A Phase III Randomized Trial of MK-3475 (Pembrolizumab) versus Standard Treatment in Subjects with Recurrent or Metastatic Head and Neck Cancer

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Primary Objectives:(1) Objective: To compare the overall survival (OS) in subjects with R/M HNSCC treated with pembrolizumab compared to standard treatment.Secondary Objectives:PD-L1 Positive Population:(1) Objective: To compare Overall Survival (OS...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Other condition
Study type	Interventional

Summary

ID

NL-OMON44471

Source
ToetsingOnline

Brief title
Ph 3 Trial of MK-3475 vs Standard Treatment in Head and Neck Cancer

Condition

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

Synonym
Neck Cancer; Head Cancer

Health condition

hoofd- en halstumoren: de mondholte, keelholte, het strottenhoofd, de neusholte, sinus paranasales, schildklier en speekselklieren

Research involving
Human

Sponsors and support

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

Intervention

Keyword: Head cancer, Neck cancer, Pembrolizumab

Outcome measures

Primary outcome

Overall survival

Secondary outcome

Progression Free Survival

Objective Response Rate

Study description

Background summary

Pembrolizumab (MK-3475, previously known as SCH 9000475) is a potent and highly selective humanized monoclonal antibody (mAb) of the IgG4/kappa isotype designed to directly block the interaction between PD-1 and its ligands, PD-L1 and PD-L2.

The PD-1 receptor-ligand interaction is a major pathway hijacked by tumors to suppress immune control. The normal function of PD-1, expressed on the cell surface of activated T-cells under healthy conditions, is to down-modulate unwanted or excessive immune responses, including autoimmune reactions.

Although healthy organs express little (if any) PD-L1, a variety of cancers were demonstrated to express abundant levels of this T-cell inhibitor. PD-1 has been suggested to regulate tumor-specific T-cell expansion in subjects with melanoma (MEL). This suggests that the PD-1/PD-L1 pathway plays a critical role in tumor immune evasion and should be considered as an attractive target for therapeutic intervention.

Subjects with locally recurrent and metastatic head and neck cancer present a therapeutic challenge. And although both conventional cytotoxic drugs and molecularly targeted compounds have activity in metastatic and recurrent head and neck cancer, the prognosis of subjects with recurrent or metastatic head and neck squamous cell cancer is generally poor despite these therapies. The median survival in most series is 6-9 months with limited treatment options and substantial morbidity. Single agent therapy and combination regimens using either conventional cytotoxic chemotherapy and/or molecularly targeted agents, combined with best supportive care is palliative for subjects with recurrent head and neck cancer. The most widely used agents include platinum compounds (cisplatin, carboplatin), taxanes (docetaxel, paclitaxel), methotrexate, 5-fluorouracil, and cetuximab.
After failure of first-line chemotherapy in the recurrent/metastatic setting, objective responses to second-line cytotoxic chemotherapy are uncommon, particularly when contemporary response criteria are applied. For example, a phase III trial comparing weekly intravenous methotrexate with gefitinib, an epidermal growth factor receptor tyrosine kinase inhibitor in a heavily pretreated population resulted in an overall response rate to methotrexate of 4 percent in 152 subjects, with a median overall survival of 6.7 months. Other single agents have produced higher response rates but this has generally been associated with increased toxicity, and without an impact on survival.
In this trial, subjects with oropharynx cancer will be stratified by HPV status (positive or negative). The favorable prognostic significance of HPV-positive head and neck cancers in the oropharynx has been increasingly established. Preliminary data of single agent pembrolizumab in head and neck cancer patients in KEYNOTE 012 demonstrate efficacy in both HPV positive and HPV negative patients. Site assessment of HPV using immunohistochemistry (IHC) staining for the p16 protein will be used for this population prior to randomization.

Study objective

Primary Objectives:

(1) Objective: To compare the overall survival (OS) in subjects with R/M HNSCC treated with pembrolizumab compared to standard treatment.

Secondary Objectives:

PD-L1 Positive Population:

(1) Objective: To compare Overall Survival (OS) in subjects with R/M HNSCC treated with pembrolizumab compared to standard treatment.

(2) Objective: To compare ORR per RECIST 1.1 as assessed by blinded independent radiology review in subjects with R/M HNSCC treated with pembrolizumab compared to standard treatment.

(3) Objective: To compare PFS per RECIST 1.1 as assessed by blinded independent radiology review in subjects with R/M HNSCC treated with pembrolizumab compared to standard treatment.

All Subjects (regardless of PD-L1 expression):

(4) Objective: To compare ORR per RECIST 1.1 as assessed by blinded independent radiology review in subjects with R/M HNSCC treated with pembrolizumab compared to standard treatment.

(5) Objective: To compare PFS per RECIST 1.1 as assessed by blinded independent radiology review in subjects with R/M HNSCC treated with pembrolizumab compared to standard treatment.

Study design

This is a randomized, active-controlled, multi-site, open-label trial

Intervention

Patients are randomly assigned to one of two groups (randomisatieverhouding 1: 1).

Patients in groep 1 will receive 200 mg pembrolizumab every 3 weeks. Patients in groep 2 will receive docetaxel or cetuximab every 3 weeks, or Methotrexate every week, depending on the choice of the physician.

Study burden and risks

The patient will receive the study drug every 3 weeks (every week for methotrexate) for up to 24 months. Additional treatment is possible (under certain conditions) for an extra year.

The patient will visit the doctor every 3 weeks. The first visit a tumor biopsy will take place (if necessary). Each visit, a physical examination will be performed, and blood samples will be taken. Volume will range from XX - XX ml per visit. The patient will also fill in three questionnaires each visit, namely a 'quality-of-life questionnaire' (EORTC QLQ-C30 and EORTC QLQ-H&N35) and a questionnaire which asked about the health of the patient (eEuroQoL EQ-5D).

The patient may experience physical and / or psychological discomfort with some of the procedures performed during a visit, such as blood sampling, the IV line, ECG, CT scan, MRI and tumor biopsy.

The main side effect reported with the use of MK3475 are fatigue, itching, rash, frequent or excessive bowel movements, joint pain and nausea.
For Vinflunine, Paclitaxel and Docetaxel some of the most common side effects are decreased amount of red and white blood cells; diarrhea, fatigue, hair loss, nausea and vomiting.

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

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.;2. Be > 18 years of age on day of signing informed consent.;3. Have histologically or cytologically-confirmed R/M HNSCC of the oral cavity, oropharynx, hypopharynx, and larynx that is considered incurable by local

therapies. Subjects may not have any other primary tumor site (e.g. nasopharynx).;4. Prior platinum failure as defined by either:;a. Disease progression after treatment with a platinum-containing regimen for recurrent/metastatic disease ;Note: Disease progression may occur at any time during or after a platinum-containing regimen (e.g. carboplatin or cisplatin) which was administered in either 1L or 2L in the recurrent/metastatic setting.
OR
b. Recurrence/progression within 6 months of prior multimodal therapy using platinum (e.g. locally advanced setting);5. Have results from local testing of HPV positivity for oropharyngeal cancer defined as p16 IHC testing using CINtec® p16 Histology assay and a 70% cutoff point.;Note: HPV stratification in this trial will be performed using local testing of HPV status in patients with oropharynx cancer. Oral cavity, hypopharynx, and larynx cancer are not required to undergo HPV testing by p16 IHC as by convention assumed to be HPV negative.;6. Have provided tissue for PD-L1 biomarker analysis from a newly obtained core or excisional biopsy - and received the PD-L1 results * (PD-L1 analysis will be blinded to both site and sponsor). Repeat samples may be required if adequate tissue is not provided or for indeterminate results. ;Note: Patients for whom newly obtained samples cannot be obtained (e.g. inaccessible or patient safety concern) may submit an archived specimen only upon agreement from the Sponsor.;Note: If emerging data indicate a high concordance in PD-L1 expression scores between newly obtained and archival samples, archived samples may be acceptable.;7. Have radiographically measurable disease based on RECIST 1.1 as determined by the site. Tumor lesions situated in a previously irradiated area are considered measurable if progression has been demonstrated in such lesions.;8. Have a performance status of 0 or 1 on the ECOG Performance Scale, as assessed within 10 days of treatment initiation.;9. Demonstrate adequate organ function as defined in Table 1 of the protocol, all screening labs should be performed within 10 days of treatment initiation. ;10. Female subjects of childbearing potential should have a negative serum pregnancy test within 72 hours prior to receiving the first dose of study medication. A urine test can be considered if a serum test is not appropriate.;11. 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 childbearing potential are those who have not been surgically sterilized or have not been free from menses for > 1 year.
Note: For UK subjects:
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 doseof study medication (and specifically through 180 days after the last dose of docetaxel or methotrexate) (Reference Section 5.7.2). Subjects of childbearing potential are those who have not been surgically sterilized or have not been free from menses for > 1 year.
Note: The Summary of Country-Specific Revisions is provided in Appendix 12.9.
Note: Abstinence is acceptable if this is the usual lifestyle, established and/or preferred contraception for the subject. ;12. 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

1. Has disease that is suitable for local therapy administered with curative intent.;2. Had progressive disease within three months of completion of curatively intended treatment for locoregionally advanced or metastatic HNSCC.
Note: This exclusion criterion is only applicable for subjects who have not had treatment in the metastatic/recurrent setting.;3. Is currently participating in or has participated in a study of an investigational agent or using an investigational device within 4 weeks prior to the first dose of trial treatment.;4. Was previously treated with 3 or more systemic regimens given for recurrent and/or metastatic disease.;5. Patients previously treated or resistant to one of the 3 standard of care agents in this trial (i.e. docetaxel, methotrexate, or cetuximab) may not receive the same agent if randomized to the standard treatment arm (see Section 5.2 for details). ;6. 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. The use of physiologic doses of corticosteroids may be approved after consultation with the Sponsor. ;7. Has had a prior anti-cancer monoclonal antibody (mAb) 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.;8. 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 or * Grade 2 alopecia 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. ;9. Has a diagnosed and/or treated additional malignancy within 5 years
prior to randomization with the exception of curatively treated basal cell
carcinoma of the skin, squamous cell carcinoma of the skin and/or
curatively resected in situ cervical and/or breast cancers.;10. Has known active 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 imaging 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 not using steroids for at least 7 days prior to trial treatment. This exception does not include carcinomatous meningitis which is excluded regardless of clinical stability.;11. Has an active autoimmune disease requiring systemic treatment within the past 3 months or a documented history of clinically severe autoimmune disease, or a syndrome that requires systemic steroids or immunosuppressive agents. Subjects with vitiligo diabetes Type I, or resolved childhood asthma/atopy would be an exception to this rule. Subjects that require intermittent use of bronchodilators, inhaled steroids, or local steroid injections would not be excluded from the study. Subjects with hypothyroidism stable on hormone replacement or Sjøgren*s syndrome will not be excluded from the study.;12. Has active, non-infectious pneumonitis; ;13. Has an active infection requiring systemic therapy.;14. 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. ;15. Has a known psychiatric or substance abuse disorders that would

interfere with co- operation with the requirements of the trial.;16. Is pregnant or breastfeeding, or expecting to conceive or father children within the projected duration of the trial, starting with the screening visit through 120 days after the last dose of trial treatment.;17. Has received prior therapy with an anti-PD-1, anti-PD-L1, or anti-PD-L2 agent.;18. Has a known history of Human Immunodeficiency Virus (HIV) (HIV 1/2 antibodies).;;19. Has known active Hepatitis B (e.g., HBsAg reactive) or Hepatitis C (e.g., HCV RNA [qualitative] is detected).;20. Has received a live vaccine within 30 days of planned start of study therapy.

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):	11-05-2015
Enrollment:	10
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Erbitux
Generic name:	Cetuximab
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	NA

Generic name:	Docetaxel
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	NA
Generic name:	Methotrexate
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	NA
Generic name:	Pembrolizumab

Ethics review

Approved WMO Date:	01-10-2014
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	11-03-2015
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	23-04-2015
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	29-04-2015
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	18-06-2015
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek

	(Assen)
Approved WMO Date:	02-07-2015
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:	21-04-2016
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	26-04-2016
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:	05-12-2016
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:	19-03-2018
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	EUCTR2014-001749-26-NL
CCMO	NL50431.056.14