A Randomized, Active-Controlled, Partially Blinded, Biomarker Select, Phase III Clinical Trial of Pembrolizumab as Monotherapy and in Combination with Cisplatin+5-Fluorouracil versus Placebo+Cisplatin+5-Fluorouracil as First-Line Treatment in Subjects with Advanced Gastric or Gastroesophageal Junction (GEJ) Adenocarcinoma;

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Primary objectives:(1) Evaluate Progression Free Survival (PFS) per RECIST 1.1 as assessed by blinded central radiologists' review in subjects with PD-L1 Combined Positive Score (CPS) *1. (2) Evaluate overall survival (OS).Secondary Objectives(...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Gastrointestinal neoplasms malignant and unspecified
Study type	Interventional

Summary

ID

NL-OMON55397

Source
ToetsingOnline

Brief title
Pembrolizumab in Advanced Gastric or GEJ Adenocarcinoma

Condition

- Gastrointestinal neoplasms malignant and unspecified

Synonym
Gastric cancer

Research involving
Human

Sponsors and support

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

Intervention

Keyword: Gastric adenocarcinoma, GEJ adenocarcinoma, Pembrolizumab

Outcome measures

Primary outcome

- Progression Free Survival (PFS) per RECIST 1.1

- Overall survival (OS)

Secondary outcome

- PFS per RECIST 1.1 and per irRECIST

- Overall Response Rate (ORR), and Duration of Response (DOR), per RECIST 1.1

- Safety and tolerability profile

Study description

Background summary

Standard of care chemotherapy in the first line setting for gastric/GEJ cancer offers a median progression free survival (PFS) of approximately 5-6 months, but ultimately all patients experience disease progression requiring later line therapies. Overall survival remains dismal with < 5% long-term survival despite the currently accepted standard of care chemotherapeutic regimens,

which comprise platinum and fluoropyrimidine based doublets and triplets. These intensive cytotoxic chemotherapies expose incurable patients to significant toxicities while not offering long term survival.

Consequently, a more effective as well as more tolerable therapy for metastatic gastric/GEJ cancer is still critically needed. Immunotherapy is a novel therapeutic modality that may offer a deeper response than conventional chemotherapy while affording incurable metastatic patients a better quality of life given the comparatively favourable toxicity profile.

This study aims to characterize the safety and tolerability as well as efficacy of pembrolizumab in subjects with advanced gastric or GEJ adenocarcinoma.

Study objective

Primary objectives:
(1) Evaluate Progression Free Survival (PFS) per RECIST 1.1 as assessed by blinded central radiologists' review in subjects with PD-L1 Combined Positive Score (CPS) *1.
(2) Evaluate overall survival (OS).

Secondary Objectives
(1) Objective: Evaluate Overall Response Rate (ORR), and Duration of Response (DOR), per RECIST 1.1 as assessed by central radiologists in subjects with PD-L1 CPS *1.
(2) Objective: Evaluate Progression Free Survival (PFS) per RECIST 1.1 as assessed by blinded central radiologists* review in subjects treated with Pembrolizumab.
(3) Objective: Evaluate the safety and tolerability profile.
4) Objective: Evaluate changes in health-related quality-of-life assessments from baseline using the EORTC QLQ-C30 and the EORTC QLQ-STO22

Study design

This is a randomized, active-controlled, multi-site, partially blinded, trial of pembrolizumab, or pembrolizumab+cisplatin+5-fluorouracil (5-FU) versus placebo+cisplatin+5-FU, as first-line treatment in PD-L1 positive, HER2/neu negative subjects with advanced gastric or gastroesophageal junction (GEJ) adenocarcinoma.

Intervention

Treatment Arm Treatment Dose and Schedule
Treatment Arm 1 Pembrolizumab 200 mg every 3 weeks (Q3W)
Treatment Arm 2* Pembrolizumab 200 mg Q3W+ Cisplatin 80 mg/m2 Q3W+5-FU 800 mg/m2/day continuous IV infusion Days 1-5 (120 hours)

Treatment Arm 3* Placebo Q3W +Cisplatin 80 mg/m2 Q3W+5-FU 800 mg/m2/day continuous IV infusion Days 1-5 (120 hours)

*Although use of 5-FU infusion is preferred, capecitabine1000 mg/m2 bid D1-14 Q3W can be used according to the local guideline. Investigator decision regarding the type of comparator used (5-FU or capecitabine) should be determined prior to randomization in the trial. Subjects should continue on the fluoropyrimidine chosen prior to randomization throughout the study. Exceptions may be permitted after consultation with the Sponsor.

Study burden and risks

Patients will receive study medication or placebo every 3 weeks for a maximum of 24 months. After achieving a complete response and subsequent discontinuation of the first treatment period, an additional treatment with MK3475 for up to 1 year is possible under certain conditions for patients who have shown progression.

The patient will visit the study doctor every 3 weeks. At the first visit a tumor biopsy (if necessary) will be taken. In addition, a biopsy will be requested at discontinuation of study medication; this is optional. Every visit from Screening up to and including End of Treatment a physical exam will be done and blood will be taken (volume 6 - 45 ml per visit). Patients will also complete questionnaires (EQ5D-3L, EORTC QLQ-C30, EORTC QLQ-ST022) at visit 1 - 5, End of Treatment and Safety Followup. Patients may experience physical and/or psychological discomfort during the visit procedures, such as blood sampling, biopsy, IV line, ECG, CT/MRI scan.

The most common adverse events reported for MK3475 are fatigue, itching, rash, decreased appetite, shortness of breath, coughing.

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)

Inclusion criteria

1. Be willing and able to provide documented 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 * 18 years of age on day of providing documented informed consent (or acceptable age according to local regulations, whichever is older)., 3. Have a performance status of 0 or 1 on the Eastern Cooperative Oncology Group (ECOG) Performance Scale within 10 days prior to the first dose of trial treatment., 4. Have histologically or cytologically confirmed diagnosis of locally advanced unresectable or metastatic gastric or GEJ adenocarcinoma. , 5. Be HER2/neu negative and PD-L1 positive., 6. Have measurable disease as defined by RECIST 1.1 as determined by investigator assessment. Tumor lesions situated in a previously irradiated area are considered measurable if progression has been demonstrated in such lesions. , 7. Have provided tumor tissue sample deemed adequate for PD-L1 biomarker analysis. , a. Notification of eligibility must be received prior to randomization., b. Additional samples may be required if adequate tissue is not provided., 8. Female subjects of childbearing potential must have a highly sensitive negative urine or serum pregnancy test as required by local regulation within 24 hours (urine) and within 72 hours (serum) 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 must be willing to use an adequate method of contraception, for the course of the study through 120 days after the last dose of study medication. Note: Abstinence is acceptable if this is the usual lifestyle and preferred contraception for the subject. , 10. Male subjects of childbearing potential must 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. Note: Abstinence is acceptable if this is the usual lifestyle and preferred contraception for the subject. , 11. Demonstrate adequate organ function. All screening labs should be performed within 10 days of treatment initiation.

Exclusion criteria

1. Has squamous cell or undifferentiated gastric cancer., 2. Has had previous therapy for locally advanced, unresectable or metastatic gastric/GEJ cancer. Subjects may have received prior neoadjuvant or adjuvant therapy as long as it was completed at least 6 months prior to randomization., 3. Has had major surgery, open biopsy or significant traumatic injury within 28 days prior to randomization, or anticipation of the need for major surgery during the course of study treatment., 4. Has had radiotherapy within 14 days of randomization. Subjects who received radiotherapy >14 days prior to randomization must have completely recovered from any radiotherapy related AEs/toxicities., 5. 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 that has undergone potentially curative therapy or in situ cervical cancer., 6. 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 at least four weeks prior to the first dose of trial treatment and 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., 7. Has an 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. , 8. Has a diagnosis of immunodeficiency or is receiving chronic systemic steroid therapy (in dosin exceeding 10 mg daily of prednisone equivalent) or any other form of immunosuppressive therapy within 7 days prior to the first dose of trial drug. , 9. Has a history of (non-infectious) pneumonitis/interstitial lung disease that required steroids or current pneumonitis/interstitial lung disease. , 10. Has an active infection requiring systemic therapy., 11. Has a history or current evidence of any condition (e.g. known deficiency of the enzyme dihydropyrimidine dehydrogenase [DPD]), 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., 12. Has known psychiatric or substance abuse disorders that would interfere with cooperation with the requirements of the trial., 13. 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., 14. Has received prior therapy with an anti-PD-1, anti-PD-L1, or anti-PD-L2 agent., 15. Has a known history of Human Immunodeficiency Virus (HIV) (HIV 1/2 antibodies)., 16. Has current active Hepatitis B (e.g., HBsAg reactive, positive and/or a detectable HBV DNA) or Hepatitis C virus (e.g., anti-HCV Ab positive and detectable HCV RNA) infection., 17. Is currently participating in and receiving study therapy or has participated in a trial of an investigational agent or has used an investigational device within 4 weeks prior to the first dose of trial treatment., 18. Has received a live vaccine within 30 days of planned start of study therapy., Note: Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, varicella/zoster (chicken pox), yellow fever, rabies, Bacillus Calmetta-Guérin (BCG), and typhoid vaccine. Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed; however, intranasal influenza vaccines (e.g., FluMist®) are live attenuated vaccines, and are not allowed.

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Other
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	01-02-2016
Enrollment:	12
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	KEYTRUDA
Generic name:	pembrolizumab
Product type:	Medicine
Brand name:	NA
Generic name:	cisplatin
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	NA
Generic name:	fluorouracil (5-fluorouracil)
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Xeloda
Generic name:	capecitabine
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	07-07-2015
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	21-08-2015
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	25-08-2015
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO	

Date:	12-11-2015
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:	26-08-2016
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:	16-12-2016
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:	27-03-2017
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek

	(Assen)
Approved WMO Date:	11-04-2017
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:	18-10-2017
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	22-02-2018
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:	30-05-2018
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	12-07-2018
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)
Approved WMO Date:	15-01-2019
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	22-01-2019
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:	28-11-2019
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	30-04-2020
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	28-10-2020
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	28-05-2021
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)

Approved WMO Date:	15-08-2021
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	01-09-2021
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	23-11-2021
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:	02-06-2022
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	02-09-2022
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	EUCTR2015-000972-88-NL
ClinicalTrials.gov	NCT02494583
CCMO	NL53770.056.15