A Randomized, Multicenter, Double Blind, Phase III Study of Adjuvant Nivolumab or Placebo in Subjects with Resected Esophageal, or Gastroesophageal Junction Cancer

Published: 21-06-2016
Last updated: 07-09-2024

This study has been transitioned to CTIS with ID 2023-509360-24-00 check the CTIS register for the current data. Primary objectives: This study has co-primary objectives:• To compare OS of nivolumab versus placebo in subjects with resected EC or GEJ...

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Malignant and unspecified neoplasms gastrointestinal NEC
Study type	Interventional

Summary

ID

NL-OMON47538

Source
ToetsingOnline

Brief title
CHECKpoint pathway and nivoluMab clinical Trial Evaluation 577

Condition

- Malignant and unspecified neoplasms gastrointestinal NEC
- Gastrointestinal neoplasms malignant and unspecified
- Gastrointestinal therapeutic procedures

Synonym
Surgically Removed Tumor of the Esophagus (Esophageal) or the Juncture between the Stomach and the Esophagus (Gastroesophageal Junction)

Research involving
Human

Sponsors and support

Primary sponsor: Bristol-Myers Squibb
Source(s) of monetary or material Support: Bristol-Myers Squibb (Sponsor)

Intervention

Keyword: Cancer, Gastroesophageal, Nivolumab

Outcome measures

Primary outcome

Overall survival and DFS are co-primary endpoints.

Overall Survival is time between the date of randomization and the date of death. For subjects without documentation of death, OS will be censored on the last date the subject was known to be alive.

Disease-Free Survival is time between randomization date and first date of recurrence or death, whichever occurs first. Recurrence is defined as the appearance of one or more new lesions, which can be local, regional, or distant in location from the primary resected site (by imaging or pathology whichever comes first). All deaths without prior recurrence will be included as DFS event - regardless of cause or of how long it has been since the last known disease evaluation. For subjects who remain alive and without recurrence, DFS will be censored on the date of last evaluable disease assessment.

Secondary outcome

Overall survival rate at 1, 2, and 3 years is defined as the probability that a subject is alive at 1, 2, and 3 years, respectively, following randomization.

Study description

Background summary

This is a phase III study of Nivolumab versus Placebo in patients with resected oesophageal or gastroesophageal junction cancer.
The purpose of the study is to compare overall survival and disease-free survival of patients who have stage II or III oesophageal or gastroesophageal junction cancer, have undergone chemotherapy plus radiation therapy, followed by surgery to remove their whole tumour. At present, there is no standard of care (SOC) for such patients beyond being followed-up after their surgery for disease return. The study will evaluate the probability of disease return in patients who receive nivolumab versus patients receiving placebo after surgical resection and will compare the survival of the two patient groups.
Globally, approximately 760 patients will be randomised to receive either nivolumab or placebo, with approximately 15 of them in the Netherlands. The study is sponsored by Bristol-Myers Squibb.
Following a screening period, two thirds of the eligible patients will receive nivolumab (the drug under investigation) and one third will receive placebo (dummy drug - no active substance). All patients will receive nivolumab or placebo for up to 12 months or until disease recurrence, whichever comes first. The first 8 infusions will be done every 2 weeks, followed by infusions every 4 weeks. After the treatment phase, patients will be followed for survival for up to 5 years, over the phone or through hospital visits.
Patients will undergo CT scan, physical exams, vital signs such as blood pressure, height, weight, body temperature, blood samples for routine safety testing and study specific testing. Patients will also be required to complete questionnaires regularly throughout the study. Additional biopsies may be performed or previous biopsies obtained if available and if patients consent.

Study objective

This study has been transitioned to CTIS with ID 2023-509360-24-00 check the CTIS register for the current data.

Primary objectives:
This study has co-primary objectives:
• To compare OS of nivolumab versus placebo in subjects with resected EC or GEJ cancer.
• To compare DFS of nivolumab versus placebo in subjects with resected EC or GEJ cancer.

Secondary objectives:
• To evaluate 1, 2, and 3 year survival rates of nivolumab versus placebo in subjects with resected EC or GEJ cancer.

Exploratory objectives:
• To assess the overall safety and tolerability of nivolumab versus placebo in subjects with resected EC or GEJ cancer.
• To evaluate the distant metastasis free survival (DMFS) in subject with resected EC or GEJ cancer.
• To evaluate whether PD-L1 status is a predictive biomarker for DFS and OS in subjects with resected EC or GEJ cancer.
• To evaluate PD-L1 status prior to CRT and at the time of surgery in subjects with resected EC or GEJ cancer
• To explore potential biomarkers associated with clinical efficacy (DFS, and OS) and/or incidence of adverse events of nivolumab by analyzing biomarker measures within the tumor microenvironment and periphery (eg, blood, serum, plasma and PBMCs) in comparison to clinical outcomes.
• To assess the effect of natural genetic variation (single nucleotide polymorphisms (SNPs)) in select genes including, but not limited to, PD-1, PD-L1, PD-L2 and CTLA4 on clinical endpoints and/or the incidence of adverse events
• To characterize the pharmacokinetics and explore exposure-response relationships with respect to safety and efficacy
• To characterize the immunogenicity of nivolumab.
• To assess the subject*s overall health status using the 3-level version of the EQ-5D (EQ-5D-3L) index and visual analog scale
• To assess the subject*s cancer-related quality of life using the Functional Assessment of Cancer Therapy-Esophageal (FACT-E) questionnaire and selected components, including the Esophageal Cancer Subscale (ECS) and 7-item version of the FACT-General (FACT-G7)

Study design

This is a phase 3, randomized, double-blind, placebo controlled study of adjuvant nivolumab in subjects with resected esophageal cancer (EC), or gastroesophageal junction (GEJ) cancer who have received chemoradiotherapy (CRT) followed by surgery.

After CRT followed by surgery, subjects will sign the informed consent form. Subjects whose tumors do not achieve pathological complete response (non-pCR) will be randomized in a blinded fashion 2:1 ratio to two arms between nivolumab (BMS-936558) or placebo monotherapy administered IV over 30 minutes at 240 mg every 2 weeks for 16 weeks (8 doses) followed by nivolumab 480 mg as a 30 minute infusion every 4 weeks beginning at Week 17 (2weeks after the 8th dose). The treatment will be given until disease recurrence, unacceptable toxicity, or subject withdrawal of consent with a maximum of 1-year total duration of study medication.
Stratification factors:
1) PD-L1 status
2) Pathologic lymph node status (positive **ypN1 vs. negative ypN0)

3) Histology (squamous vs. adenocarcinoma)

Intervention

Approximately 760 subjects will be randomized in a 2:1 ratio to the nivolumab and placebo arms.

Study burden and risks

As part of the trial, patients will be expected to attend multiple clinic visits where they will undergo physical examinations, vital sign measurements , blood tests for safety assessments, pregnancy testing (for females of child bearing potential) and monitoring for adverse events. Subjects will be evaluated for presence or continued lack of tumour.

Blood will also be collected at certain visits for research purposes (PK, immunogenicity and biomarker studies), The frequency of visits and number of procedures carried out during this trial would typically be considered over and above standard of care. The procedures are carried out by trained medical professionals and every effort will be made to minimise any risks or discomfort to the patient. Treatment for cancer often has side effects, Including some that are life threatening. An Independent Data Monitoring Committee (DMC) will be utilized in this trial to ensure that the safety data is reviewed during the study.

New Immune system targeted therapy (immunotherapies) such as Nivolumab could potentially provide clinical benefit and Improvement in the outcome for patients with this disease (disease improvement and Improvement in survival). However, as with all experimental drugs and clinical trials, there are known and unknown risks. Study medication and procedure-related risks are outlined in the patient information sheet in detail to ensure the patients are fully informed before agreeing to take part in the study.

Contacts

Public
Bristol-Myers Squibb

Orteliuslaan 1000
Utrecht 3528 BD
NL
Scientific
Bristol-Myers Squibb

Orteliuslaan 1000
Utrecht 3528 BD
NL

Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

• All subjects must have Stage II or Stage III (per AJCC 7th edition) carcinoma of the esophagus or gastroesophageal junction and have histologically confirmed predominant adenocarcinoma or squamous cell carcinoma esophageal or gastroesophageal junction cancer at the time of initial diagnosis.
• Subjects must complete pre-operative chemoradiotherapy followed by surgery prior to randomization. Platinum based chemotherapy should be used. Chemotherapy and radiation regimens can be followed as local standards of care per NCCN or ESMO guidelines.
• Subject must have complete resection (R0), have been surgically rendered free of disease with negative margins on resected specimens. Subject must have residual pathologic disease, i.e. non-pathologic complete response (non-pCR) of their EC or GEJ, with at least ypN1 or ypT1 listed in the pathology report of resected specimens. The pathology reports of detectable lesion(s) confirming malignancy must be reviewed, dated, and signed by the investigator prior to randomization.
• Complete resection must be performed in a window of 4-16 weeks prior to randomization.
• ECOG performance status score of 0 or 1.
• All subjects must have disease-free status documented by a complete physical examination and imaging studies within 4 weeks prior to randomization. Imaging studies must include CT scan of chest, and abdomen.
• Tumor tissue from the resected site of disease must be provided for biomarker analyses. In order to be randomized, a subject must have a PD-L1 expression classification (>1%, < 1% or indeterminate or non-evaluable) as determined by the central lab. If insufficient tumor tissue content is provided for analysis, acquisition of additional archived tumor tissue (block and /or slides) for the biomarker analysis is required.

Exclusion criteria

• Subjects with cervical esophageal carcinoma. Location of tumor as it relates to eligibility can be discussed with BMS medical monitor.
• Subjects who do not receive concurrent CRT prior to surgery. Subjects who only receive chemotherapy or only radiation prior to surgery are not eligible.
• Subjects with Stage IV resectable disease.
• Subjects with an active, known or suspected autoimmune disease. Subjects with type I diabetes mellitus, hypothyroidism only requiring hormone replacement, skin disorders (such as vitiligo, psoriasis, or alopecia) not requiring systemic treatment, or conditions not expected to recur in the absence of an external trigger are permitted to enroll.
• Subjects with a condition requiring systemic treatment with either corticosteroids (> 10 mg daily prednisone equivalent) or other immunosuppressive medications within 14 days of randomization. Inhaled or topical steroids, and adrenal replacement steroid > 10 mg daily prednisone equivalent, are permitted in the absence of active autoimmune disease.

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:	Prevention

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	05-12-2016
Enrollment:	15
Type:	Actual

Medical products/devices used

Product type:	Medicine

Brand name:	Opdivo
Generic name:	Nivolumab
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	21-06-2016
Application type:	First submission
Review commission:	METC NedMec
Approved WMO Date:	30-09-2016
Application type:	First submission
Review commission:	METC NedMec
Approved WMO Date:	13-01-2017
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	20-01-2017
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	09-08-2017
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	11-08-2017
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	23-03-2018
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	12-04-2018

Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	29-11-2018
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	14-02-2019
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	11-04-2019
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	23-05-2019
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	16-09-2019
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	27-09-2019
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	20-10-2020
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	12-11-2020
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	16-09-2021

Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	14-10-2021
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	08-04-2022
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	30-08-2022
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	06-09-2022
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	07-08-2023
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	16-08-2023
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	04-09-2023
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	29-09-2023
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	CTIS2023-509360-24-00
EudraCT	EUCTR2015-005556-10-NL
ClinicalTrials.gov	NCT02743494
CCMO	NL56855.031.16