A MULTI-CENTRE RANDOMISED CLINICAL TRIAL OF BIOMARKER-DRIVEN MAINTENANCE TREATMENT FOR FIRST-LINE METASTATIC COLORECTAL CANCER (MODUL)

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EFFICACY OBJECTIVESWithin each cohort, the study has the following co-primary efficacy objectives:· Assessing early efficacy during the Maintenance Treatment Phase based on a 20%reduction in tumour size after 2 months of treatment· Evaluating PFSThe...

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

Summary

ID

NL-OMON45025

Source
ToetsingOnline

Brief title
MO29112 (MODUL)

Condition

- Malignant and unspecified neoplasms gastrointestinal NEC

Synonym
colorectal cancer, metastatic colorectal cancer

Research involving
Human

Sponsors and support

Primary sponsor: Roche Nederland B.V.
Source(s) of monetary or material Support: Farmaceutische industrie.

Intervention

Keyword: Biomarker-driven, Colorectal cancer, First line, Maintenance treatment

Outcome measures

Primary outcome

The primary efficacy outcome measures will be assessed within each cohort (experimental arm vs. control arm) during the Maintenance Treatment Phase. These are:

· Early efficacy defined as the proportion of patients with a 20% reduction in tumour size after 2 months of treatment in the Maintenance Treatment Phase

· PFS defined as the time from randomisation into the Maintenance Treatment Phase until disease progression according to RECIST 1.1 per Investigator assessment or death from any cause, whichever occurs first

Secondary outcome

The secondary efficacy outcome measures are:

· OS, defined as the time from randomisation into the Maintenance Treatment Phase to death from any cause

· ORR (defined as PR or CR) during the Maintenance Treatment Phase, with response confirmed ³ 28 days later. Response will be determined by the Investigator according to RECIST 1.1 based on comparisons to the tumour assessment done at Week 16 of the Induction Treatment Phase.

· DCR (defined as CR, PR or SD) during the Maintenance Treatment Phase, with

response confirmed ³ 28 days later. Response will be determined by the Investigator according to RECIST 1.1 based on comparisons to the tumour assessment done at Week 16 of the Induction Treatment Phase.

· TTR defined as the time from randomisation into the Maintenance Treatment Phase to the first subsequent occurrence of a documented objective response (PR or CR), as determined by the Investigator according to RECIST 1.1

· DOR, defined as the time from the first occurrence of a documented objective response (PR or CR) during the Maintenance Treatment Phase to the time of progression, as determined by the Investigator according to RECIST 1.1, or death from any cause

· ECOG performance status during and after treatment

Study description

Background summary

Advances in the treatment of mCRC have led to an improvement in survival from 12 months with fluorouracil monotherapy to approximately 2.5 years with current combination regimens. However, there are significant molecular differences between tumours and between tumour microenvironments that can affect both prognosis and response to treatment. Many new cancer drugs target specific molecular aberrations or cell-signalling pathways, but these drugs are only active in a subset of patients due to molecular differences between tumours. Personalized medicine has made some major advances in CRC, with RAS testing to guide treatment with the anti-EGFR monoclonal antibodies cetuximab and panitumumab now being part of routine clinical practice. However, not all patients who are RASwt respond to anti-EGFR therapy and, despite extensive research into other biomarkers for anti-angiogenic drugs, chemotherapy and other targeted agents, these are not yet established in clinical practice, and a validated biomarker for anti-angiogenic therapy is still lacking. Therefore, there is a clear need for both molecular screening approaches to understand the disease better and to fully characterize tumours and identify patients who are most likely to benefit from targeted treatments, as well as for new biomarkers to assist with predicting response to both existing drugs as well as to drugs

currently under investigation.

On June 3rd 2016 Roche submitted a temporary halt to recruitment notification. The study was a year ahead of its planned enrolment schedule. The aim of our halt was to amend the design of the trial to allow future enrolment of screened `no-biomarker patients* into new treatment arms. Cohort 2 (no *biomarker cohort) is fully recruited. The planned protocol amendment (version 6) to add a new `no-biomarker* cohort is being submitted and Roche would like to re-start recruitment into the trial as soon as this protocol amendment is approved.
The following substantial changes are introduced with this amendment; two new treatment cohorts have been added including three new IMPs: trastuzumab, pertuzumab and cobimetinib . Patients in the experimental treatment arm of Cohort 3 will receive capecitabine, trastuzumab and pertuzumab, and those in Cohort 4 will receive cobimetinib and atezolizumab. For a full rational for the addition of the new IMPs please refer to the protocol version 6, section 1.3.

Study objective

EFFICACY OBJECTIVES
Within each cohort, the study has the following co-primary efficacy objectives:
· Assessing early efficacy during the Maintenance Treatment Phase based on a 20% reduction in tumour size after 2 months of treatment
· Evaluating PFS
The secondary efficacy objectives include the evaluation of efficacy through other endpoints:
· OS
· ORR
· Disease control rate (DCR)
· Time to treatment response (TTR)
· Duration of response (DoR)
· ECOG performance status

SAFETY OBJECTIVES
The safety of this study are to assess the safety of each treatment including:
· Incidence, nature and severity of adverse events (AEs)
· Incidence and reasons for any dose reductions, interruptions or premature discontinuation of any component of study treatment
· Clinically significant laboratory values
AEs refer to all treatment-emergent adverse events occurring after the initiation of study
medication (i.e. on or after Day 1, Cycle 1 of the Induction Treatment Phase). AEs will
continue to be collected during the Maintenance Treatment Phase and Post-Treatment
Follow-up Phase as applicable.

EXPLORATORY OBJECTIVES

The exploratory efficacy objective of this study is:
· To evaluate PFS measured according to mRECIST in patients treated with MPDL3280A
(anti-PD-L1 antibody)
The exploratory biomarker objectives of this study are as follows:
· To explore whether there is differential benefit from treatment in patient subgroups
defined by different biomarkers, e.g. but not limited to biomarker panels (mutation and
expression profiles), immune panels etc.
· If applicable, to assess correlations between biomarkers/marker panels and safety
· Where possible, to investigate if changes in expression/mutation panels of biomarkers
during treatment correlate with treatment efficacy or failure i.e. to explore potential
resistance/escape mechanisms to (targeted) treatment
· Explore prognostic and potentially predictive effects of markers/marker profiles
· Explore prevalence of specific markers at Baseline and/or salvage/resistance markers to
guide targeted therapy approaches beyond MODUL, e.g. but not limited to programmed
cell death-1 (PD-L1)

Study design

This is a randomised, multi-centre, active-controlled, open-label, parallel-group clinical trial of biomarker-driven maintenance treatment for first-line metastatic colorectal cancer (mCRC). Patients with mCRC are eligible for entry, and cannot have received any prior chemotherapy in the metastatic setting.

Potential patients will undergo screening assessments to determine study eligibility within 28 days prior to starting study induction treatment. The primary tumour tissue block prepared at the time of the initial diagnosis will be used for biomarker assessment for maintenance treatment cohort assignment. An optional core biopsy of metastatic tumour will also be collected from all patients during Screening. Biopsies already done as part of routine practice within two months of the 28-day. Screening Phase are also acceptable. Eligible patients will enter a 4-month Induction Treatment Phase. Treatment during this phase, based on Investigator*s choice, will be either:
· Eight 2-week cycles of 5-fluorouracil (5-FU), leucovorin (LV) and oxaliplatin (FOLFOX) in combination with bevacizumab
or
· Six 2-week cycles of FOLFOX in combination with bevacizumab, followed by two 2-week cycles of 5-FU/LV with bevacizumab

Patients will be assessed for AEs at every cycle, and remaining safety parameters (such as concomitant medications, physical examination and clinical laboratory assessments) will be assessed every 4 weeks (two treatment cycles) during the Induction Treatment Phase.
Tumour assessments will be evaluated according to the Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST 1.1) during the Induction Treatment Phase. Tumour assessments during treatment will be based on local standard of care, but are required at the
end of the Induction Treatment Phase (see Appendix 1).
Patients who do not have progressive disease and who have completed the Induction Treatment Phase can then proceed to the Maintenance Treatment Phase.
Each cohort will consist of a cohort-specific experimental treatment arm and a standard control arm of fluoropyrimidine (5-FU or capecitabine) and bevacizumab.
For details of the experimental treatment arms, refer tot protocol section 3.1.2. The study will follow an adaptive design, where additional cohorts can be added or existing cohorts may be modified over the course of the study via protocol amendment.

Efficacy, safety and tolerability will be assessed during the entire Maintenance Treatment Phase.
All patients will undergo a Study Treatment Discontinuation visit within 30 days following their last study treatment and will enter the Post-Treatment Follow-up Phase of the study. During the Post-Treatment Follow-up Phase, patients will be followed every 3 months for subsequent
anti-cancer therapies, survival, and AEs including therapy-specific safety assessments. Patients who discontinue study treatment in either the Induction or Maintenance Treatment Phases prior to disease progression will also enter the Post-Treatment Follow-up Phase but will also continue to be followed for progression, with disease status followed according to local practice until progression or the end of the study, whichever
comes first. All patients will remain in the Post-Treatment Follow-up Phase until death or the end of the study, whichever comes first.

Intervention

Patients eligible for participation in this study are treated in the induction treatment pahse with a standard treatment of:
5-fluorouracil (5-FU), leucovorine (LV), oxaliplatine and bevacizumab during 16 weeks or
5-FU, LV, oxaliplatine en bevacizumab during 12 weeks, followed by 5-FU, LV eand bevacizumab during 4 weeks.

Each cohort exists of a cohort-specific experimental arm and a standard control arm of fluoropyrimidine (5-FU of capecitabine) en bevacizumab. For details of the experimental treatment arms, see protocol section 3.1.2. (figure 2 page 69 protocol) The allocation will be done according to the study specific schedule

as described in figure 2.

Study burden and risks

The test procedures and treatments may entail risks and cause discomfort. There is a slight chance of pain or a bruise when blood is collected. Some people may faint when blood is collected. During this study, with patient approval, biopsies may be performed. The following risks are associated with a biopsy: bruising, bleeding, infection and side-effects of the numbing medication (anaesthetic) that may be given for the procedure. In rare cases, these risks may be life-threatening and make hospitalization necessary. In order to reduce the risks, the site of the biopsy will be numbed and sterile techniques will be used. Undergoing an MRI or PET / CT scan may entail additional discomfort, specifically, a sense of claustrophobia (being *locked in*) or suffering from the noise during the scan. The disadvantages of participating in this study are: time investment to undergo various procedures for this study, additional or prolonged hospitalization(s), additional blood collection, additional examinations, biopsies and any side effects of the study medications.

An allergic reaction to one of the study medications may be mild (skin rash, fever, chills, headache, nausea or vomiting) or severe (low blood pressure, elevated heart rate, anxiety and / or difficulty swallowing or breathing). These side-effects are most common during the first few doses, but may occur during any administration. The research physician may prescribe medication and other supportive care in order to reduce or prevent the severity of these side-effects. In rare cases, these symptoms can be so severe that they possibly require the administration of the study medications to be stopped permanently. Sometimes, side-effects develop and get worse over time due to the development of antibodies against the study medication. Usually these side-effects involve skin rashes, joint and muscle pain, fever and fatigue. Medication may be prescribed to reduce the effect of these symptoms. If these side-effects are serious or persist for a very long time, it may be necessary to permanently stop administration of the study medications.

Risk of drug interactions:
It is possible that treatment with the study medications may affect the activity of other medication.
Patient may experience one or more of these side-effects, or currently unknown side effects, and they may be mild, moderate, severe, or (in very rare cases) life-threatening or even fatal. If side-effects do occur, the study physician must be notified immediately. He / she may prescribe medication to combat any discomfort. Furthermore, in the event of a serious reaction, the study physician may decide to suspend or permanently terminate treatment with the study medications.

Contacts

Public
Roche Nederland B.V.

Beneluxlaan 2a
Woerden 3446 GR
NL
Scientific
Roche Nederland B.V.

Beneluxlaan 2a
Woerden 3446 GR
NL

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

All cohorts:
- Male and female patients >/<= 18 years of age
- Eastern Cooperative Oncology Group (ECOG) performance status of - At least 16 weeks of life expectancy at time of entry into the study
- Histologically confirmed colorectal cancer (CRC) with metastatic CRC confirmed radiologically
- Measureable, unresectable disease according to Response Evaluation Criteria in Solid Tumors (RECIST) criteria version 1.1
- No prior chemotherapy for CRC in the metastatic setting
- Archival tumor formalin-fixed paraffin-embedded tissue block from the primary tumor obtained at the time of the initial diagnosis is available
- Adequate hematological, liver and renal function

- Agreement to use highly effective measures of contraception

Exclusion criteria

All cohorts (pages 78-81 protocol):
- Positive test for human immunodeficiency virus (HIV)
- Active hepatitis B or hepatitis C at Screening
- Active tuberculosis
- Administration of a live, attenuated vaccine within four weeks prior to start of maintenance treatment or anticipation that such a live attenuated vaccine will be required during the remainder of the study
- Prior treatment with CD137 agonists, anti-CTLA4, anti-PD-1, or anti-PD-L1 therapeutic antibody or pathway-targeting agents
- Treatment with systemic immunostimulatory agents (including but not limited to interferons or interleukin-2) within four weeks or five half-lives of the drug, whichever is longer, prior to start of maintenance treatment
- Treatment with systemic corticosteroids or other systemic immunosuppressive medications within 2 weeks prior to start of maintenance treatment, or anticipated requirement for systemic immunosuppressive medications during the remainder of the study. The use of inhaled corticosteroids and mineralocorticoids is allowed.
-If receiving a RANKL inhibitor (e.g. denosumab), unwilling to adopt alternative treatment such as (but not limited to) bisphosphonates, while receiving atezolizumab.
Cohort-specific criteria: pages 81-87 protocol

Study design

Design

Study phase:	2
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):	29-06-2015
Enrollment:	70
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Bevacizumab
Generic name:	Avastin
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Cetuximab
Generic name:	Erbitux
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Cotellic
Generic name:	Cobimetinib
Registration:	Yes - NL outside intended use
Product type:	Medicine
Brand name:	MPDL3280A
Generic name:	Atezolizumab
Product type:	Medicine
Brand name:	Vemurafenib
Generic name:	Zelboraf
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	18-11-2014
Application type:	First submission
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	27-01-2015

Application type:	First submission
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	09-03-2015
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	16-04-2015
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	26-05-2015
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	18-06-2015
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	06-07-2015
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	14-07-2015
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	23-07-2015
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)

Approved WMO Date:	21-10-2015
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	13-11-2015
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	21-01-2016
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	02-03-2016
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	31-03-2016
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	08-04-2016
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	25-05-2016
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	20-06-2016
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Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
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Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
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Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	15-09-2016
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	10-11-2016
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	22-12-2016
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	25-01-2017
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Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	29-03-2017
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO	

Date:	06-04-2017
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)

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Date:	03-07-2017
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Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)

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Date:	25-07-2017
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Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)

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Date:	01-08-2017
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)

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Date:	07-08-2017
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Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)

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Date:	01-11-2017
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Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)

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Date:	21-11-2017
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Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)

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Date:	24-11-2017
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Review commission:	MEC-U: Medical Research Ethics Committees United

	(Nieuwegein)
Approved WMO Date:	29-11-2017
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Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
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Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	24-01-2018
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Approved WMO Date:	09-04-2018
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Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	18-05-2018
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Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	11-04-2019
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	01-05-2019
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	11-10-2019
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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	EUCTR2014-001017-61-NL
CCMO	NL50698.100.14

Study results

Results posted: 24-03-2022

First publication
01-01-1900