A Randomized Phase III study of pembrolizumab given concomitantly with chemoradiation and as maintenance therapy versus chemoradiation alone in subjects with locally advanced head and neck squamous cell carcinoma (KEYNOTE-412)

Published: 09-01-2017
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Primary: To compare Event-free survival (EFS) per RECIST in subjects treated with pembrolizumab in combination with CRT and subjects treated with placebo in combination with CRT.Secondary:(1) To compare Overall Survival (OS) in subjects treated with...

Ethical review	Approved WMO
Status	Completed
Health condition type	Other condition
Study type	Interventional

Summary

ID

NL-OMON49768

Source
ToetsingOnline

Brief title
MK3475-412

Condition

- Other condition
- Miscellaneous and site unspecified neoplasms malignant and unspecified

Synonym

head- and neck cancer, head and neck squamous cell carcinoma

Health condition

hoofd-hals tumoren

Research involving
Human

Sponsors and support

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

Intervention

Keyword: chemoradiation, Head & Neck carcinoma, pembrolizumab

Outcome measures

Primary outcome

Event free survival (EFS) by RECIST 1.1

Secondary outcome

Overall Survival (OS)

Safety and tolerability of pembrolizumab + CRT

Changes with regard to baseline of global health status / quality of life, and

swallowing, speech and pain symptoms, as measured by EORTC QLQ-C30 and

QLQ-H&N35

Study description

Background summary

Head and neck squamous cell carcinoma (HNSCC) is the seventh most common cancer worldwide with around 600,000 new cases diagnosed per year. Around 50% of HNSCC are diagnosed at a locally advanced stage. The survival rates for all subjects with HNSCC are around 70% at 1 year and 40-60% at 5 years. The treatment choice depends on the location of the primary tumor, the stage of the disease, and the

expected oncological and functional outcomes. Early stage HNSCC is usually treated with single modality therapy, i.e., surgery or RT. The standard of care for locally advanced HNSCC cancers not treated by surgery is concomitant CRT with high-dose cisplatin. Meta-analysis of chemotherapy in combination with radiation therapy (RT) for HNSCC showed that the addition of chemotherapy concomitantly to RT improves the absolute 5-year survival by 6.5%. There is a huge need to identify new treatment strategies that can increase the efficacy of CRT. Preclinical studies suggesting the importance of immune priming would support the notion that administering pembrolizumab prior to CRT may be important. An initial phase IB Merck Investigator Studies Program (MISP) study of pembrolizumab in combination with CRT for locally advanced HNSCC has been initiated to evaluate the safety and tolerability of pembrolizumab combined with cisplatin and RT. The preliminary results of the combination of pembrolizumab with CRT in this MISP study supports further investigation into the potential activity and safety of this treatment regimen.

Study objective

Primary:
To compare Event-free survival (EFS) per RECIST in subjects treated with pembrolizumab in combination with CRT and subjects treated with placebo in combination with CRT.

Secondary:
(1) To compare Overall Survival (OS) in subjects treated with pembrolizumab in combination with CRT and subjects treated with placebo in combination with CRT.
(2) To evaluate and compare the safety and tolerability profile of pembrolizumab in combination with CRT and subjects treated with placebo in combination with CRT.
(3) To compare mean change from baseline in quality of life and physical functioning, and swallowing, speech and pain symptoms in subjects treated with pembrolizumab in combination with CRT and subjects treated with placebo in combination with CRT.

Study design

This is a Phase III, randomized, placebo-controlled, double-blind study to determine the efficacy and safety of pembrolizumab given concomitantly with chemoradiation (CRT) and as maintenance therapy versus placebo plus CRT in subjects with locally advanced head and neck squamous cell carcinoma (LA HNSCC).

Intervention

Group 1:
Pembrolizumab 200 mg IV Q3W (up to 17 cycles) +

Cisplatin 100 mg/m2 IV Q3W (up to 3 cycles) +
Radiotherapy AFX (6 weeks) of SFX (7 weeks), 70Gy

Group 2:
Placebo (up to 17 cycles) +
Cisplatin 100 mg/m2 IV Q3W (up to 3 cycles) +
Radiotherapy AFX (6 weeks) of SFX (7 weeks), 70Gy

Study burden and risks

The patients will receive standard treatment for HNSCC during the first 8 weeks. Standard treatment consists of chemoradiation therapy. Intravenously administered pembrolizumab or placebo will be added concomitantly. In this phase, the patients will visit the clinic on a weekly basis.
After the first 8 weeks, the patients will receive either pembrolizumab or placebo, intravenously, every three weeks, up to a maximum of 17 treatments in total (approximately 1 year).
The standard treatment for this indication is quite invasive in itself. Many of the procedures mentioned hereafter are part of the standard treatment as well. The burden for the patient consists of;

- CT of head/neck or a CT of the chest + MRI of the head/neck, and FDG-PET or FDG-PET/CT scan.
- Oral and dental exam, neurological exam, audiometric testing.
- If needed (if not done in six weeks prior to screening), a fiber-optic exam + endoscopy with biopsy.
- A physical exam will be done during each study visit, and blood samples will be collected.
- Neck-dissection (if indicated)
- Completion of questionnaires

The patient may experience physical or psychological discomfort during the procedures taking place during the visits, such as blood collection, biopsy, administration of IV line, ECG, CT/MRI/PET scan. The most common side effects that have been reported with the use of MK3475 are fatigue, itching, decreased appetite, shortness of breath, coughing.

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. Have a pathologically proven new diagnosis of squamous cell carcinoma of:
a. Oropharyngeal p16 positive
b. Oropharyngeal p16 negative
c. Larynx/hypopharynx/oral cavity (independent of p16)
2. Be willing and able to provide written informed consent for the trial. The subject may also provide consent for Future Biomedical Research. However, the subject may participate in the main trial without participating in Future Biomedical Research.
3. Have results from (local) testing of HPV status for oropharyngeal cancer. If HPV status was previously tested using the method as prescribed by protocol, no additional testing is required.
4. Have provided adequate tissue in terms of quality and quantity for PD-L1 biomarker analysis from a core or excisional biopsy. If an excisional or incisional biopsy has been performed, subjects remain eligible for the study provided the residual disease meets the staging criteria required for the trial (e.g., excisional biopsy of a lymph node with residual T4 primary). Prior surgical debulking, including tonsillectomy, for the head and neck cancer under study is not allowed.
5. Be >=18 years of age on day of signing informed consent.
6. Have evaluable tumor burden (measurable and/or non-measurable tumor lesions)

assessed by CT scan or MRI, based on RECIST version 1.1.
7. Be eligible for definitive CRT and not considered for primary surgery based on investigator decision.
8. Have an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0 or 1 performed within 10 days of treatment initiation.
9. Female subjects of childbearing potential must have a negative urine or serum pregnancy test within 72 hours prior to receiving the first dose of trial treatment. If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required.
10. Female subjects of childbearing potential must be willing to use an adequate method of contraception as outlined in the protocol, for the course of the study through 180 days after the last dose of study medication.
11. Male subjects of childbearing potential must agree to use an adequate method of contraception as outlined in the protocol, starting with the first dose of study therapy through 180 days after the last dose of study therapy.
12. Demonstrate adequate organ function as defined in the protocol. All screening labs should be performed within 10 days prior to treatment initiation and assessed prior to randomizing the subject.

Exclusion criteria

1. Has current participation or treatment with an investigational agent or use of an investigational device within 4 weeks of the first dose of trial treatment.
2. Has received prior therapy with an anti-PD-1, anti-PD-L1, anti-PD-L2 agent or with an agent directed to another co-inhibitory T-cell receptor or has previously participated in Merck MK-3475 clinical trials.
3. Has received a live vaccine within 30 days prior to the first dose of study treatment.
4. Has cancer outside of the oropharynx, larynx, and hypopharynx or oral cavity, such as nasopharyngeal, sinus, other para-nasal, or other unknown primary HNC.
5. Has had prior systemic therapy, targeted therapy, radiotherapy treatment or radical surgery for head and neck cancer under study.
6. Has Grade >=2 audiometric hearing loss. Audiometric abnormalities without corresponding clinical symptoms of Grade >=2 hearing loss will not be grounds for exclusion.
7. Has Grade >=2 neuropathy.
8. Has Grade 3-4 bleeding due to the underlying malignancy.
9. If subject has received major surgery, and the subject has not recovered adequately form the toxicity and/or complications from the intervention prior to starting trial treatment.
10. Has known active Hepatitis B or C.
11. Has known history of Human Immunodeficiency Virus (HIV) (HIV-1/2 antibodies).

12. Has a diagnosis of immunodeficiency or is receiving systemic steroid therapy or any other form of immunosuppressive therapy within 7 days prior to the first dose of trial treatment. Corticosteroid use as pre-medication for allergic reactions (e.g. IV contrast), or as a prophylactic management of adverse events related to the chemotherapies specified in the protocol is allowed. A short course of steroids may be used as concomitant medication for either treatment of an adverse event or medical condition with Sponsor approval. The use of physiologic doses of corticosteroids may be approved after consultation with the Sponsor.
13. Has a history of (non-infectious) pneumonitis that required steroids or current pneumonitis.
14. Has an active autoimmune disease that has required systemic treatment in the 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.
15. Has history of a diagnosed and/or treated hematologic or primary solid tumor malignancy, unless in remission for at least 5 years prior to randomization. A T1-2 prostatic cancer Gleason score <=6, superficial bladder cancer, non melanomatous skin cancer or carcinoma in situ of the cervix is eligible. Other exceptions may be considered with Sponsor consultation.
16. Has known active central nervous system (CNS) metastases and/or carcinomatous meningitis.
17. Has had previous allogeneic tissue/solid organ transplant.
18. Has active infection requiring systemic therapy.
19. Has a history of severe hypersensitivity reaction (e.g., generalized rash/erythema, hypotension, bronchospasm, angioedema or anaphylaxis) to pembrolizumab, cisplatin or radiotherapy or their analogs.
20. Is a female subject who is pregnant or breast feeding or a male expecting to conceive or father children within the projected treatment phase of the trial, starting with the screening visit through 180 days after the last dose of trial treatment.
21. Have severe comorbidities that, in the opinion of the Investigator, might hamper participation in the study and/or the treatment administration.
22. Has a history or current evidence of any condition, therapy, or laboratory abnormality that might confound the results of the trial, interfere with the subject*s participation for the full duration of the trial, or is not in the best interest of the subject to participate, in the opinion of the treating investigator.
23. Has known psychiatric or substance abuse disorders that would interfere with cooperation with the requirements of the trial.

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Completed
Start date (anticipated):	07-09-2017
Enrollment:	40
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Cisplatin
Generic name:	cisplatin
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	KEYTRUDA
Generic name:	pembrolizumab
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO

Date:	09-01-2017
Application type:	First submission
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:	16-03-2017
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	27-03-2017
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:	04-10-2017
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	13-10-2017
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	19-02-2018
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	18-03-2018
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek

	(Assen)
Approved WMO Date:	11-06-2018
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	16-07-2018
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	26-07-2018
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	15-01-2019
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	09-09-2019
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	07-11-2019
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	11-11-2019
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	20-04-2020

Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	26-11-2020
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	18-03-2021
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	10-06-2021
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	16-10-2021
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	31-01-2022
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	11-06-2022
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	29-12-2022
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)

Approved WMO Date:	27-02-2024
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	EUCTR2016-003934-25-NL
CCMO	NL60000.056.16