A Phase 3 Randomized Clinical Trial of Nivolumab alone, Nivolumab in Combination with Ipilimumab, or an Investigator's Choice Chemotherapy in Participants with Microsatellite Instability High (MSI-H) or Mismatch Repair Deficient (dMMR) Metastatic Colorectal Cancer

Published: 02-08-2019
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This study has been transitioned to CTIS with ID 2023-503956-29-00 check the CTIS register for the current data. Primary Objective:All lines1) To compare the BICR-assessed PFS of participants with centrally confirmed dMMR/MSI-H mCRC and randomized...

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

Summary

ID

NL-OMON56215

Source
ToetsingOnline

Brief title
CheckMate 8HW

Condition

- Malignant and unspecified neoplasms gastrointestinal NEC

Synonym
Metastatic Colorectal Cancer

Research involving
Human

Sponsors and support

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

Intervention

Keyword: Chemotherapy, Ipilimumab, Metastatic Colorectal Cancer, Nivolumab

Outcome measures

Primary outcome

PFS means the length of time a patient lives with their cancer from the point of diagnosis or start of treatment without it getting worse. It is a good indicator of how well the treatment is working and is often used as a standard measure in clinical trials. PFS will be assessed by Blinded Independent Central Review (BICR).

Secondary outcome

Objective response rate or ORR is defined as the number of patients having a reduction in tumour size of a certain size and for a defined length of time.

Disease control rate or DCR is defined as the percentage of patients with advanced or metastatic cancer who have achieved complete response, partial response and stable disease to a therapeutic intervention in clinical trials of anticancer agents.

Overall survival means the length of time a patient lives with their cancer from the point of diagnosis or start of treatment. It is a good indicator of

how well the treatment is working and is often used as a standard measure in

clinical trials.

Study description

Background summary

Colorectal cancer is one of the leading causes of cancer-related death worldwide with a 5-year survival rate of approximately 14% in patients with metastatic disease (mCRC).
The current Standard of Care (SOC) for the patients with dMMR/MSI-H mCRC who haven*t received any prior systemic therapy (1L) or who have received one prior line of systemic therapy (2L) consists of combination of cytotoxic agents that are frequently used together with anti-VEGF or - anti-EGFR antibodies. These combinations are referred as chemotherapy.
Patients with metastatic dMMR/MSI-H CRC have a worse outcome when treated with this standard of care, yet they may have potential durable benefit if treated with checkpoint inhibitors.

The purpose of this study is to assess the effectiveness (how well the drug works), safety, and how well the patient can tolerate one of the following three treatment regimens:
• A - nivolumab
• B - nivolumab plus ipilimumab
• C - chemotherapy (SOC)
Nivolumab and Ipilimumab are antibodies (a type of human protein) that are being tested to see if it will stimulate the body*s immune system to work against tumour cells. Nivolumab is approved to treat certain cancer types in many countries (including countries in the EU and the US). Nivolumab is approved in the US for treatment of mCRC (Aug-2017).

In this trial, patients will undergo screening tests to check that it is safe for them to take part in the trial. Those patients who are suitable will be randomly allocated to receive one of the treatment regimens.

Patients will undergo the following procedures during the study: tumour tissue biopsy (possible), CT/MRI scans, physical exams, blood, urine and stool sampling for routine safety testing and study specific testing.

974 participants are expected to be treated in the study, with approximately 28 participants treated in the NLD. The study is sponsored by Bristol Myers Squibb

Study objective

This study has been transitioned to CTIS with ID 2023-503956-29-00 check the CTIS register for the current data.

Primary Objective:
All lines
1) To compare the BICR-assessed PFS of participants with centrally confirmed dMMR/MSI-H mCRC and randomized to nivolumab plus ipilimumab combination therapy arm or nivolumab monotherapy arm

1L
1) To compare the BICR-assessed PFS of participants with centrally confirmed dMMR/MSI-H mCRC who have not received prior treatment for metastatic disease and randomized to nivolumab plus Ipilimumab combination therapy arm or chemotherapy arm

Secondary Objectives:

All lines
1) To compare the BICR-assessed ORR of participants with centrally confirmed dMMR/MSI-H mCRC and randomized to nivolumab plus ipilimumab combination therapy arm or nivolumab monotherapy arm.

2) To compare the OS of participants with centrally confirmed dMMR/MSI-H mCRC and randomized to nivolumab plus ipilimumab combination therapy arm or nivolumab monotherapy arm.

3) To estimate the Investigator-assessed PFS of participants with centrally confirmed dMMR/MSI-H mCRC and randomized to nivolumab plus ipilimumab combination therapy arm or nivolumab monotherapy arm.

4) To estimate the BICR-assessed PFS of participants with dMMR/MSI-H mCRC per local testing who were randomized to nivolumab plus ipilimumab combination therapy arm or nivolumab monotherapy arm

1L:
1)To compare the BICR-assessed PFS of participants with centrally confirmed dMMR/MSI-H mCRC who have not received prior treatment for metastatic disease and randomized to nivolumab plus Ipilimumab combination therapy arm or nivolumab monotherapy arm.

2) To compare the BICR-assessed ORR of participants with centrally confirmed dMMR/MSI-H mCRC who have not received prior treatment for metastatic disease and randomized to nivolumab plus Ipilimumab combination therapy arm or chemotherapy arm.

3) To compare the BICR -assessed ORR of participants with centrally confirmed

dMMR/MSI-H mCRC who have not received prior treatment for metastatic disease and randomized to nivolumab plus Ipilimumab combination therapy arm or nivolumab monotherapy arm.

4) To compare the OS of participants with centrally confirmed dMMR/MSI-H mCRC who have not received prior therapy and randomized to nivolumab plus ipilimumab combination therapy arm or nivolumab monotherapy arm.

5) To estimate the BICR-assessed PFS of participants with centrally confirmed dMMR/MSI-H mCRC who have not received prior treatment for metastatic disease and randomized to nivolumab monotherapy arm or chemotherapy arm.

6) To estimate the OS of participants with centrally confirmed dMMR/MSI-H mCRC who have not received prior therapy and randomized to nivolumab plus ipilimumab combination therapy arm or chemotherapy arm.

7) To estimate the BICR-assessed ORR of participants with centrally confirmed dMMR/MSI-H mCRC who have not received prior treatment for metastatic disease and randomized to nivolumab monotherapy arm or chemotherapy arm.

8) To estimate the BICR-assessed PFS of participants with dMMR/MSI-H mCRC per local testing who have not received prior treatment and randomized to nivolumab plus ipilimumab combination therapy arm or chemotherapy arm.

9) To estimate the BICR-assessed PFS of participants with dMMR/MSI-H mCRC per local testing who have not received prior treatment and randomized to nivolumab plus ipilimumab combination therapy arm or nivolumab monotherapy arm.

Companion Diagnostics (CDx) (all lines and 1L):
1) To estimate the BICR-assessed PFS of participants with confirmed dMMR/MSI-H status by each central test who have not received prior therapy and randomized to nivolumab plus ipilimumab combination therapy arm or chemotherapy arm.

2) To estimate the BICR-assessed PFS of participants with confirmed dMMR/MSI-H status by each central test and randomized to nivolumab plus ipilimumab combination therapy arm or nivolumab monotherapy arm.

Crossover cohort:
1) To estimate the BICR-assessed PFS of participants with centrally confirmed dMMR/MSI-H mCRC treated in the crossover cohort.

2) To estimate the BICR-assessed ORR of participants with centrally confirmed dMMR/MSI-H mCRC treated in the crossover cohort

Study design

This is a Phase 3, randomised, open-label 3-arm study of nivolumab monotherapy (Arm A), nivolumab plus ipilimumab combination therapy (Arm B) or an investigator*s choice chemotherapy (Arm C) for the treatment of participants with recurrent or metastatic dMMR/MSIH CRC. The study will enroll participants across all lines of therapy, however randomisation to Arm C will be restricted to participants who have received no more than 1 prior line of systemic therapy (0 or 1). Study specific definition of the line of therapy (number of prior systemic treatments for metastatic disease) is provided in Appendix 10 of the protocol. Participants will receive treatment until progression, toxicity, discontinuation for other reasons, or reaching maximum treatment duration. Study participants from all three arms that discontinue study treatment will enter the Follow Up phase (first treatment Follow Up) and will follow the assessment schedules outlined in Table 2-5 of the protocol. Participants assigned to Arm C that experience documented progression of disease (PD) per RECIST 1.1 by Blinded Independent Central Review (BICR) will have an option to crossover to nivolumab plus ipilimumab therapy (Crossover Cohort) provided that they complete at least Follow Up Visit 1 within the Follow Up phase and meet all other crossover criteria outlined in the protocol Section 6.2.1. Crossover Cohort participants will receive treatment until progression, toxicity, discontinuation for other reasons, or reaching maximum treatment duration. After study treatment discontinuation, they will also enter the Follow Up phase (second treatment Follow Up) and will follow the assessment schedules outlined in Table 2-5 of the protocol

Intervention

Patients will be randomly assigned to one of three treatment Arms:
Arm A (Nivolumab monotherapy): Nivolumab 240 mg administered every 2 weeks (Q2W) for up to 6 doses (2 cycles), followed by nivolumab 480 mg administered every 4 weeks (Q4W) until disease progression, unacceptable toxicity, withdrawal of consent, or until reaching maximum treatment duration.
Arm B (Nivolumab plus ipilimumab): Nivolumab 240 mg plus ipilimumab 1 mg/kg both administered every 3 weeks (Q3W) for up to 4 doses (2 cycles), followed by nivolumab 480 mg administered every 4 weeks (Q4W) until disease progression, unacceptable toxicity, withdrawal of consent, or until reaching maximum treatment duration.
Arm C (Investigator*s Choice Chemotherapy): One of 6 Investigator*s choice chemotherapy regimens (FOLFOX; FOLFOX + bevacizumab; FOLFOX + cetuximab; FOLFIRI; FOLFIRI + bevacizumab; FOLFIRI + cetuximab) administered every 2 weeks (Q2W) until disease progression, unacceptable toxicity, withdrawal of consent, or until reaching maximum treatment duration.
Details of Arm C treatment are listed below:
FOLFOX- oxaliplatin 85 mg/m2, leucovorin 400 mg/m2, fluorouracil 400 mg/m2 bolus followed by fluorouracil 2400 mg/m2 in continuous infusion administered over 46 hours IV on Day 1, Day 15 and Day 29 during Cycles 1 and 2. Starting from Cycle 3 the drugs will be administered on Day 1 and Day 15 of each cycle.
FOLFOX +Bevacizumab - Bevacizumab 5 mg/kg administration will then be followed

by oxaliplatin 85 mg/m2, leucovorin 400 mg/m2, fluorouracil bolus 400 mg/m2 and fluorouracil 2400 mg/m2 in continuous infusion administered over 46 hours IV on Day 1, Day 15 and Day 29 for the first 2 cycles and thereafter on Day 1 and Day 15 for all subsequent cycles.
FOLFOX + Cetuximab - Cetuximab 500 mg/m2 administration will then be followed by oxaliplatin 85 mg/m2, leucovorin 400 mg/m2, fluorouracil bolus 400 mg/m2 and fluorouracil 2400 mg/m2 in continuous infusion administered over 46 hours IV on Day 1, Day 15 and Day 29 for the first 2 cycles and thereafter on Day 1 and Day 15 for all subsequent cycles
FOLFIRI - irinotecan 180 mg/m2, leucovorin 400 mg/m2, fluorouracil bolus 400 mg/m2 and fluorouracil 2400 mg/m2 in continuous infusion administered over 46 hours IV on Day 1, Day 15 and Day 29 for the first 2 cycles. Starting from Cycle 3 the drugs will be administered on Day 1 and Day 15 of each cycle.
FOLFIRI + Bevacizumab - Bevacizumab 5 mg/kg administration will then be followed by irinotecan 180 mg/m2, leucovorin 400 mg/m2, fluorouracil bolus 400 mg/m2 and fluorouracil 2400 mg/m2 in continuous infusion administered over 46 hours IV on Day 1, Day 15 and Day 29 for the first 2 cycles and thereafter on Day 1 and Day 15 for all subsequent cycles.
FOLFIRI + Cetuximab - Cetuximab 500 mg/m2 administration will then be followed by irinotecan 180 mg/m2, leucovorin 400 mg/m2, fluorouracil bolus 400 mg/m2 and fluorouracil 2400 mg/m2 in continuous infusion administered over 46 hours IV on Day 1, Day 15 and Day 29 for the first 2 cycles and thereafter on Day 1 and Day 15 for all subsequent cycles

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 & serious adverse events. Stool samples will be collected at screening and once during treatment. Patients will be asked to complete questionnaires (EQ-5D-3L, EORTC QLQ-C30 and QLQ-CR29) about their quality of life. Blood will also be collected at certain visits for research purposes (PK, immunogenicity and biomarker studies). If there is no archival tumour tissue available or the sample was taken too long ago (>= 3 months), patients will be required to have a biopsy in order to participate. Surgery will be performed on patients post completion of neo-adjuvant therapy. A tumour biopsy will also be performed at disease progression. Patients will undergo radiographic assessment of their tumours by CT or MRI at screening and brain MRI if clinically indicated. Subsequent imaging assessments will be performed every 6 weeks for the first 24 weeks, then every 8 weeks until disease recurrence or progression (confirmed by blinded independent central review). The frequency of visits and number of procedures carried out during this trial would be typically 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. A Data monitoring committee will not be used for this study and a rationale for this has been provided by BMS and enclosed within this application. BMS will conduct rigorous safety monitoring to ensure patients* safety by regularly and systematically reviewing safety data; the reported safety events will be closely followed-up; sites and study investigators will receive training on the implementation of nivolumab toxicity management strategies. New immune system targeted therapy (immunotherapies) such as nivolumab could potentially provide clinical benefit and improvements in the outcomes for patients with this disease. 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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Bristol-Myers Squibb

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

- Histologically confirmed recurrent or metastatic colorectal cancer (CRC) irrespective of prior treatment history with chemotherapy and/or targeted agents not
amenable to surgery (Applicable only during Part 1 enrollment of the study)
-Histologically confirmed recurrent or metastatic CRC with no prior treatment history with chemotherapy and/or targeted agents for metastatic disease and not
amenable to surgery (Applicable during Part 2 enrollment of the study)
- Known tumor MSI-H or dMMR status per local standard of practice
- Eastern cooperative oncology group (ECOG) performance status lower than or equal to 1
- Other protocol-defined inclusion/exclusion criteria apply

Exclusion criteria

- Participants with an active, known or suspected autoimmune disease
- History of interstitial lung disease or pneumonitis
- Known history of positive test for human immunodeficiency virus (HIV) or known acquired immunodeficiency syndrome (AIDS)
- Other protocol-defined inclusion/exclusion criteria apply

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:	Recruiting
Start date (anticipated):	18-10-2019
Enrollment:	28
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Opdivo
Generic name:	Nivolumab
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:	02-08-2019
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	08-10-2019
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	17-12-2019
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	01-05-2020
Application type:	Amendment

Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	23-12-2020
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	13-01-2021
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	18-06-2021
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	12-07-2021
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	18-12-2021
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	18-03-2022
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	17-06-2022
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO	

Date:	25-10-2022
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	28-01-2023
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	02-06-2023
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	02-07-2023
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	11-07-2023
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	13-09-2023
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	13-11-2023
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	05-12-2023
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
EU-CTR	CTIS2023-503956-29-00
EudraCT	EUCTR2018-000040-26-NL
CCMO	NL68433.056.19
Other	U1111-1207-2702