A Phase III Randomized Open-Label Study of Single Agent Pembrolizumab vs. Physicians' Choice of Single Agent Docetaxel, Paclitaxel, or Irinotecan in Subjects with Advanced/Metastatic Adenocarcinoma and Squamous Cell Carcinoma of the Esophagus that have Progressed after First-Line Standard Therapy (KEYNOTE-181)

Published: 28-12-2015
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Primary:1) To compare OS in subjects with squamous cell carcinoma of the Esophagus.2) To compare OS in subjects with PD-L1 Combined Positive Score (CPS)*10%3) To compare OS in all subjectsSecondary:1) To evaluate the progression free survival (PFS)...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Benign neoplasms gastrointestinal
Study type	Interventional

Summary

ID

NL-OMON45950

Source
ToetsingOnline

Brief title
MK3475-181

Condition

- Benign neoplasms gastrointestinal

Synonym
gulletcancer

Research involving
Human

Sponsors and support

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

Intervention

Keyword: Carcinoma of the Esophagus, Pembrolizumab

Outcome measures

Primary outcome

1. Overall Survival (OS) in subjects with squamous cell carcinoma of the

Esophagus.

2. Overall Survival (OS) in subjects with PD-L1 CPS*10%

3. Overall Survival (OS) in all subjects.

Secondary outcome

1.Progression-free survival (PFS) * RECIST 1.1 by central imaging

vendor review in all subjects, defined as the time from randomization to

the first documented disease progression per RECIST 1.1 or death.

2.Objective Response Rate (ORR) * RECIST 1.1 by central imaging

vendor review in all subjects, defined as the proportion of the subjects in

the analysis population who have a complete response (CR) or partial

response (PR).

3. Safety and tolerability Endpoints

Study description

Background summary

Esophageal cancer is the 6th most common cause of cancer deaths in the world and is more prevalent in men than women. However, in the developing countries esophageal cancer is endemic and is the 4th most common cause of cancer deaths. Globally close to 480000 cases occur annually. In the US, in 2015, an estimated 15980 esophageal cancers will be diagnosed and it is estimated that 15590 people will eventually die of their disease. Majority of the patients are diagnosed with advanced/metastatic cancer and in this setting response to chemotherapeutic agents is poor. Given the high incidence and mortality worldwide and lack of good therapeutic options esophageal cancer patients represent a high unmet need for drug development.
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The incidence of esophageal cancer represents one of the widest variations with a 60-fold difference between high and low prevalence regions. High prevalence areas include Asia, Africa and France where squamous esophageal cancers predominate. A dramatic shift in the histology and location of upper gastrointestinal (GI) tumors has occurred over the past decades. In Western countries, the most common site of esophageal cancer is in the lower third of the esophagus, which often involves the EGJ . For the purpose of our study, we will use the Siewert classification for adenocarcinoma of the EGJ and thus type I patients (about 20% of the EGJ adenocarcinoma patients) will be eligible. Siewert type I tumors are adenocarcinomas of the lower esophagus with the center located within 1cm to 5cm above the anatomic EGJ. Type II and III Siewert adenocarcinomas of the EGJ are managed as gastric cancer patients and therefore participate in the second line (2L) gastric trial, KN-061.
Adenocarcinoma has been gradually increasing in men of all ethnic backgrounds and also in women. Squamous cell carcinoma (SCC) seems to be more sensitive to chemotherapy, chemoradiation, and radiation therapy than adenocarcinoma, but the long-term outcome is similar for both histologies thus emphasizing the need for better improved therapies in both histologies.

Study objective

Primary:
1) To compare OS in subjects with squamous cell carcinoma of the Esophagus.
2) To compare OS in subjects with PD-L1 Combined Positive Score (CPS)*10%
3) To compare OS in all subjects

Secondary:

1) To evaluate the progression free survival (PFS) per RECIST 1.1assessed by central vendor review in all subjects, when treated with pembrolizumab compared to investigator's choice of paclitaxel,docetaxel, or irinotecan.
2) To evaluate the Objective Response Rate (ORR) per RECIST 1.1 assessed by central vendor review in all subjects, when treated with pembrolizumab compared to investigator's choice of paclitaxel, docetaxel, or irinotecan.
3) To evaluate the PFS and ORR per RECIST 1.1 assessed by central vendor review in subjects with squamous cell carcinoma of the esophagus and subjects with PD-L1 CPS*10%, when treated with pembrolizumab compared to investigator's choice of paclitaxel, docetaxel, or irinotecan.
4) Evaluate the safety and tolerability profile of pembrolizumab in all subjects, when treated with pembrolizumab compared to investigator's choice of paclitaxel, docetaxel, or irinotecan.

Study design

This is a Randomized, multi-center, open-label trial of pembrolizumab (MK-3475) versus investigator*s choice of paclitaxel, docetaxel or irinotecan in subjects with advanced/metastatic adenocarcinoma or squamous cell carcinoma of the esophagus, or advanced/metastatic Siewert type I adenocarcinoma of the esophagogastric junction (EGJ).

Intervention

Arm 1: Pembrolizumab (MK-3475) 200 mg IV every 3-weeks
Arm 2: Investigator*s choice of:
- Paclitaxel 80-100 mg/m2 on Days 1, 8, and 15 of every 28-day (4-week) cycle, OR
- Docetaxel 75 mg/m2 on Day 1 of every 21-day (3-week) cycle, OR
- Irinotecan 180 mg/m2 on Day 1 of every 14-day (2 week) cycle

Study burden and risks

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

The patient will visit the doctor every week or 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. The patient will also fill in three questionnaires each visit concerning the quality of life, namely the EORTC QLQ C30, the eEuroQoL EQ-5D and the EORTC QLQ-OES18.

The patient may experience physical and I 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.

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

Subjects must: ;1. Be * 18 years of age on the day of signing the informed consent. ;2. Have histologically or cytologically confirmed diagnosis of adenocarcinoma or squamous cell carcinoma of the esophagus or Siewert type I adenocarcinoma of the EGJ. ;3. Have metastatic disease or locally advanced, unresectable disease. ;4. Have a life expectancy greater than 3

months. ;5. Have measurable disease based on RECIST 1.1 as determined by the local site investigator/radiology assessment. ;6. Have an ECOG performance status of 0 or 1. ;7. Have experienced documented radiographic or clinical disease progression on one previous line of standard therapy. ;8. Provide either a newly obtained or archival tissue sample for intratumoral immune-related GEP analysis.;9. Demonstrate adequate organ function. ;10. Negative pregnancy test for females of child bearing potential prior to starting study and male and female subjects of childbearing potential must be willing to use an adequate method of contraception.

Exclusion criteria

The subject will be excluded from participating in the trial if the subject:
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 an active autoimmune disease that has required systemic treatment in past 2 years. ;3. 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. ;4. Has known central nervous system (CNS) metastases and/or carcinomatous meningitis (includes past history or current metastasis). ;5. Has received prior anti-cancer monoclonal antibody (mAb), 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. The specified 2-week period between last dose of prior therapy and first dose of pembrolizumab is the minimum amount of time required. Subjects may not receive study medication less than 2 weeks from the last dose of a prior therapy. However, a period of more than 2 weeks may be used if
indicated both clinically and due to concern between possible negative interactions between prior therapy and study therapy.;6. Has received prior therapy with an anti-PD-1, anti-PD-L1, or anti-PD-L2 agent, or if the subject has previously participated in Merck pembrolizumab (MK-3475) clinical trials. ;7. Previously had a severe hypersensitivity reaction to treatment with another
monoclonal antibody (mAb);8. Has experienced documented objective radiographic or clinical disease progression during or after receiving more than 1 line of therapy.;9. Has a diagnosed additional malignancy within 5 years prior to treatment allocation 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 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.;11. Has a known history of Human Immunodeficiency Virus (HIV) infection. ;12. Has untreated known active Hepatitis B or known Hepatitis C. ;13. Has a history of (non-infectious) pneumonitis that required steroids or current
pneumonitis;14. Has an active infection requiring systemic therapy. ;15. Has known psychiatric or substance abuse disorders that would interfere with cooperation 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 pembrolizumab or through 180 days after the last dose of paclitaxel, docetaxel or irinotecan.;17. Has a Known allergy, hypersensitivity, or contraindication to preselected
chemotherapy agent (i.e. paclitaxel, docetaxel, or irinotecan) or any components used in their preparation. ;18. Experienced weight loss > 10% over approximately 2 months prior to first dose of study therapy.;19. Has clinically apparent ascites or pleural effusion by physical exam.

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):	08-12-2015
Enrollment:	10
Type:	Actual

Medical products/devices used

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

Generic name:	Docetaxel
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	NA
Generic name:	Irinotecan
Registration:	Yes - NL outside intended use
Product type:	Medicine
Brand name:	NA
Generic name:	Paclitaxel
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	28-12-2015
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	06-06-2016
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	06-06-2016
Application type:	First submission
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:	01-03-2017
Application type:	Amendment

Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	29-03-2017
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	03-05-2017
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:	19-10-2017
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	26-10-2017
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	EUCTR2015-002782-32-NL
ClinicalTrials.gov	NCT02564263
CCMO	NL55808.056.15