A Phase 2, Fast Real-time Assessment of Combination Therapies in Immuno-Oncology Study in Participants with Advanced Gastric Cancer (FRACTION-Gastric Cancer)

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The objective of this study is to investigate the safety and effectiveness of different combinations of cancer immunotherapies compared to either Nivolumab or Ipilimumab, as determined by comparing the Overall Response Rate, at 24 weeks in patients...

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

Summary

ID

NL-OMON55766

Source
ToetsingOnline

Brief title
CA018-003 Fraction- Gastric

Condition

- Malignant and unspecified neoplasms gastrointestinal NEC

Synonym
Gastric Cancer

Research involving
Human

Sponsors and support

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

Intervention

Keyword: Combination Therapies, FRACTION, Gastric Cancer, Immuno-Oncology

Outcome measures

Primary outcome

To investigate the efficacy (by measuring Overall Response Rate, duration of response, and progression free survival rate at 24 weeks) of each treatment combination within the FRACTION study(as compared to Nivolumab in combination with Ipilimumab when applicable) in patients with advanced Gastric Cancer

Secondary outcome

To investigate the additional safety and tolerability of each study treatment combination in patients with advanced Gastric Cancer.

Exploratory objectives:

-To determine the pharmacodynamics effects of the medications by evaluating a selection of biomarkers in blood and tumour biopsy samples.

-To assess the overall survival in treated patients

-To explore the potential associations between anti-tumour activity or safety and select biomarker measures in tumor biopsy specimens and blood prior to study treatment and following drug administration.

-To evaluation the pharmacokinetics of each investigational product.

-To evaluate the immunogenicity of each investigational product.

-To evaluate disease-related symptoms improvement using the GaCs in treated

patients.

-To evaluate general health using the EQ-5D in treated patients.

Study description

Background summary

CA018-003 is a multi-centre, Phase 2 study involving adult patients with advanced gastric cancer. The study will compare the safety and effectiveness of different combinations of trial medications compared to the combination of Nivolumab and Ipilimumab. Approximately 300 patients world wide will participate in this study and approximately 30 of these will be from the Netherlands.

Gastric cancer is the 5th leading cancer and the 3rd leading cause of cancer-related deaths worldwide. The incidence of Gastric Cancer varies depending on geographic regions with over 70% of this type of cancer occurring in developing countries. Gastric cancer often presents as advanced disease upon diagnosis, consisting of approximately 40% of newly diagnosed cases in the United States and Europe.
Treatment options for patients with advanced Gastric Cancer include, surgery, radiation, chemotherapy or hormonal therapy. Despite the advances in these therapies, the majority of patients with metastatic disease die from progressive disease.

Cancer Immunotherapy is based on the knowledge that tumours can be recognized as foreign rather than as self and can be effectively attacked by an activated immune system. Immunotheraputic approaches have demonstrated clinical efficacy and have been approved in multiple countries worldwide and in several solid tumour malignancies, including melanoma, renal cell, lung and hormone-refractory prostate cancer. As there has been previous success of Immunotherapy agents in these cancers, the field of tumour immunotherapy is growing rapidly. As well as Nivolumab and Ipilimumab (these are immunotherapeutic monoclonal antibodies that work by blocking inhibitory signalling pathways in the immune response) there are other medications that via a different pathway have the same effect of blocking the immune system from shutting down. Anti-Lag-3 is a new trial medication that works via the anti-CTLA-4 pathway however the ultimate effect on the immune system is the same. With these new therapies emerging that show significant activity of single-agent medications, it is possible and indeed likely , that combination therapies could potentially lead to a better response and an increase in

overall survival. This also raises the possibility the combining these agents that use different pathways within the cells of the immune system could lead to durable, long term responses and possibly even a cure in this cancer population.

The aim of this study is to determine the safety and effectiveness of these combinations of immunotherapy agents in patients with Gastric Cancer who have either had prior therapy with an immunotherapy agent or have had not had prior exposure to these agents. This study called Fraction aims to quickly assess new agents in patients with Advanced Gastric Cancer with the goal of reducing the time and number of patients required to bring these therapies to those who need them.

Study objective

The objective of this study is to investigate the safety and effectiveness of different combinations of cancer immunotherapies compared to either Nivolumab or Ipilimumab, as determined by comparing the Overall Response Rate, at 24 weeks in patients with advanced Gastric Cancer.

Study design

This is a rolling, Phase 2, adaptive study that will evaluate the preliminary efficacy, safety, tolerability, PK, and pharmacodynamics of novel FRACTION-Gastric Cancer study treatment combinations in participants with advanced Gastric Cancer. The details pertaining to the specific study treatment regimens are provided in each FRACTION-Gastric Cancer Sub-Protocol.

Participants will be enrolled in 1 of the 2 tracks. Participants who are anti-PD-1, anti-PD-L1, and anti-CTLA-4 treatment naïve will be enrolled for Track 1. Participants who have had prior anti-PD-1, anti-PD-L1, or anti-CTLA-4 treatment will be assigned to Track 2,

Participants on Tracks 1 and 2 will begin on the Treatment Phase (with a total duration of approximately 2 years). Tumor assessments will be conducted according to the timing described in each FRACTION-Gastric Cancer Sub-Protocol.

Participants in Tracks 1 and 2 will be treated until completion of the Treatment Phase, progression, toxicity, or protocol-specified discontinuation. The decision to continue treatment beyond investigator assessed progression is possible (for up to completion of that Treatment Phase) and should be discussed with the BMS Medical Monitor (or designee) and documented in the study records. In addition, a participant with PD has the option to enter into Track 2, assuming that he/she continues to fulfil all eligibility criteria at each new randomization point, including a life expectancy of >= 3 months.

Participants who are naïve to anti-PD-1, anti-PD-L1, and anti-CTLA-4 treatment will be enrolled in Track 1, and they will be randomized to nivolumab in combination with ipilimumab or to one of the FRACTION-Gastric Cancer study treatment combinations. These participants will receive their assigned study treatment in Track 1 until completion of the Treatment Phase.

Participants who have received prior anti-PD-1, anti-PD-L1, or anti-CTLA-4 treatment will be enrolled in Track 2 and randomized to nivolumab in combination with ipilimumab, or to one of the FRACTION-Gastric Cancer study treatment combinations. In addition, participants with PD who were treated in Track 1 or 2 and continue to fulfill all entry criteria may be enrolled in Track 2 and re-randomized to a new combination other than that previously received, if applicable. These participants will receive their assigned study treatment in Track 2 until completion of the Treatment Phase.

Participants will complete up to 4 phases of the study: Screening, Treatment, Safety Follow-up, and Response/Survival Follow-up within each track (not considering re-randomization and retreatment), as described below.

The Screening Phase for each track will last for up to 28 days. Participants will be enrolled using Interactive Response Technology (IRT).

Participants will generally be allowed to continue study treatment until the first occurrence of one of the following: 1) completion of 2 years of study treatment, 2) PD (subject to treatment beyond progression 3) clinical deterioration suggesting that no further benefit from study treatment is likely, 4) intolerable toxicity, and 5) meeting of criteria for discontinuation of study treatment. Individual participants with confirmed CR will be given the option to discontinue study treatment, on a case-by-case basis, after specific consultation and agreement between the investigator and the BMS Medical Monitor (or designee) in settings where the benefit/risk ratio justifies discontinuation of study treatment.

Upon completion of the Treatment Phase, all participants will enter the Safety Follow-up Phase once the decision is made to discontinue the participant from study treatment.

Intervention

The current sub-protocol allows the patients to receive the following combinations of study treatment:
1. Nivolumab + Ipilimumab: Nivolumab will be given at 1mg/kg in combination with Ipilimumab 3mgkg every 3 weeks for four doses. After this patients will receive 6 weeks after the last combination dose, a dose 480mg of Nivolumab every 4 weeks for 3 doses.
2. Nivolumab + BMS986016(Anti-Lag-3): Nivolumab will be given at 240mg in combination with BMS 986016(Anti-Lag-3) 80mg ever two weeks for 12 doses.

In SubProtocolC there will be 3 arms for each track:
1) Arm D: Combination of nivolumab 480 mg Q4W with rucaparib 600 mg BID
2) Arm E: Combination of ipilimumab 3 mg/kg Q4W with rucaparib 600 mg BID
3) Arm F: Combination of nivolumab 480 Q4W, low dose ipilimumab 1 mg/kg Q6W and rucaparib 600 mg BID

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 assessment, pregnancy testing (for females of child bearing potential) and monitoring for adverse events. Blood will also be collected at certain visits for research purposes (PK, Immunogenicity and biomarker samples).
Patients will be asked to undergo a biopsy to provide a biopsy sample at screening, at Day 28 and at End Of Treatment.
In addition every 8 weeks, patients will undergo a radiographic assessment of their tumours (by CT or MRI) for 24 weeks of treatment. If a patient continues on study treatment or re-enters the study and is assigned another treatment the radiographic assessments will continue every 8 weeks for 24 weeks. 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 and Ipilimumab and Anti-Lag-3 could potentially provide clinical benefit and improvement in the outcome for patients with this disease (disease improvement and improvement in survival). However ,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

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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) Participants must provide consent for 3 mandatory tumor biopsy samples (as detailed in*J* below).
2) All participants must have inoperable, advanced, or metastatic GC or GEJ carcinoma(including adenocarcinoma arising from the lower esophagus) and have histologically confirmed predominant adenocarcinoma. The documentation of GEJ involvement can include biopsy, endoscopy, or imaging.
3) Participants with human epidermal growth factor receptor 2 (HER2) overexpressing tumor who progress after trastuzumab (or are ineligible for or unwilling to be treated with trastuzumab) are eligible to be enrolled.
4) Prior adjuvant or neoadjuvant chemotherapy, radiotherapy, and/or chemoradiotherapy are permitted as long as the last administration of the last regimen (whichever was given last) occurred at least 4 weeks prior to randomization.
5) Participants must have an Eastern Cooperative Oncology Group performance status of <= 1 (see Appendix 7)., 6) Track-specific eligibility criteria
Track 1: anti-PD-1, anti-PD-L1, and anti-CTLA-4 treatment-naïve participants
1).Participants must not have received any anti-PD-1, anti-PD-L1, or anti-CTLA-4 treatment prior to this study. Participants previously treated with agents other than anti-PD-1, anti-PD-L1, or anti-CTLA-4 are eligible for Track 1.
2).Participants may have been offered platinum-based chemotherapy for

progressive or recurrent disease.
3).Participants must have documented PD-L1 tumor status following a required pretreatment biopsy as described below.
After signing informed consent, participants will be required to submit a fresh tumor biopsy meeting the criteria defined above for IHC staining to determine PD-L1 status., Track 2: anti-PD-1, anti-PD-L1, or anti-CTLA-4 treatment-experienced participants
1).Participants must have had progressive or recurrent disease during or after anti-PD-1, anti-PD-L1, or anti-CTLA-4 treatment. (Participants treated with any study treatment targeting PD-1, PD-L1, or CTLA-4 will be considered anti-PD-1, anti-PD-L1, or anti-CTLA-4 treatment experienced, respectively)
2).Participants may have been offered a platinum-based chemotherapy for GC or GEJ.
The platinum-based chemotherapy may have been in the adjuvant, neoadjuvant, or recurrent setting.
3).Participants who have had prior treatment with any 1 of the agents (or any other agent targeting PD-1, PD-L1, or CTLA-4) in monotherapy or in any combination regimen in a FRACTION-Gastric Cancer Sub-Protocol are eligible for treatment on Track 2.
4).Participants who have had prior combination treatment with the same IO combination agents (or IO agents directed against the same targets) as 1 of the combination regimens in a FRACTION-Gastric Cancer Sub-Protocol are eligible for study treatment on Track 2 but must be randomized to another combination regimen.
5).After signing informed consent, participants will be required to submit a fresh tumor biopsy for IHC staining to determine PD-L1 status., 7) At the time of screening, participants must have a life expectancy of at least 3 months following their most recent chemotherapy or immunotherapy for entry into all Tracks.
a. Participants who wish to be re-randomized to a new study treatment combination on Track 2 following progression on a prior study treatment in Tracks 1 or 2 must have a life expectancy of at least 3 months following the last study treatment.
8) Participants receiving prior palliative radiotherapy to a non-central nervous system (CNS) lesion must have completed that treatment at least 2 weeks prior to the first dose of study treatment.
9) Participants with symptomatic tumor lesions at baseline who may require palliative radiotherapy within 4 weeks of the first dose of study treatment are strongly encouraged to receive palliative radiotherapy prior to enrollment, and they must complete that treatment at least 2 weeks prior to the first dose of study treatment.
10) Participants must have at least 1 lesion with measurable disease as defined by RECIST v1.1 criteria for solid tumors response assessment
a. Participants with lesions in a previously irradiated field as the sole site of measurable disease will be permitted to enroll, provided that the lesion(s) have demonstrated clear progression and can be measured accurately.
11) Participants with toxicity from any prior anti-cancer treatment must have

their toxicity returned to Grade <= 1 (NCI CTCAE Version 4.03) or baseline before administration of study treatment.
12) Participants with Grade >= 2 toxicities attributed to prior anti-cancer treatment that are not expected to resolve and result in long-lasting sequelae, such as neuropathy after a platinum-based treatment, are eligible.
13) Participants must allow a tumor biopsy at the following time points: 1) baseline (prior to study treatment); 2) on-study (Day 28 on-treatment); and 3) EOT.
14) Participants who do not have accessible or suitable lesions are not eligible.
a. ii).Baseline biopsies may be collected from participants with a single measureable lesion (primary or metastatic), as long as it is not an excisional biopsy.
b. iii) For participants whose pretreatment biopsy yields inadequate tissue quantity or quality,(as determined by a pathologist in the central laboratory) re-biopsy is permitted.
c. iv) The solid tumor tissue specimen must be a core-needle biopsy or an excisional or incisional biopsy.
d. v) The biopsy at progression of disease after treatment on any Track may function as the pretreatment biopsy for subsequent treatment on Track 2

Exclusion criteria

a) Participants with overexpressing HER2 positive tumor and previously untreated with trastuzumab are excluded; participants who are ineligible for or unwilling to be treated with trastuzumab are still eligible.
b) Participants with ascites that cannot be controlled with appropriate interventions.
c) Participants must not have suspected, known, or progressive CNS metastases; have untreated CNS metastases; or have the CNS as the only site of disease.
i) Participants are eligible if CNS metastases are adequately treated and participants neurologically return to baseline (except for residual signs or symptoms related to the CNS treatment) for at least 2 weeks prior to study entry. In addition, participants mus tbe either off corticosteroids or on a stable or decreasing dose of prednisone <= 10 mg daily (or equivalent) for at least 2 weeks prior to study entry.
ii) Participants must not have leptomeningeal disease or carcinomatous meningitis.
d) Participants must not have prior malignancy active within the previous 3 years except for locally curable cancers that have been apparently cured, such as basal or squamous cell skin cancer, superficial bladder cancer, or carcinoma in situ of the prostate, cervix, or breast.
e) Participants must not have other active malignancy requiring concurrent intervention.
f) Participants must not have received a prior organ allograft.

g) Participants must not have received any anti-cancer treatment (eg, chemotherapy,
radiotherapy [except for palliative radiotherapy, which can be received at least 2 weeks prior to study treatment]; biologics; or immunotherapies, including investigational treatments) within 4 weeks prior to the first dose of study treatment administration.
i) Participants who have received noncytotoxic anti-cancer therapies (eg, prior use of targeted treatment) and who completed treatment at least 4 weeks or 5 half-lives (whichever is shorter) prior to the first dose of study treatment are eligible to enroll.
h) Participants must not have active, known, or suspected autoimmune disease.
i) Participants with type I diabetes mellitus, hypothyroidism only requiring hormone
replacement treatment, 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.
Participants must not have a condition requiring systemic treatment with either corticosteroids (prednisone > 10 mg daily or equivalent) or other immunosuppressive medications within 14 days of study treatment administration.
i) Inhaled or topical steroids and adrenal replacement steroid (prednisone > 10 mg daily or equivalent) are permitted in the absence of active autoimmune disease.
j) Participants must not have a history of life-threatening toxicity related to prior IO
treatment (eg, anti-CTLA-4 or anti-PD-1/PD-L1 treatment or any other antibody or treatment specifically targeting T-cell co-stimulation or immune checkpoint pathways).
k) Participants must not have interstitial lung disease that is symptomatic or may interfere with the detection or management of suspected treatment-related pulmonary toxicity.
l) Participants must not have uncontrolled or significant cardiovascular disease including, but not limited to, any of the following:
i) Myocardial infarction or stroke/transient ischemic attack within the past 6 months
ii) Uncontrolled angina within the past 3 months
iii) Any history of clinically significant arrhythmias (such as ventricular tachycardia,
ventricular fibrillation, or torsades de pointes)
iv) QT interval corrected with Fridericia*s formula > 480 ms
v) History of other clinically significant heart disease (eg, cardiomyopathy, congestive
heart failure with New York Heart Association functional classification III to IV,
myocarditis, pericarditis, or significant pericardial effusion)
m) Participants who require daily supplemental oxygen treatment are excluded.
n) Participants must not have any positive test result for hepatitis A,

hepatitis B virus or hepatitis C virus (HCV) indicating presence of virus, eg, hepatitis B surface antigen (Australia antigen) positive, or hepatitis C antibody (anti-HCV) positive (except if HCV-ribonucleic acid [RNA] negative).
i) Participants with a history of resolved hepatitis A virus infection are eligible
o) Participants must not have evidence of active infection requiring antibacterial, antifungal,or antiviral treatment * 7 days prior to initiation of study treatment.
p) Participants must not have a known history of testing positive for human immunodeficiency virus (HIV) or known acquired immunodeficiency syndrome.
i) Testing for HIV must be performed at sites mandated by local requirements.
q) Participants must not have known or suspected active tuberculosis.
r) Participant must not have had any major surgery within 4 weeks of study treatment
administration. Participants must have recovered from the effects of major surgery or
significant traumatic injury at least 14 days before the first dose of study treatment.
s) Participants must not have received nononcology vaccines containing live virus for
prevention of infectious diseases within 12 weeks prior to the first dose of study treatment.
t) Participants must not have received packed red blood cell or platelet transfusion within 2 weeks prior to the first dose of study treatment.
u) Participants must not have a known or underlying serious or uncontrolled medical condition that, in the opinion of the investigator or Sponsor, could make the administration of study treatment hazardous to the participants or could adversely affect the ability of the participant to comply with or tolerate the study.

Study design

Design

Study phase:	2
Study type:	Interventional
Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Health services research

Recruitment

NL

Recruitment status:	Completed
Start date (anticipated):	03-10-2017
Enrollment:	17
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Anti-Lag-3
Generic name:	Anti-Lag-3
Product type:	Medicine
Brand name:	IDO1 inhibitor
Generic name:	IDO1 inhibitor
Product type:	Medicine
Brand name:	Opdivo
Generic name:	Nivolumab
Registration:	Yes - NL outside intended use
Product type:	Medicine
Brand name:	Rucaparib (PARP inhibitor)
Generic name:	Rucaparib (PARP inhibitor)
Registration:	Yes - NL outside intended use
Product type:	Medicine
Brand name:	Yervoy
Generic name:	Ipilimumab
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO

Date:	27-02-2017
Application type:	First submission
Review commission:	METC Amsterdam UMC

Approved WMO

Date:	11-08-2017
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	05-09-2017
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	02-10-2017
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	08-01-2018
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	19-03-2018
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	06-06-2018
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	20-08-2018
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	10-04-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	14-05-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO	

Date:	18-11-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	20-11-2020
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	19-03-2021
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	01-04-2021
Application type:	Amendment
Review commission:	METC Amsterdam UMC

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	EUCTR2016-002807-24-NL
CCMO	NL59770.018.17

Study results

Date completed:	11-05-2022

Results posted: 12-05-2023

First publication
01-01-1900