment, while patients with a negative PET response will continue their pembro treatment without receiving RT.

Study burden and risks

Participants in this clinical study are not garantueed to directly benefit from treatment during participation. However, the investigational agent pembrolizumab, inhibitor of PD-1 signaling, has been registered for adult patients with relapse/refractory cHL. Based on current evidence, no difference in mechanism of action and activity are expected in cHL between children and adults. In addition, the safety profile of pembrolizumab in pediatric patients was similar to that seen in adults. Therefore, pembrolizumab has the potential to offer children with newly diagnosed cHL a therapy that is expected to be well tolerated and in addition may improve the response to early chemotherapy and reduce cumulative drug toxicity.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adolescents (12-15 years)
Adolescents (16-17 years)
Children (2-11 years)

Inclusion criteria

Type of participants and disease characteristics
- Must be a male or female between the age 3-25 years inclusive on the day of signing informed consent/assent
- Newly diagnosed, pathologically confirmed classical Hodgkin Lymphoma: stage IIEB, IIIEA, IIIEB, IIIB, IVA, IVB
- Measurable disease per investigator assessment
Contraception
- Male participants are eligible to participate if they agree to follow the contracaption guidance clarified in the protocol. The lenght of time required to continue contraception after the last dose for each study intervantion is clarified in the protocol.
- A female participant is eligible if she is not pregnant, not breastfeeding and not a woman of chilbearing potential OR agreeing to follow contraceptive guidance according to protocol.
Informed consent
- The participant (or legally acceptable representative if applicable) provides written informed consent/assent for the study
Additional Criteria
- Performance status:

- Lansky Play-Performance Scale >=50 for children up to 16 years of age
-Karnofsky score >=50 for participants >=16 years of age
- Adequate organ function

Exclusion criteria

Medical Conditions
- Has undergone solid organ transplant at any time, or prior allogeneic hematopoietic stem cell transplantation within the last 5 years.
- A WOCBP who has a positive urine pregnancy test within 24 hours before the first dose of study treatment.
- Baseline left ventricular ejection fraction value <50% or shortening fraction of <27%
Prior/Concomitant Therapy
- Has received prior therapy with anti-PD1/PD-L1/PD-L2 or with an agent directed to another co-inhibitory T cell receptor or has previously participated in a Merck pembro clinical study
- Received prior systemic anti-cancer therapy, including investigational agent
- Received a live or live-attenuated vaccine within 30 days before the first dose of study intervention.
Prior/Concurrent Clinical Study Experience
- Has received an investigational agent or has used an investigational device within 4 weeks prior to study intervention administration

Diagnostic assessments
- Has a diagnosis of lymphocyte-predominant HL
- Has a diagnosis of immunodeficiency or is expected to be receiving chronic systemic steroid therapy or any other immunosuppressive therapy within 7 days prior to the first dose of pembro.
- Has a known additional malignancy that is progressing or requires active treatment within the past 3 years
- Has radiographically detectable central nervous system metastases and/or carcinomatous meninginitis as assessed by local site investigator at the time of diagnosis.
- Has severe hypersensitivity to any study therapies including any excipients.
- Has an active autoimmune disease that has required systemic treatment in past 2 years except replacement therapy.
- Has a history of (non-infectious) pneumonitis that required steroids or has current pneumonitis.
- Has an active infection requiring systemic therapy.
- Has a known history of human immunodeficiency virus (HIV) infection.
- Has a known history of Hepatitis B or known active Hepatitis C virus infection.
- Has a history or current evidence of any condition, therapy, or laboratory abnormality that might confound the results of the study, interfere with the

participant's participation for the full duration of the study, or is not in the best interest of the participant to participate, in the opinion of the treating investigator.
- Has known psychiatric or substance abuse disorders that would interfere with cooperating with the requirements of the study.
- Participants who have not adequately recovered from major surgery or have ongoing
surgical complications.

Study design

Design

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

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	26-03-2021
Enrollment:	25
Type:	Actual

Medical products/devices used

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

Ethics review

Approved WMO

Date:	05-08-2020
Application type:	First submission
Review commission:	METC NedMec
Approved WMO Date:	27-10-2020
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	30-12-2020
Application type:	First submission
Review commission:	METC NedMec
Approved WMO Date:	07-06-2021
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	27-07-2021
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	28-07-2021
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	09-11-2021
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	24-11-2021
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	01-02-2022
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO	

Date:	25-02-2022
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	29-07-2022
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	02-08-2022
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	02-09-2022
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	14-09-2022
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	19-01-2023
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	31-01-2023
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	13-05-2023
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	23-05-2023
Application type:	Amendment
Review commission:	METC NedMec

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
EU-CTR	CTIS2023-504821-38-00
EudraCT	EUCTR2017-001123-53-NL
ClinicalTrials.gov	NCT03407144
CCMO	NL72212.041.20