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

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STATISTICAL ANALYSIS PLAN

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

COHORT 1

PROTOCOL NUMBER: MO29112

COHORT 1 STUDY DRUGS: bevacizumab (RO4876646)
vemurafenib (RO5185426)
cetuximab

VERSION NUMBER: 1.1

IND NUMBER: N/A

EUDRACT NUMBER: 2014-001017-61

SPONSOR: F. Hoffmann-La Roche Ltd

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HISTORY CHANGE

Version	Date	Changes
Final 1.0	04-Apr-2019	N/A
Final 1.1	06-Jun-2019	Update in sample size section to add some scenarios in order to provide power calculation considering the actual number of patients.

LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	adverse event
AESI	adverse events of special interest
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANC	absolute neutrophils count
aPTT	activated partial thromboplastin time
AST	aspartate aminotransferase
BMI	body mass index
BOR	best overall response
$BRAF^{mut}$	BRAF mutation
BSA	body surface area
CI	confidence interval
CR	complete response
cSCC	cutaneous squamous cell carcinoma
CSR	clinical study report
DCR	disease control ate
DoR	duration of response
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic Case Report Form
EU	European Union
FP	fluoropyrimidine
Hb	haemoglobin
HER2	human epidermal growth factor receptor 2
HER2+	human epidermal growth factor receptor 2 positive
HR	hazard ratio
IC	informed consent
ICH	International Conference on Harmonization
iDMC	Independent Data Monitoring Committee
IHC	immunohistochemistry
INR	international normalized ratio
ITP	Induction Treatment Phase
IxRS	interactive voice or web-based response system
KM	Kaplan Meier
LDH	lactate dehydrogenase
mCRC	metastatic Colorectal Cancer
MedDRA	Medical Dictionary for Regulatory Activities

Abbreviation	Definition
mRECIST	modified Response Evalution Criteria in Solid Tumors
MSI-H	high microsatellite instability
MSS	microsatellite stable
MTP	Maintenance Treatment Phase
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NE	not evaluable
NGS	next generation sequencing
ORR	objective response rate
OS	overall survival
PD	progressive disease
PDMS	protocol deviation management system
PFS	progression free survival
PK	pharmacokinetic
PP	Per protocol
PR	partial response
PS	performance status
PT	preferred term
PTFUP	Post-treatment follow-up phase
RBC	red blood cell
RDI	relative dose intensity
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	serious adverse event
SAF	safety population
SAP	statistical analysis plan
SC	Steering Committee
SCC	squamous cell carcinoma
SD	stable disease
SI	Système International
SOC	System Organ Class
SOD	sum of target lesions diameter
TEAE	treatment emergent adverse event
TSH	thyroid-stimulating hormone
TTR	time to treatment response
WBC	white blood cells counts or leukocytes

1. BACKGROUND

The study is a randomized, multi-center, active-controlled, open-label, parallel-group clinical study of biomarker-driven maintenance treatment for first-line metastatic colorectal cancer (mCRC) patients. All patients will receive induction treatment with FOLFOX and bevacizumab. Induction treatment will be followed by maintenance treatment with chemotherapy combined with targeted therapy within one of several maintenance treatment cohorts. Only those patients who experience disease response or disease control during induction and who are not assessed as resectable at completion of induction will proceed to further treatment in the Maintenance Treatment Phase (MTP) of the study. Patients will be assigned to a maintenance treatment cohort based on their primary tumour biomarker results. The primary study objective within each cohort is to evaluate progression-free survival (PFS).

Maintenance treatment cohorts may be added or modified over the course of the study. This SAP describes planned analyses of patients who were assigned, or would have been assigned, to maintenance treatment Cohort 1 based on their primary tumour biomarker profile. Analyses of patients assigned to all other MODUL cohorts will be described in SAPs applicable to each specific cohort.

A Steering Committee (SC) is responsible for overseeing the general conduct of the study.

In addition, an independent Data Monitoring Committee (iDMC) is responsible for evaluating the safety of the patients participating in the trial at regular intervals throughout the study. The iDMC makes recommendations as to whether cohort recruitment should continue based on benefit-risk evaluations that include efficacy as well as safety data. To minimize the impact of such reviews on efficacy endpoint analyses, efficacy data included in these reviews has to be specified by the iDMC at a preceding iDMC meeting and has to be documented in the iDMC meeting minutes. In addition, the iDMC evaluates the safety data from a prespecified number of initial patients for experimental combinations with inadequate prior safety experience to assure appropriate dosing (e.g. as required for the initial patients treated with the Cohort 1 experimental combination of '5-FU/LV + cetuximab + vemurafenib').

2. STUDY DESIGN

Patients continuing from the Induction Treatment Phase (ITP) to the Maintenance Treatment Phase are assigned to a maintenance treatment cohort based on their primary tumour biomarker status. Following eligibility assessment for their assigned cohort, eligible patients are randomized to the experimental or control arm within their cohort.

The study was initiated with 2 maintenance treatment cohorts, Cohorts 1 and 2. Two additional cohorts, Cohorts 3 and 4, were added with protocol amendment 5 (protocol version 6). With the addition of these new cohorts, primary tumour biomarker criteria for assignment to Cohort 1 were revised as shown in Table 1.

In this open-label study, all patients will receive 8 cycles induction treatment that is considered standard in many countries and that has been shown to improve outcomes in the first-line setting. Treatment during the ITP, 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

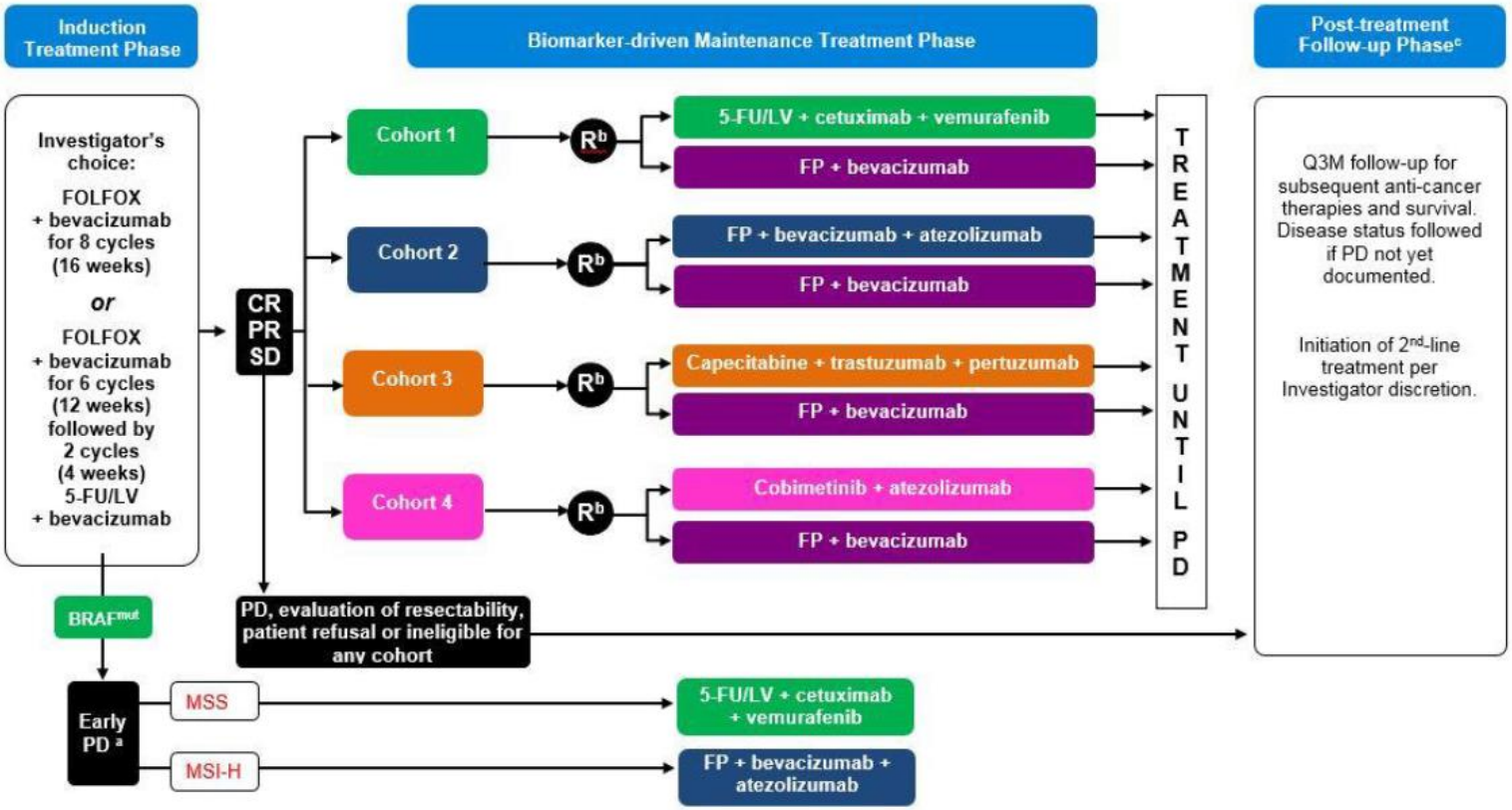
- Six 2-week cycles of FOLFOX in combination with bevacizumab, followed by two 2-week cycles of 5-FU/LV with bevacizumab

Patients who prematurely discontinue study treatment for any reason during the ITP, who experience progressive disease (PD) at any time during or at the end of the ITP, who are evaluated as resectable at the end of ITP, who refuse to proceed to the MTP or who are not eligible for any maintenance cohort will undergo a study treatment discontinuation visit and enter post-treatment follow-up. Patients who experience disease control or tumor response to induction treatment will continue to the randomized MTP of the study wherein the effects of experimental and control groups will be compared. Patients in study screening prior to June 28, 2016 were assigned to Cohort 1 if their primary tumour was $BRAF^{mut}$. Patients in screening after June 28, 2016, were were assigned to Cohort 1 if their primary tumour was HER2-/MSS/$BRAF^{mut}$/RAS^{wt}. Treatment in each cohort is shown in Figure 1.

Table 1: Biomarker Profile by Cohort

	Biomarker profile	
	Patients in Screening Prior June 28, 2016	Patients in Screening After June 28, 2016
Cohort 1	$BRAF^{mut}$	HER2-/MSS/$BRAF^{mut}$/RAS^{wt}
Cohort 2	$BRAF^{wt}$ or biomarker status unknown	Closed to patients screened after June 28, 2016
Cohort 3	Not applicable	HER2+
Cohort 4	Not applicable	HER2-/MSI-H; HER2-/MSS/$BRAF^{wt}$; HER2-/MSS/$BRAF^{mut}$/RAS^{mut}

Figure 1: Study Design as of protocol version 6



FP = fluoropyrimidine (5-FU/LV or capecitabine); 5-FU/LV = 5-fluorouracil/leucovorin; MSI -H= high microsatellite instability; MSS = microsatellite stable

a. Patients who progress early and who are not $BRAF^{mut}$ will enter the Post-treatment Follow-up Phase with initiation of 2nd-line treatment per Investigator discretion

b. Randomization stratified by: Cohorts 1 and 2- region (EU, Americas, Africa or Asia), induction treatment response (CR/PR vs. SD); Cohort 3- induction treatment response (CR/PR vs. SD), HER2 IHC (IHC0/ IHC1+/IHC2+ vs. IHC3+); Cohort 4- region (EU vs. rest of world), induction treatment response (CR/PR vs. SD), microsatellite stability (MSI-H vs. MSS), RAS status (wild-type KRAS and NRAS vs. mutant KRAS and/or NRAS)

c. Patients discontinuing study treatment for any reason during the Induction or Maintenance Treatment Phases will enter the Post-treatment Follow-up Phase.

Primary objective of this study:

The primary study objective within each cohort is to evaluate PFS.

An iDMC is responsible for regularly reviewing safety data.

2.1 PROTOCOL SYNOPSIS

The Protocol version 8 synopsis is provided in Appendix 1. For additional details, see the Schedule of Assessments in Appendix 2.

2.2 OUTCOME MEASURES

As mentioned in the protocol, each cohort will be analysed separately and therefore this SAP focuses on the description of the analysis required for cohort 1 data only, i.e. applicable to enrolled patients eligible for cohort 1 based on primary tumour biomarker status.

2.2.1 Primary Efficacy Outcome Measures

PFS is defined as the time from randomization into the MTP until documented disease progression as per investigator assessment using Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 or death from any cause, whichever occurs first. If no progression / death is observed at the time of clinical cut-off or by the date of any on-study colorectal anti-cancer surgery with palliative or curative intent, patients will be censored at the date of the last evaluable tumor assessment or date of randomization, whichever comes last.

(Of note: (i) Progressive disease are identified by the Overalll Response=’PD’, even if solely based on symptomatic deterioration, (ii) Only surgery occurring between baseline tumor assessment for MTP and PFS events are considered for censoring PFS)

2.2.2 Secondary Efficacy Outcome Measures

2.2.2.1 Overall Survival (OS)

OS is defined as the time from randomization into the MTP to time of death from any cause. Patients still alive at time of clinical cut-off will be censored at their last date known to be alive as defined in section 4.3. For imputation of “Partial Death Date”, please refer to section 4.14.

2.2.2.2 Best Overall Response (BOR)

Main definition

BOR (e.g. complete response [CR], partial response [PR], stable disease [SD], progressive disease [PD], not evaluable [NE]) for the MTP will be defined as the best response recorded from the randomization date until progressive disease (taking as reference for progressive disease the smallest measurements recorded since randomization date). For patients under maintenance treatment at the time of primary analysis, the BOR will be defined based on available tumor assessments at time of clinical cut-off. The overall response per time point reported on the electronic Case Report Form (eCRF) by the investigator (as per RECIST v1.1) will be used for the derivation of the BOR. No confirmation of response is required as per protocol.

A minimum interval of 28 days will be considered for SD to be assigned as best overall response, i.e. in the case the single response is SD, SD must have been assessed no less than 28 days after randomization date of the MTP, otherwise the best overall response will be NE.
If the patient has missing baseline tumor assessment, best overall response will be NE.
Patients without tumor assessment after randomization will be assigned a tumor response of NA (Not applicable).
Patients with only non-target lesions classified as having an eCRF tumor response status of "Non-CR/Non-PD" are classified as SD.

2.2.2.3 Objective Response Rate (ORR)

ORR is defined as the number of patients with a BOR of CR or PR during the MTP phase divided by the number of patients in the studied population.

2.2.2.4 Disease Control Rate (DCR)

DCR is defined as the number of patients with a BOR during the MTP of CR, PR or SD divided by the number of patients in the studied population.

2.2.2.5 Time to Treatment Response (TTR)

TTR will be calculated for responders (i.e. patients with a MTP BOR of CR or PR) only. It will be defined as the time from randomisation to the first occurrence of a documented objective response (CR or PR).

2.2.2.6 Duration of Response (DoR)

DoR will be calculated for responders only. It will be defined as the time from the first assessment of CR or PR until disease progression or death from any cause, whichever occurs first. Patients who do not progress or die after they have had a response are censored at the date of their last tumor measurement.

2.2.2.7 Other

- Change from baseline in tumor size during MTP

The change from baseline in tumor size at a specific assessment occurring during the maintenance treatment phase will be defined as:

100*((SOD at visit x– baseline SOD) / baseline SOD)

with:

- SOD at visit x corresponding to the Sum Of target lesions Diameter (SOD) at visit
- Baseline SOD is the last SOD recorded on or prior to the randomization date in the MTP. This baseline assessment should correspond to the tumor assessment performed at the end of ITP as defined in section 4.10.1.

- Eastern Cooperative Oncology Group (ECOG) Performance Status (PS) during and after MTP

2.2.3 Exploratory Efficacy Outcome Measures

2.2.3.1 Progression Free Survival (PFS) Sensitivity Analysis

PFS is defined as the time from randomization into the MTP until documented disease progression as per investigator assessment using Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 or death from any cause, whichever occurs first. If no progression / death is observed at the time of clinical cut-off, patients will be censored at the date of the last evaluable tumor assessment or date of randomization, whichever comes last.

2.2.3.2 Best Overall Response (BOR) Sensitivity Analysis

BOR (e.g. CR, PR, SD, PD, NE) for the MTP will defined as the best response recorded from the randomization date until end of maintenance treatment or progressive disease whichever comes first (taking as reference for progressive disease the smallest measurements recorded since randomization date).

The derivation of the BOR will be the same as for the main definition (section 2.2.2.2), the only change being the time window during which the best overall response is observed. In other words, the main definition for BOR considers all tumor assessments collected on study (i.e. including post-treatment tumor assessments phase for patients withdrawing maintenance treatment for other reason than PD) whereas the secondary/sensitivity definition considers only tumor assessments collected on maintenance treatment phase (i.e within 30 days from last day of treatment of MTP, up to the day before the start of further anti-cancer therapy, whichever comes first). Therefore, the secondary/sensitivity analysis regarding BOR is an on-treatment analysis.

2.2.4 Safety Outcome Measures

The safety outcome measures for this study are as follows

- Incidence, nature and severity of all adverse events (graded according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) v4.0)
- Incidence and nature of all Grade 3- 5 AEs
- Grade 5 AEs or AEs leading to death on study treatment
- All serious adverse events (SAEs)
- Incidence and reasons for any dose reductions, interruptions or premature discontinuation of any component of study treatment
- Adverse events of special interest (AESI)

- Clinically significant changes in laboratory values
- Vital signs

2.2.5 Pharmacokinetic (PK) Outcome Measures

There are no PK outcome measures for this study.

2.2.6 Exploratory Biomarker Outcome Measures

The exploratory biomarker outcome measures for this study include molecular markers/marker profiles and efficacy and/or safety outcomes. Efficacy outcomes considered for this analysis may include, but are not limited to ORR, PFS and OS, as appropriate. Biomarkers, biomarker profiles and microbiomes may be assessed using various methodologies including, but not limited to, immunohistochemistry (IHC) (single and multiplex), RNA and DNA analysis (e.g. polymerase chain reaction, next generation sequencing [NGS], mutation expression and microsatellite instability [MSI] analyses) of tumour and/or blood samples collected from all study patients.

Next-generation sequencing was introduced with protocol amendment 5. Retrospective NGS will be conducted on samples collected provided appropriate consent has been obtained. Statistical analysis will be covered in a separate SAP.

2.3 DETERMINATION OF SAMPLE SIZE

Before study enrolment was closed prematurely, approximately 1820 patients were planned for enrolment in the Induction Treatment Phase of the whole study in order to randomise 126 patients in Cohort 1, with around 10% of patients assumed to be eligible for Cohort 1 based on biomarker status. Due to early closure of study enrolment in February 2018, target sample size will not be reached in Cohort 1 (final n=60). Therefore, Cohort 1 analysis will be highly under-powered due to lower event number. Table 2 provide some scenarios including the actual number of patients, assuming 45 events are observed, a hazard ratio ranging from 0.5 to 0.7 and the corresponding power.

The estimated proportion of patients enrolled into the study that are eligible for cohort 1 is based on published reports (*di Nicolantonio et al. 2008).* Approximately 25% of all patients enrolled are expected to have disease progression prior to randomisation into the Maintenance Treatment Phase.

Table 2: Sample Size Determination per Cohort

	Cohort 1			
	Protocol scenario	Scenarios with actual number of randomized patients and assumed number of events		
Estimated median PFS [a] (months) - Experimental group	7	7	8.2	9.8
Estimated median PFS [a] (months) - Control group	4.9	4.9	4.9	4.9
Hazard ratio (HR)	0.7	0.7	0.6	0.5
Number of expected/observed PFS events	96	45	45	45

	Cohort 1			
Statistical test	1-sided	2-sided	2-sided	2-sided
Alpha level	10%	5%	5%	5%
Power	65%	20%	36%	59%
Randomized patients	126	60	60	60
Randomization ratio (experimental vs control)	2:1	2:1	2:1	2:1
a. Per RECIST 1.1				

2.4 ANALYSIS TIMING

Cohort 1 will not reach its target sample size and thus target number of 96 PFS events. As originally planned for cohorts reaching their target number of PFS events (applies to Cohort 2 only), an update analysis of efficacy and safety parameters was planned to be conducted based on 24 months survival follow-up after the clinical cut-off date for the primary analysis. The cut-off date for the Cohort 2 primary analysis was May 31, 2017 so the Cohort 2 update analysis will be conducted based on a cut-off date of May 31, 2019. The primary analysis for cohort 1 will be conducted at the same time as the Cohort 2 update analysis (i.e. based on the same cut-off date of May 31, 2019).

The final analysis of cohort 1, which will consist of updating main time-to-event and safety endpoints, will take place after the end of the study, defined as the date when all study patients have discontinued study treatment and completed the adverse event reporting period (i.e. until 28 days after their last dose of study drug for patients not randomized in the MTP and for Cohort 1) and cohort-specific post-treatment follow-up safety assessments (patients in the experimental arm of Cohort 1 must complete assessments for SCC and cuSCC six months after their last study treatment.). Results of primary and final cohort 1 analyses will be reported in a separate clinical study report (CSR).The outputs to be provided for the analyses (primary or final) are listed in Appendix 5.

Analysis for cohorts other than cohort 1 is not covered in this SAP and will be documented in separate SAPs.

3. STUDY CONDUCT

3.1 RANDOMIZATION ISSUES

Patients will be assigned to a cohort based on the results of biomarker assessments conducted on archival primary tumour tissue obtained during their initial CRC diagnosis. Once assigned to a cohort, patients will be randomized on a 2:1 basis to either the experimental treatment group or the control group of that cohort. Randomization in Cohort 1 will be stratified by geographical region (EU, Americas, Africa or Asia), and by patient response after the Induction Treatment Phase (CR/PR vs. SD).

3.2 INDEPENDENT REVIEW FACILITY

Not applicable.

3.3 DATA MONITORING

An iDMC is responsible for:

- evaluating the safety of the patients participating in the trial at regular intervals throughout the study,
- making recommendations as to whether cohort recruitment should continue based on benefit-risk evaluations that include efficacy as well as safety data. To minimize the impact of such reviews on efficacy endpoint analyses, efficacy data included in these reviews has to be specified by the iDMC at a preceding iDMC meeting and has to be documented in the iDMC meeting minutes,
- performing a review of the safety data from a prespecified number of initial patients for experimental combinations with inadequate prior safety experience to assure appropriate dosing (e.g. as required for the Cohort 1 experimental combination of '5-FU/LV + cetuximab + vemurafenib').

4. STATISTICAL METHODS

4.1 GENERAL DESCRIPTIVE METHODS

Categorical variables

For categorical variables, summary tabulations of the number and missing observations as well as the number and percentage within each category of the parameter will be presented. Missing will not be considered as a separate category and thus missing observations will not be part of the denominator to compute the percentages. Percentages will be rounded to one decimal place. Therefore, there may be cases where for instance the total of the percentages does not exactly equal 100%. If number of patients is '0' then 0 will be reported instead of '0 (0.0%)'

Continuous variables

For continuous variables, N, the mean, median, standard deviation, 25th and 75th percentile, minimum and maximum values will be presented.

Time-to-event efficacy variables

Time-to-event efficacy variables (e.g. PFS and OS) summaries will include number of patients in the population (N), number of patients with the event of interest, number of patients censored, median and two-sided 95% confidence interval (CI) computed according to Brookmeyer and Crowley (1982) method. Kaplan-Meier (KM) estimates and median survival times are calculated with the PROC LIFETEST procedure in SAS. KM curves (product-limit method) will be presented as well as the event rates at certain time points with the relevant CIs calculated via log-log transformation method (default option CONFTYPE=LOGLOG in SAS) based on standard errors computed using the Greenwood's formula.

Cox proportional hazards models

Cox proportional hazards model will be implemented using PHREG procedure with option TIES=EXACT. It assumes that there is a true but unknown ordering for the tied event times as contrasted to option TIES=DISCRETE which assumes that the events occurred at exactly the same time.

Missing values

For categorical variables, summary tabulations of the number and missing observations as well as the number and percentage within each category of the parameter will be presented. For continuous variable, number of missing is displayed between brackets next to 'n', unless otherwise specified.

Decimals

Mean, standard deviation, and median (Q1 and Q3 if applicable) will be presented with one more decimal place compared to the raw data, minimum and maximum will be presented with same number of decimal places as the raw data. Hazard ratio, odds ratio will be provided with two decimals. P-value will be provided with three decimals. If <0.001, then '<0.001' will be displayed.

4.2 DEFINITION OF TREATMENT PHASE

In this study, there are 3 treatment phases:

1. Patients are treated first in the Induction Treatment Phase (ITP) for a planned duration of 8 cycles, i.e. 16 weeks.

2. If they do not experience any progressive disease before or at the end of the ITP, are not considered resectable at the end of the ITP and do not withdraw from the study and are still eligible for any cohort, they are randomized and treated in the Maintenance Treatment Phase (MTP).

3. If they discontinue study treatment for any reason during the Induction or Maintenance Treatment Phases, do not withdraw from the study and are still alive, they enter the Post-Treatment Follow-up Phase.

4.2.1 Induction Treatment Phase (ITP)

ITP is defined as the time from first study drug administration until

- the day before the randomization for patients continuing treatment in the MTP
- the last assessment date otherwise

The first day of treatment in the ITP is defined as the earliest day of a non-null administration of any induction phase treatment.

The last day of treatment in the ITP is defined as the last day of the last initiated cycle of the induction phase, or as the death day if the patient died in between. A two-week cycle duration is assumed.

Baseline evaluations for the ITP will be those performed not earlier than 28 days prior to the first day of treatment in the induction phase, unless otherwise stated. The latest available assessment up to start of the first day of treatment in the induction phase will be considered as baseline. For laboratory examinations, weight, vital signs and ECOG PS, assessments performed on the first day of treatment of the ITP will be assumed to have been performed before drug was given and, thus, will be considered as baseline evaluations.

On-treatment evaluations for the ITP will be post baseline evaluations performed until

- the day before the randomization for patients continuing treatment in the MTP

- (including) the study treatment discontinuation visit within 30 days after last day of treatment of the ITP (as defined above), for patients not randomized in the MTP.

4.2.2 Maintenance Treatment Phase (MTP)

MTP is defined as the time from randomization into MTP until (including) the study treatment discontinuation visit in the MTP.

The first day of treatment in the MTP is defined as the earliest day of a non-null administration of any maintenance phase treatments.

The last day of treatment in the MTP is defined as the last day of the last initiated cycle of the maintenance phase, or as the death day if the patient died in between. A two-week cycle duration is assumed.

Baseline evaluations for the MTP will be those performed prior to the first day of treatment in the maintenance, unless otherwise stated. The latest available assessment prior to the first day of treatment in the maintenance phase will be considered as baseline for safety assessments. For laboratory examinations, weight and vital signs, assessments performed on the first day of treatment of the MTP will be assumed to have been performed before drug was given and, thus, will be considered as baseline evaluations. For subjects randomized but not treated in the MTP, the latest available assessment before or on randomization date (including assessments from ITP) will be considered as baseline for the MTP.

For efficacy assessments, the latest available assessment prior or on the randomization date will be considered as baseline.

On-Treatment evaluations for the MTP will be evaluations performed on or after the first day of treatment in the MTP within 30 days from last day of treatment in the maintenance phase. On-treatment laboratory will be all values collected after the first day of treatment in the maintenance phase and within 30 days from last day of treatment in the maintenance phase (as defined above). For adverse events, treatment emergent adverse events (TEAEs) will be events occurring on or after the first day of treatment in the MTP within 30 days from last day of treatment in the maintenance phase (as defined above).

4.2.3 Post-Treatment Follow-up Phase

Post treatment Follow-up Phase is defined as the time from (excluding) the study treatment discontinuation visit until the last available assessment date before clinical cut-off date. For patients who discontinue study treatment but without any study treatment discontinuation visit date, please refer to 4.14 for imputation of this missing visit date.

Post-Treatment Follow-up evaluations will be evaluations performed according to the protocol after the study treatment discontinuation visit.

4.3 DATA CONVENTION

All data will be listed (e.g. pre-treatment serious adverse events), whereas only baseline and on-treatment assessments will be considered for summary tables.

Baseline and on-treatment data will be flagged in the data listings as well as the different phases of the study.

The overall column will not be displayed in any summary tables.

The following conversion factors will be used to convert days to months or years, where applicable:

- 1 week= 7 days
- 1 month = 30.4375 days
- 1 year = 365.25 days

Age at informed consent (IC) {in years} = (date of informed consent – date of birth) / 365.25

To calculate **duration / time between** two dates the following convention will be used:

[later date] – [earlier date] + 1 day

Durations and times between two dates will be calculated only when both start and end dates are available (imputed dates cannot be used for computation), apart for overall survival when date of death has only day as missing).

Body surface area (BSA) will be recalculated based on the height and weight of the patient using the following formula:

BSA (m^2) = ([Height {cm} x Weight {kg}] / 3600)^{½}

Body mass index (BMI) will be calculated using the following formula:

BMI (kg/m^2) = Weight {kg} / Height^2 {m}

The last known date to be alive will be the latest date among all dates specified in the eCRF except the following:

- Survival Follow-up date when status is either dead (in this case the date of death is specified on the Adverse events or Study Completion/Early Discontinuation or SAE reporting summary form) or lost to follow-up (in this case last date known to be alive is specified on the Survival follow-up form)
- Study Completion/Early Discontinuation date when reason is either death or lost to follow-up.
- A sample / record with test 'Not Done'.

4.4 COMPUTING ENVIRONMENT

All statistical analyses will be performed using SAS statistical software (Version 9.2 or newer version), unless otherwise noted.

4.5 GRADING AND CODING OF ADVERSE EVENTS, LABORATORY PARAMETERS AND MEDICATIONS

Laboratory results, adverse events, and other symptoms will be graded using the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Event (CTCAE), version 4.0, except where CTC grades are not available.

Adverse events and relevant Medical History data fields (i.e. prior symptoms / AEs) will be coded using the most recent version of Medical Dictionary for Regulatory Activities (MedDRA) dictionary available at the time of analysis.

Prior and concomitant anti-cancer therapy / other medications will be coded using the most up-to-date version of the in house Genentech Drug Thesaurus Dictionary.

Dictionary versions used will be displayed in analysis outputs.

4.6 ADUSTMENTS FOR COVARIATES

When indicated, efficacy analysis will be adjusted i.e. the covariates will be incorporated in the model used to assess the treatment effect upon the efficacy endpoints. The covariate below will be considered:

- Patient response after induction treatment as per eCRF data: CR/PR vs. SD. For inferential analysis, “SD” will be used as reference, unless otherwise specified.

  (Of note: no adjustment will be made for region since most of patients are in Europe.)

4.7 SUBGROUP ANALYSIS

The following subgroups will be considered to repeat PFS and OS analysis by subgroup:

- Demographic characteristics:
  - Age (<65 years, >= 65 years)
  - Gender (male vs female)
  - Tumor response at end of ITP (SD vs. CR/PR) as per eCRF
  - Baseline ECOG performance status (0 vs. 1/2),
- Baseline disease characteristics:
  - Initial AJCC/UICC stage (stage I/II/III vs. stage IV)
  - Prior systemic adjuvant therapy (yes vs no)
  - Number of metastatic sites at screening (<2 x vs. >= 2)
  - Liver metastatic site at baseline (yes vs no)
  - Cancer type (colon vs rectal)
  - Tumor colon location (right vs left)
  - Initial diagnosis (synchronous vs metachronous)

The subset tumor colon location (left, right) will be derived based on the primary tumor location information collected on the colorectal cancer history eCRF page. Right colon is defined as patients with ceacum, appendix, ascending colon or right hepatic flexture or transverse colon as primary tumor location. Left colon is defined as patients with left splenic flexture or descending colon or sigmoid or rectum as primary tumor location.

The subset cancer type (colon, rectal) will be derived based on the primary tumor location collected on the colorectal cancer history eCRF page. Colon cancer type is defined as patients with ceacum, appendix, ascending colon or right hepatic flexure or transverse colon or left splenic flexure or descending colon or sigmoid as primary tumor location. Rectal cancer type is defined as patients with rectum as primary tumor location.

The subset initial diagnosis (synchronous, metachronous) will be derived based on the time from initial histological diagnosis to first diagnosis of metastatic disease. If this time is longer than 6 months then the initial diagnosis of the corresponding patient will be considered metachronous, or as synchronous otherwise. In case date of first diagnosis of metastatic disease is missing, this one will be replaced by the date of first diagnosis of locally recurrent disease. In case both are missing, the corresponding patients will be excluded from the corresponding subgroup analysis. In case one of the dates (i.e. date of initial histological

diagnosis or date of first diagnosis of metastatic disease or date of first diagnosis of locally recurrent disease) is partially missing, it will be imputed as described in section 4.14.

4.8 ANALYSIS POPULATIONS

The following patient populations will be evaluated and used for presentation and analysis of the data.

4.8.1 All Population

ALL Population: The ALL population consists of all enrolled patients with $BRAF^{mut}$ primary tumor if in study screening prior to June 28, 2016 and all enrolled patients with HER2-/MSS/$BRAF^{mut}$/RAS^{wt} biomarker profile if in study screening after June 28, 2016).

Induction Treatment Phase (ITP) Population: all patients included in the ALL Population and who are treated in the ITP, i.e. who received at least one non-null dose of any study medications during the ITP. The ITP population is the main population to be used to summarize ITP data and Post Induction Treatment data. The 2 following groups will be considered when tabulating ITP data: patients randomized into MTP versus patients not randomized into MTP. Post Induction Treatment data will be summarized using one single group, i.e. patients not randomized into MTP. ITP population will be the main population for the data listings, unless otherwise specified; the 3 following groups will be displayed in listings: patients randomized in the experimental group of MTP, patients randomized in the control group of MTP, patients not randomized into MTP.

4.8.2 Randomized Population

Maintenance Treatment Phase (MTP) Population is defined as all patients randomized into the Cohort 1 MTP of the study, irrespective of whether or not they received study medication. Patients will be allocated to the treatment group into which they were randomized (as per interactive voice or web-based response system [IxRS]). The MTP population is the primary population for the analysis of efficacy parameters and baseline characteristics for the MTP. The MTP population will be used as well to report the Post Maintenance Treatment data.

4.8.3 Safety Population

Safety (SAF) Population: all patients randomized in Cohort 1 who have been treated, i.e. who received at least one non-null dose of any study medications during the MTP.

Patients will be allocated to the treatment group they actually received using the following rule:

- Patients receiving at least one dose (non-null) of cetuximab or vemurafenib, while on treatment will be allocated to the experimental group 5-FU/LV+cetuximab+vemurafenib. Even if a patient was allocated to the control group and received by mistake a dose of cetuximab or vemurafenib, then this patient will be reallocated to the experimental group.
- Patients who did not receive any dose of cetuximab or vemurafenib will be allocated to the control group FP+bevacizumab.

The SAF population is the primary population for the analysis of MTP safety parameters.

4.8.4 Per Protocol (PP) Population

As stated in the protocol, the PP Population will not be defined for this study but major protocol violations will be listed.

4.8.5 Pharmacokinetic-Evaluable Population

Not applicable.

4.8.6 Biomarker-Evaluable Population

Not applicable.

4.9 ANALYSIS OF STUDY CONDUCT

This SAP focuses only on the description of the analysis required for cohort 1 data. All MTP data will be reported. ITP data for BRAF mutant patients (if in screening prior to June 28, 2016) and HER2-/MSS/$BRAF^{mut}$/RAS^{wt} patients (if in screening after June 28, 2016) randomized and not randomized into the MTP will be tabulated in 2 separate columns. Post-treatment data will be reported separately for induction and maintenance treatments. This Post-treatment data includes adverse events, deaths, subsequent anti-cancer therapies and tumor assessments (until PD if PD not experienced before study treatment discontinuation visit), but this last one applies only for Post Maintenance treatment.

4.9.1 Patient Disposition

The patient disposition table for ITP will be based on the ALL population and will include the following information:

- Number of patients enrolled (ALL)
- Number of patients not treated in ITP who discontinued trial without being treated and associated reason
- Number of patients treated with induction treatment (ITP population)
- Number of patients who completed the ITP
- Number of patients treated in induction who discontinued early ITP and reason for early discontinuation
- Number of patients treated in induction and not randomized who went to post-treatment follow-up phase post induction
- Number of patients being treated in induction who discontinued study prior to MTP and associated reason

The patient disposition table for MTP will include the following information:

- Number of randomized patients (MTP population) (percentage based on MTP)
- Number of randomized patients without being treated in MTP still on-trial
- Number of randomized patients who discontinued trial without being treated in MTP and the corresponding reason for trial discontinuation (percentages based on MTP)

- Number of treated patients with maintenance treatment (SAF) (percentages based on MTP)
- Number of patients treated who discontinued all treatments received in MTP and the reason for discontinuation from each maintenance treatment (percentage based on MTP). All reasons for treatment discontinuation will be displayed and will be taken from the individual treatment completion/Early discontinuation eCRF pages.
- Number of patients treated in MTP who discontinued trial during MTP and the corresponding reason for trial discontinuation (percentages based on MTP)
- Number of patients who entered in the follow-up post-MTP
- Number of patients being treated in MTP who discontinued trial during follow-up and the corresponding reason for trial discontinuation (percentages based on MTP)

A consort flow diagram will be provided to show progress of screened patients and especially for BRAF mutant patients (if in screening prior to June 28, 2016) and HER2-/MSS/$BRAF^{mut}$/RAS^{wt} patients (if in screening after June 28, 2016). Another diagram for patients randomized in Cohort 1 will be provided.

The following supportive listings will be provided:

- Patient disposition (including the tumor response status at the end of ITP) and study termination information based on ITP
- Patients who discontinue treatment due to AE (based on ITP)

4.9.2 Protocol Deviations

All major protocol deviations from Protocol Deviation Management System (PDMS) will be reported for each phase separately and will be summarized by group. The ITP population will be used for ITP data and the MTP population for the MTP data.

The following will be displayed

- Number of patients having at least one major protocol deviation
- Number of patients by major protocol deviations category

Listings for protocol deviations will be provided based on ITP population. Listing for analysis population will be provided on ALL population.

4.10 ANALYSIS OF TREATMENT GROUP COMPARABILITY

4.10.1 Demographics and Baseline Disease Characteristics

Baseline and demographic characteristics will be summarized using descriptive statistics. No formal statistical comparisons will be performed.

Summaries of Patient Demographics will be provided based on the ITP and MTP population and will present the following information:

- Age at informed consent (yrs)
- Age categories (yrs): < 18, 18-64, 65-84, 85 and over
- Sex
- Ethnicity: Hispanic or Latino, Not Hispanic or Latino, Not reported, Unknown

- Race
- Region: Europe, Americas, Africa, Asia (derived based on country information from the clinical database)
- Smoking status: Never, Current, Previous
- Alcohol use history: Never, Current, Previous
- Drug Use: Never, Current, Previous
- ECOG Performance Status at baseline: 0,1,> 1,
- Baseline Weight (kg)
- BMI (see definition in section 4.3)
- BSA (see definition in section 4.3)
- Baseline Height (cm)
- Female reproductive status (for female participants only. Percentage will be based on the total number of female patients)

The summary of patient's characteristics based on MTP will be included. For the summary based on MTP only, ECOG and weight collected just prior to or on the first day of MTP will be used as baseline. Please refer to sections 4.2.1 and 4.2.2 for further details related to definition of baseline evaluations.

All the biomarker outcomes of interest as per section 4.7 will be summarized using descriptive statistics by treatment group on ITP and MTP population:

Given that the end of the induction phase is the same timepoint as the baseline tumor response for the MTP, two summary tables presenting the information as mentioned below will be produced. One for the tumor response status at the end of the induction phase based on ITP population and as per data collected on the eCRF and will present the following information.

- Number of patients with CR or PR at end of ITP
- Number of patients with SD at end of ITP
- Number of patients with PD at end of ITP
- Number of patients with NE at end of ITP
- Number of patients with NA at end of ITP (i.e. no tumor response during ITP)

Another table will be generated for baseline tumor response for the MTP based on MTP population and as per data collected on the eCRF and will present the following information.

- Number of patients with CR or PR at end of ITP
- Number of patients with SD at end of ITP
- Number of patients with tumor response other than CR, PR or SD at end of ITP

The number of patients in MTP population will be summarized by country and study center (as per clinical database) and by treatment group based on the MTP population.

In addition, the number of patients will be summarized by the following stratification factors as per IxRS, by treatment group on the MTP:

- Region
    - European Union
    - Americas
    - Africa
    - Asia
- Tumor response at the end of ITP

- CR/PR
- SD

A table will show the concordance between the tumor response status at the end of ITP as per IxRS and the tumor response status at the end of ITP as per data collected on the eCRF. This table will be based on the MTP population and will display the following categories:

- CR/PR, SD, Total for the IxRS tumor response
- CR, PR, CR/PR, SD for eCRF tumor response

eCRF Tumor response status (CR, PR, SD, PD, NE) at the end of ITP is defined as the last tumor response observed during the ITP. Patients without tumor assessment after first day of induction treatment will be assigned a tumor response of NA (Not available). Patients with only non-target lesions classified as having an eCRF tumor response status at the end of the ITP of "Non-CR/Non-PD" are classified as SD for the 2 summary tables mentioned above.

Summary of colorectal cancer history will be provided based on the ITP and MTP population and will present the following information:

- Histological grade at diagnosis
- Location of primary tumor
- Colon Location: left, right
- Cancer type: colon, rectal
- Initial AJCC/UICC stage
- Initial diagnosis: synchronous, metachronous
- Locally recurrent disease: yes, no
- Metastatic disease: yes, no
- Sites of metastatic disease at time of study enrolment (adrenal gland, ascites, bone, liver, lung, mediastinum, skin, other)
- Liver as metastatic site: yes, no
- Extent of disease by number of sites at time of study enrolment: 0, 1, > 1
- Time from initial diagnosis to first dose of ITP (in years)
- Time from first diagnosis of locally recurrent disease to first dose of ITP (in years)
- Time from first diagnosis of metastatic disease to first dose of ITP (in years)
- Number of target lesions at baseline

Of note, if start and/or end dates are incomplete or missing the corresponding time between the start and the end date cannot be derived. In this case, time from initial diagnosis to first dose of ITP or time for first diagnosis of locally recurrent disease to first dose of ITP or time from first diagnosis of metastatic disease to first dose of ITP cannot be derived and will be missing.

Summary of RECIST tumor-specific characteristics at baseline will be generated on the MTP population and will provide the following information:

- Number of site/organs involved; 1, 2, >2
- Site/organ type involved: colon, rectum, liver, lung, lymph nodes, peritoneum, brain, other

- Type of lesions: target only, non-target only, target and non-target lesions

Of note for the above summary table, tumor-specific characteristics at baseline refer to the tumor assessment prior to randomization in MTP, i.e. last tumor assessment from the induction treatment phase.

The following listings will be provided:

- Patient Demographics based on ITP population
- Biomarker status based on MTP population
- Patients by randomization stratification factors as per IxRS and eCRF (based on MTP)
- Colorectal cancer history based on ITP population

4.10.2 Medical History

Medical history, as collected on the "General Medical History and Baseline Conditions" eCRF page will be summarized using the ITP and MTP populations. These summary tables will include the number and percentage of patients with at least one medical history by Primary System Organ Class (SOC) sorted in a descending order of the total frequency count and by preferred term [PT] (sorted in a descending order of the total frequency count within each SOC).

A patient with more than one occurrence of the same medical history in a particular SOC/PT will be counted only once in the total of those experiencing events in that particular system organ class/preferred term.

Medical history data will be listed based on ITP population.

4.10.3 Prior and Concomitant Medications

4.10.3.1 Prior Anti-Cancer Treatment/Procedure

Prior anti-cancer treatments/procedures summaries based on the ITP and MTP populations will present the following information:

- Number of patients with prior colorectal cancer surgery: Yes, No
- Number of patients by site of prior colorectal cancer surgery: Colon, Rectum, Colon and Rectum, Other.
- Number of patients with prior radiotherapy: yes, no
- Number of patients with prior anti-cancer therapies: yes, no
- Number of patients by setting of prior systemic therapy
- Number of patients with prior systemic adjuvant therapy: yes, no
- Number of regimens for prior systemic therapy: 0, 1, 2, >=3.

The following listings will be provided based on the ITP population:

- Prior anti-cancer therapy
- Prior and on-study cancer radiotherapy
- Prior and on-study cancer colorectal surgery

4.10.3.2 Non Anti-Cancer Treatment/Procedure

A prior medication/therapy is defined as any medication/therapy with an end date prior to the start of the induction treatment.

Concomitant medication for ITP

Concomitant medication includes both medication concomitant at baseline and concomitant medication initiated post-baseline. It is defined as any medication/therapy with

- start date before or on:
  - the randomization date for patients randomized in the MTP
  - last dosing date of ITP+30 days for patients not randomized in the MTP
- and end-date on or after first dosing date of the ITP or with a missing (ongoing) end-date

Concomitant medication for MTP

It is defined as any medication/therapy with

- start date before or on last dosing date in the MTP+30 days
- and end-date on or after first dosing date of the MTP or with a missing (ongoing) end-date.

Post-treatment Medication

It is defined as any medication/therapy with a start date more than 30 days after the last dosing date.

In case a medication has an incomplete or missing start date/end date, please refer to section 4.14 for the rules to be applied in order to identify prior, concomitant or post-treatment medications.

Prior and Concomitant Medications/therapies will be summarized. Summary tables will present number and percentage of patients with any medication overall and by Drug Thesaurus Class and Generic Name. At each level of summation (overall, Drug Thesaurus Class, Generic Name), patients reporting more than one medication are counted only once. Drug Thesaurus Class will be sorted in a descending order of the total frequency count and the generic names with the highest frequency will be displayed first within each Drug Thesaurus class, unless otherwise indicated. The analysis population will be the ITP population and the MTP population for ITP data and MTP data, respectively.

The following tables will be provided:

- Prior medications based on ITP population
- Concomitant medications for the ITP based on ITP population
- Concomitant medications for the MTP based on SAF population
- Concomitant radiotherapy performed during the ITP based on ITP population (as collected on the On-Study Cancer Radiotherapy eCRF page): Number of patients with radiotherapy, site (colon, other) and setting (neo-adjuvant, adjuvant, palliative. other) of therapy
- Concomitant radiotherapy performed during the MTP based on SAF population (as collected on the On-Study Cancer Radiotherapy eCRF page): Number of patients with radiotherapy, site (colon, other) and setting (neo-adjuvant, adjuvant, palliative, other) of therapy

- Concomitant colorectal cancer surgery during ITP based on ITP population: Number of patients with at least one surgery, site of surgery, surgical procedure and intent
- Concomitant colorectal cancer surgery during MTP based on SAF population: Number of patients with at least one surgery, site of surgery, surgical procedure and intent

Corresponding listings will be provided using the ITP population.

4.10.4 Subsequent Anti-Cancer Therapy

Post Induction Treatment and Post Maintenance Treatment anti-cancer therapies will be listed using the ITP population patients who have a study treatment discontinuation visit date.

4.11 EFFICACY ANALYSIS

Efficacy analysis will be conducted on the data collected during the MTP/Post maintenance treatment (when applicable) and using the MTP population. Analysis will be performed by randomized treatment group. Tumor assessments collected during the ITP will be listed only but will not be part of the efficacy analysis and will be listed on the ITP population. ITP and MTP tumor assessments will be flagged, as appropriate for patients randomized in the MTP.

As Cohort 1 will not reach its target sample size, the analysis is not event driven as described in the study protocol, but is time driven instead. As a consequence, all p-values will be reported descriptively only, due to low power. All formal statistical tests will be two-sided and performed at an alpha of 5%, therefore 95% two sided CI will be presented. No adjustment will be made for multiplicity of testing secondary endpoints or subgroups for single efficacy endpoints.

4.11.1 Primary Efficacy Endpoint

The primary efficacy objective of this study is to evaluate PFS.

To answer the primary objective, the following null and alternative hypotheses will be tested

- H0: the distribution of the PFS time is the same in the two treatment groups, i.e. PFS (Experimental group) = PFS (Control group)
- H1: the distribution of the PFS time is different in the two treatment groups, i.e. PFS (Experimental group) ≠ PFS (Control group)

The primary analysis of PFS will be a comparison between the experimental and the control group using an unstratified log-rank test. Please refer to Appendix 4 for the SAS code to be used.

PFS for each treatment group will be estimated using KM product-limit method estimates. PFS will be summarized by treatment group and will display the following information:

- Number of patients in the population (N)
- Number of patients with PFS event
- Number of patients censored
- Median and two-sided 95% CI computed according to Brookmeyer and Crowley method,
- 25th and 75th quantile, and the corresponding two-sided 95% CI computed according to Brookmeyer and Crowley method,
- Minimum and maximum
- The PFS rates (with the two-sided 95% CI) at 3, 6, 9, 12, 15 and 18 months

- Unstratified log-rank test p-value

KM plot of PFS by treatment group will be generated.

PFS time will be listed on MTP population in a dedicated time to event listing.

Model checking

Sensitivity analyses concerning proportional hazards assumption will consist of log-log-Survival plots (log(-log(S(t))) vs log(time) by treatment group (plots=(lls) in PROC LIFETEST).

4.11.2 Secondary Efficacy Endpoints

4.11.2.1 Overall Survival

This study is not powered for OS, so adequately powered statistical testing for this endpoint will not be possible. However, the results of an unstratified log-rank test will be provided in an exploratory manner to assess the difference between treatment groups for OS.

The same analysis as those described for the primary endpoint will be repeated for OS on MTP population The survival rate will be displayed at the following time points: 6, 9, 12 and higher (every 3 months) if appropriate.

OS time will be listed on MTP population in a dedicated time to event listing.

4.11.2.2 Overall Response Rate (based on Primary Definition of BOR)

The Best Overall Response for MTP as per main definition will be tabulated on MTP by treatment group.

ORR for the MTP will be summarized in each treatment group of the MTP population and will present the number and percentage of patients with objective response (CR or PR) as best response along with the two-sided 95% Clopper-Pearson confidence interval. The difference in ORR among treatment groups will be estimated with associated two-sided 95% CI using the Hauck-Anderson approach. The treatment difference will be tested using a Chi-square test at a two-sided alpha level of 5%.

A logistic regression analysis, using treatment and tumor response at end of induction as per eCRF data (SD vs CR/PR) as covariates will be performed. An estimate of the odds ratio with an associated two-sided 95 % confidence interval and a p-value for the coefficient will be presented for each covariate, including treatment. Please refer to Appendix 4 for the SAS code to be used.

Note: SD will be used as reference. The region stratification factor won't be used as a covariate as almost all the patients are in Europe (only 5 patients from other regions).

Forest plots displaying ORR odds ratio from the logistic regression by subgroups will be generated, for further details please refer to section 4.11.5.

Waterfall plots (both treatment groups one the same plot) of the best percentage change from baseline in sum of diameter collected during the MTP will be provided.

A listing of tumor assessments per timepoint will be provided based on the ITP. It will include:

- MTP/ITP/Post-treatment flag
- visit
- imaging date

- lesions number
- location, site/organ, assessment method and type of lesion
- diameter (mm) for target lesion, status for non-target lesion
- sum of diameter of target lesions (mm)
- response per timepoint for target lesion and non-target lesion, presence/absence of new lesion(s)
- overall Response per timepoint

Information will be collected from the “RECIST 1.1 Target Lesions”, “RECIST 1.1 Non-Target Lesions”, “RECIST 1.1 New Lesions” and "RECIST 1.1 - Overall Response Assessment" eCRF pages.

Another listing based on the MTP population will provide the best overall response (main and secondary definitions), time to response and the duration of response. Censored patients for the duration of response will be flagged as per section 2.2.2.6.

4.11.2.3 Overall Response Rate (based on Secondary Definition of BOR)

The analyses performed for Overall Response Rate for MTP based on main definition of BOR will be repeated using secondary definition of BOR (refer to section 2.2.3.2).

4.11.2.4 Disease Control Rate

The same analysis as described for ORR for MTP will be provided for the following endpoints:

- DCR for MTP based on main definition of BOR using the MTP population
- DCR for MTP based on secondary definition of BOR using the MTP population

All corresponding information will be listed on the MTP population.

4.11.2.5 Time to Treatment Response

Time to objective response (CR and PR) for each treatment group will be summarized separately based on the main and secondary definition of BOR using descriptive statistics (median, minimum and maximum) which will be calculated using PROC UNIVARIATE and are based on MTP population restricted to responders.

Two separate summary tables will be created: one for the time to response by considering all tumor assessments as in the main definition of BOR and another one by considering on-treatment tumor assessment as in the secondary definition of BOR. No formal statistical comparisons between the treatment groups are planned.

Time to response will be listed on MTP.

4.11.2.6 Duration of Response

The duration of response (DoR) for each treatment group will be estimated using KM product-limit method estimates. Summary table for duration of response based on MTP population restricted to responders will display, by treatment group, the number of patients with best overall response CR or PR (N), number of patients with progression or death, number of patients censored, min, max, 25th quantile, 75th quantile and median with the associated two-sided 95% CIs computed according to Brookmeyer and Crowley method.

Two separate summary tables will be created: one for duration of response by considering all tumor assessments as in the main definition of BOR and another one by considering on-treatment assessments as in the secondary definition of BOR.

The duration of response will be compared between the experimental and the control group using an unstratified log-rank test.

Duration of response will be listed on MTP.

4.11.2.7 Eastern Cooperative Oncology Group (ECOG) Performance Status

Summary table presenting the number of patients and percentage by ECOG performance status will be displayed by visit occurring during the MTP. In addition, a shift table of MTP baseline ECOG PS versus ECOG PS at the end of MTP will be provided. Supportive listing will be provided for the MTP.

ECOG PS data will be listed based on the ITP population. ITP and MTP evaluations will be flagged.

4.11.2.8 Additional Tumor Assessments

Listing for each specific assessments to Cohort 1 (head and neck assessment for SCC, Chest CT assessment for SCC, dermatology evaluation, anal and pelvic exam) will be provided.

4.11.3 Exploratory Efficacy Endpoints

Not Applicable.

4.11.4 Sensitivity Analyses

In addition, the following sensitivity analyses will be performed on PFS, the primary efficacy endpoint:

- The PFS hazard ratio, and its 95% two-sided confidence interval, of experimental group versus control group, will be estimated using a Cox proportional hazards model with treatment as the single covariate. Please refer to Appendix 4 for the SAS code to be used.
- The PFS hazard ratio, and its 95% two-sided confidence interval, of experimental group versus control group, will be estimated using different adjusted Cox proportional hazards models, using as covariates the treatment and one of the stratification factors, i.e. response at the end of induction treatment as mentioned below
    - cov1 (SD vs CR/PR as per eCRF)
    - cov1 (SD vs CR/PR as per IxRS)

  Note: No adjustment on the region will be performed as almost all the patients are in Europe.
- A sensitivity analysis will be performed for PFS by considering all PFS events reported in MTP regardless of the surgery.

  An unstratified log-rank test will be performed to compare PFS between the experimental and the control group. PFS will be estimated for each treatment group using KM product-limit method estimates. PFS will be summarized by treatment group and will display the information as mentioned in section 4.11.1. The PFS hazard ratio, and its 95% two-sided confidence interval, of experimental group versus control group, will be estimated using a Cox proportional hazards model with treatment as the single covariate.

- The OS hazard ratio, and its 95% two-sided confidence interval, of experimental group versus control group, will be estimated using a Cox proportional hazards model with treatment as the single covariate. Please refer to Appendix 4 for the SAS code to be used.
- For ORR and DCR, a logistic regression analysis, using treatment as single covariates will be performed. An estimate of the odds ratio with an associated two-sided 95 % confidence interval and a p-value for the coefficient will be presented for treatment. Please refer to Appendix 4 for the SAS code to be used.
- To assess any bias regarding the completeness of the follow up to capture PFS events, KM curve with reverse censoring will be produced by treatment group. In this analysis, censored patients in the primary analysis will be considered as having an event, for these patients the event date will be the date of last evaluable tumor assessment or date of randomization, whichever comes last. Patients with a PFS event in the primary analysis will be censored in this analysis, for these patients the censor date will be the earliest date between PD date and death date.

4.11.5 Subgroup Analyses

Subgroup analyses of PFS and OS will be conducted based on:

- Stratification factor (reponse at the end of ITP)
- Tumor colon location

The following information will be provided/computed within each subset:

- Number of patients in the subgroup
- Number of patients with PFS or OS event
- Number of patients censored
- Median and two-sided 95% CI computed according to Brookmeyer and Crowley method,
- 25th and 75th quantile, and the corresponding two-sided 95% CI computed according to Brookmeyer and Crowley method,
- PFS HR of experimental versus control group and its two-sided 95% CI computed by means of an un-stratified Cox proportional hazards model with treatment as the single covariate.

Forest plots presenting the PFS HR of experimental group versus control group and corresponding 95% CI obtained from adjusted Cox model for each subset as defined in section 4.7 will be generated.

Forest plots presenting the OS HR of experimental group versus control group and corresponding 95% CI obtained from adjusted Cox model for each subset as defined in section 4.7 will be generated.

The Best Overall Response for MTP as per main and secondary definition (see section 2.2.2.2 and 2.2.3.2) will be tabulated on MTP by treatment group on reponse at the end of ITP and tumor colon location

For each of these subsets, ORR for the MTP will be summarized in each treatment group on MTP and will present the number and percentage of patients with objective response (CR or PR) as best response along with the two-sided 95% Clopper-Pearson confidence interval.

The difference in ORR among treatment groups will be estimated with associated two-sided 95% CI using the Hauck-Anderson approach.

For each of these subsets, a logistic regression analysis, using treatment as single covariate will be performed. An estimate of the odds ratio (experimental vs control group) with an associated two-sided 95 % confidence interval will be provided.

Forest plots displaying the ORR odds ratio of experimental group compared to control group and corresponding 95% CI from the logistic regression with treatment as unique covariate for each subset as defined in section 4.7 will be provided. One forest plot will be generated for each subgroup.

No formal statistical comparisons will be conducted within subsets.

4.12 PHARMACOKINETIC AND PHARMACODYNAMIC ANALYSES

Not applicable

4.13 SAFETY ANALYSES

Separate safety summaries will be produced for ITP, MTP, Post Induction Treatment and Post Maintenance Treatment.

For ITP data, outputs will be generated on the ITP displaying randomized vs. non randomized patients in MTP. MTP outputs will be based on the SAF population and will be presented by treatment group. For Post Induction Treatment data, outputs will be generated on ITP for patients who completed study treatment discontinuation visit, whereas for Post Maintenance Treatment data, outputs will be generated on MTP for patients who completed study treatment discontinuation visit.

No inferential statistical analyses are planned.

4.13.1 Exposure of Study Medication

4.13.1.1 Treatment Duration and Dose Exposure

A patient will be considered as having initiated a cycle in the ITP if at least one (non-null) dose of any study drugs of the ITP has been administered in the corresponding cycle.

The overall number of cycles initiated during the ITP is defined as the sum of all initiated cycles (as defined above) in the ITP.

For the MTP, the overall number of cycles initiated (i.e. for drug combination) will be computed as the sum of all initiated cycles as defined below:

- Day 1 of a cycle is defined as the first day in the considered cycle when treatment is administered.
- The cycle length is assumed to be 2 weeks
- For experimental group:
    - a cycle will be assumed to be initiated if cetuximab, vemurafenib and 5-FU and LV or any LV substitute are administered at any time during the same cycle
- For control group:

- If capecitabine is administered: a cycle will be assumed to be initiated if capecitabine and bevacizumab are administered at any time during the same cycle
- If 5-FU/LV or LV substitute is administered: a cycle will be assumed to be initiated if bevacizumab and 5-FU and LV or any LV substitute are administered at any time during the same cycle

The overall duration (in weeks) for all components of maintenance treatment is defined as follows:

- Experimental group:

[MAX(min(last dosing date of 5-FU/LV+13, death), min(last dosing date of cetuximab+13, death date), min(last dosing date of vemurafenib, death date)) – MIN (first dosing date of FP, first dosing date of cetuximab, first dosing date of vemurafenib) + 1]/7

with last dosing date of 5-FU/LV = max(last dosing date of 5-FU, last dosing date of LV) and first dosing date of 5-FU/LV = min(first dosing date of 5-FU, first dosing date of LV)

- Control group:
  - If capecitabine is administered in the last cycle:

[MAX(min(last dosing date of capecitabine+6, min(last doing date of bevacizumab+13, death date)) – MIN (first dosing date FP, first dosing date of bevacizumab) + 1]/7.

  - If 5-FU/LV is administered in the last cycle:

[MAX(min(last dosing date of 5-FU/LV+13, death), min(last dosing date of bevacizumab+13, death date)) – MIN (first dosing date of FP, first dosing date of bevacizumab) + 1]/7

with first dosing date of FP = min(fist dosing date of 5-FU, first dosing date of LV or any LV substitute, first dosing date of capecitabine) and last dosing date of 5-FU/LV = max(first dosing date of last administration of 5-FU, first dosing date of last administration of LV or any LV substitute)

The number of cycles administered, duration of dosing, cumulative dose, dose intensity and relative dose intensity (RDI) definitions are provided for each drug individually in Table 3 and Table 4 for induction and maintenance, respectively.

According to protocol, the cycle length is 2 weeks, excepted for capecitabine in the control arm for which each cycle length is as per local practise. A 2-week cycle schedule will be considered for drugs other than capecitabine and for the drug combinations. For capecitabine, a cycle is defined as any continuous administration separated by a rest period, regardless of the duration of the continuous administration and the duration of the rest period. A patient will be considered as having initiated a cycle in the MTP for a specific drug if at least one (non-null) dose of this study drug has been administered in the corresponding cycle.

Table 3: Exposure Definitions for Induction Treatments

	FOLFOX	5-FU/LV	bevacizumab
Number of cycles	sum of all cycles in which at least one non-null dose of FOLFOX has been administered	sum of all cycles in which at least one non-null dose of 5-FU and LV has been administered. Of note, consider only cycles where oxaliplatin is not administered concomitantly with 5-FU/LV.	sum of all cycles in which at least one non-null dose of bevacizumab has been administered
Duration of dosing (weeks) (1)	[min (last date of FOLFOX+13, death date) – first FOLFOX dosing date+1] / 7 or If FOLFOX-4 or FOLFOX-7 or modified FOLFOX-7 is administered in the last cycle initiated [min (last date of FOLFOX +12, death date) – first FOLFOX dosing date+1] / 7	max (min(last date of 5-FU+13, death date), min(last date of LV+13, death date)) – min (first date of 5-FU, first date of LV) +1] / 7 Of note, consider only records/cycles where oxaliplatin is not administered concomitantly with 5-FU/LV.	[min (last date of bevacizumab +13, death date)) – (first bevacizumab dosing date in the induction) +1] / 7

(1) According to the proposed formula, the duration of dosing may be overestimated in case patients discontinued treatment prior to the end of the last cycle.

Table 4: Exposure Definitions for Maintenance

	capecitabine	**5-FU or LV or cetuximab**	**bevacizumab**	**vemurafenib**
Number of cycles	The sum of all cycles in which at least one non-null dose of <*treatment*> has been administered			NA
Duration of dosing (weeks) (1)	[min (last dosing date of <treatment> + x, death date)) – (first <treatment> dosing date in the maintenance) +1] / 7 Where x=6 for capecitabine x=13 for 5FU, LV, cetuximab, bevacizumab x=0 for vemurafenib For 5-FU and LV, last dosing date of treatment will be replaced by the first dosing date of the last administration			
Actual dose	<treatment> dose administered (in mg) as collected on the dosing eCRF page Unit: mg			
Planned dose	<treatment> planned dose (in mg) as collected on the dosing eCRF page Unit: mg			
Normalized dose	dose / recalculated BSA(2) Unit: mg/m^2		dose / weight(3) Unit: mg/kg	NA
Cumulative dose	The cumulative dose will be derived for each records as below: (end date of administration - start date of administration +1) * normalized actual dose for the record * 2 Cumulative dose= sum of cumulative dose across all records Unit: mg/m2	sum of the all <treatment > normalized actual doses (in mg/m^2) administered in all cycles	sum of the all bevacizumab normalized actual doses (in mg/kg) administered in all cycles	The cumulative dose will be derived for each records as below: (end date of administration - start date of administration +1) * actual dose for the record Cumulative dose= sum of cumulative dose across all records Unit: mg

	capecitabine	**5-FU or LV or cetuximab**	**bevacizumab**	**vemurafenib**
Dose intensity	Cumulative dose / (duration of dosing *7) Unit: mg/m^2/day	Cumulative dose / duration of dosing Unit: mg/m^2/week	Cumulative dose / duration of dosing Unit: mg/kg/week	Cumulative dose / (duration of dosing * 7) Unit: mg/day
Cumulative planned dose (CPD)	Sum of all normalized planned dose (in mg/m^2) in all cycles	Sum of all normalized planned dose (in mg/m^2) in all cycles	Sum of all normalized planned dose (in mg/kg) in all cycles	Sum of the all planned doses (in mg) reported in all cycles
Planned dose intensity	CPD / (duration of dosing *7) Unit: mg/m^2/day	CPD / duration of dosing Unit: mg/m^2/week	CPD / duration of dosing Unit: mg/kg/week	CPD / (duration of dosing*7) Unit: mg/ day
Relative dose intensity (RDI) (%)	100 * (dose intensity) / (planned dose intensity)			

(1) According to the proposed formula, the duration of dosing may be overestimated in case patients discontinued treatment prior to the end of the last cycle.
(2) The BSA will be recalculated based on the height and weight (see point 3 for identification of weight) of the patient using the formula as mentioned in section 4.3.
(3) The baseline weight will be used as reference. If the last available weight of the patient prior to or on the cycle start has changed by 10% or greater (i.e. patient has gained or lost more than 10% of their body weight since baseline) the patient new weight will be set as the baseline weight and will be used at the patient current and subsequent cycles. If a patient weight has changed by 10% or greater at a later cycle, then this new weight will be set as the base weight as aforementioned.

The following information will be tabulated for the ITP using the ITP population:

- Summary of total number of cycles initiated per patient
  - Total number of cycles initiated (1,2,3,4,5,6,7,8)
  - Summary statistics of total number of cycles initiated
- Summary of drug exposure
  - The number of cycles administered and treatment duration (in weeks) for bevacizumab, FOLFOX and 5-FU/LV alone

The following information will be tabulated for the MTP using the SAF population:

- Summary of overall duration of treatment and overall number of cycles initiated
  - Overall duration of maintenance treatment (in weeks)
  - Overall number of cycles initiated: 1,2,3,4,5,6,7,8,9,10, 10-15, >=15
  - Summary statistics of overall number of cycles initiated per patient
- Summary of drug exposure
  - Total number of cycles administered (tabulated separately for each drug)
  - Duration of dosing (in weeks) (tabulated separately for each drug)
  - Cumulative dose (tabulated separately for each drug according to definition provided in table 3)
  - Dose intensity (tabulated separately for each drug according to definition provided in table 3)
  - Relative dose intensity: ≤90%, >90%-≤100%, >100% (tabulated separately for each drug according to definition provided in table 3) Note: Number and percentage will be based on the patients who received the corresponding drug.

Supportive listings presenting the study drug administration as well as the exposure information will be provided separately based on ITP population and SAF population for the induction and for the maintenance, respectively.

4.13.1.2 Cycle Delay

Cycle delay is applicable to the following treatments: FP (5-FU, LV or capecitabine), bevacizumab and cetuximab.

Cycle delay is defined as follow:

- For 5-FU, LV, cetuximab, bevazicumab, which have planned cycle of 2 weeks:

A cycle delay for <treatment> will be defined as the number of days in excess of the expected days between two consecutive doses of <treatment> (14 days) and will be calculated as D1Cn+1 - D1Cn where D1Cn+1 and D1Cn correspond to date of administration of <treatment> in cycle n+1 and cycle n, respectively. An excess of more than 3 days will qualified cycle Cn+1 as delayed for <treatment>. Of note, the first cycle (C1) cannot be identified as cycle delay.

- For capecitabine:

Cycle delay will be defined as the number of days in excess of the expected days between two non-zero administrations (21 days, i.e. 14 days of administration and a rest period of 7 days) and will be calculated as D1Cn+1 - D1Cn where D1Cn+1 and D1Cn correspond to the start date of the first administration of capecitabine in cycle n+1 and cycle n, respectively. An excess of more than 3 days will qualify cycle Cn+1 as delayed for capecitabine. Of note, the first cycle (C1) cannot be identified as cycle delay.

The following information will be tabulated for the MTP on the SAF population:

- Summary of <*treatment*> cycle delay (for 5-FU, LV, capecitabine, bevazicumab and cetuximab) at the patient level
  - Number of patients with at least one cycle delayed for <*treatment*>,
  - Number of patients with 1, 2, 3, ≥3 cycles delayed for <*treatment*>
- Summary of <*treatment*> cycle delay (for 5-FU, LV, capecitabine, bevazicumab and cetuximab) at the cycle level
  - Number of cycles delayed
  - Length of cycle delayed (>3 -7 days, >7-14, >14-21, >21)

4.13.2 Adverse Events

Adverse events variables are defined in Table 5.

Table 5: Adverse Events Definitions

Variable	Definition
Treatment Emergent Adverse Events (TEAEs) for the induction treatment phase (1)	Any adverse events (serious and non-serious) with an onset date on (only if the "Event occurred prior to first study drug administration" from the AE eCRF page is not checked) or after the first day of treatment of the ITP and up to the: • first day of treatment of the MTP (excluding) if it occurs within the 30 days from last day of treatment of induction treatment for patients treated with maintenance treatment • within 30 days from last day of treatment of induction treatment (as defined in section 4.2.1), for patients not treated with maintenance treatment or for patients treated with maintenance treatment but with first day of treatment of MTP being more than 30 days after last day of treatment of ITP.
TEAEs for the maintenance treatment phase(1)	Any adverse events (serious and non-serious) with an onset date on (only if the "Event occurred prior to first study drug administration" from the AE eCRF page is not checked) or after the first day of treatment of the MTP and up to 30 days from the last day of treatment of MTP (as defined in section 4.2.2)
Post induction treatment Adverse Events	Any adverse events (serious and non-serious): • with an onset date more than 30 days after the last day of treatment of the ITP (as defined in section 4.2.1) for patients not treated with maintenance treatment. • with an onset date more than 30 days after the last day of treatment of the ITP and prior the first day of treatment of the MTP, for patients treated with maintenance treatment with first day of treatment of MTP being more than 30 days after last day of treatment of ITP..

Post maintenance treatment Adverse events	Any adverse events (serious and non-serious) with an onset date more than 30 days after the last day of treatment of the MTP (as defined in section 4.2.2) (as defined in section 4.2.2).
Adverse Events NCI CTCAE grade	The adverse events grade will be the one with tick box checked for "AE most extreme NCI CTCAE grade"
Serious Adverse Events (SAEs)	Any adverse events qualified as “serious” by the investigator.
Adverse Events with fatal outcome	Any adverse events with outcome of “Fatal”.
Adverse events related to <FOLFOX, bevacizumab, FP, cetuximab, vemurafenib>	Any adverse events with an “AE suspected to be caused by study drug <FOLFOX, bevacizumab, FP, cetuximab, vemurafenib > as ‘Yes’. For AE suspected to be caused by FOLFOX while starting in the maintenance phase, the unique text ‘“AE considered related to Folfox”‘ has been reported in the comment field ‘
Adverse events leading to <FOLFOX, bevacizumab, FP, cetuximab, vemurafenib > discontinuation	Any adverse events with an “Action taken with <FOLFOX, bevacizumab, FP, cetuximab, vemurafenib> due to SAE/AE” of “drug withdrawn”
Adverse events of Special Interest (AESI) as reported on eCRF	AESIs will be selected based on the tick box from the eCRF.
<Bevacizumab, Vemurafenib> AESIs based on pre-defined terms	AESIs will be selected from AEs based on the <bevacizumab, vemurafenib> list of pre-defined terms.

(1) Of note, in case an event has an incomplete or missing start date, which consequently prevents its allocation to only one treatment phase of the study, the event will be allocated to both the induction and maintenance phase. Refer to section 4.14 for further details.

Safety summaries will be produced for the ITP on the ITP population and for the MTP on the SAF population, unless otherwise specified. ITP summaries will display patients randomized vs. patients not randomized in MTP. MTP summaries will be done by actual maintenance treatment

group as defined for the SAF. Descriptive statistics will be generated as appropriate. No inferential statistical analyses are planned.

Summaries of adverse events for ITP and MTP will be generated for those events that are considered treatment emergent. The AE tables will include the number and percentage of patients with at least one AE, by MedDRA primary System Organ Classes (SOC) (sorted in a descending order of the total frequency count) and MedDRA Preferred Terms (PT) (sorted by descending order of the overall frequency count within each SOC) unless otherwise indicated. A patient with more than one occurrence of the same adverse event in a particular system organ class/preferred term will be counted only once in the total of those experiencing adverse events in that particular system organ class/preferred term. For the overall summary tables, information presented by grade will not be restricted to the worst grade per patient i.e. all events will be presented. Any AEs with a missing CTC grade will be reported in the "missing" category grade.

An overview table will be produced for the ITP based on the ITP population and will present:

- Number of TEAEs
- Number of patients with at least one TEAE
- Number of patients with at least one TEAE by CTC grade: 1, 2, 3, 4, 5, ≥3, missing
- Number of patients with at least one related TEAE
    - Any study drug
    - FOLFOX
    - 5-FU/LV
    - bevacizumab
- Number of patients with at least one serious TEAE
- Number of patients with at least one related serious TEAE
    - Any study drug
    - FOLFOX
    - 5-FU/LV
    - bevacizumab
- Number of patients with at least one TEAE with fatal outcome
- Number of patients with at least one TEAEs leading to treatment discontinuation of:
    - Any study drug
    - FOLFOX
    - 5-FU/LV
    - bevacizumab

An overview table will be produced for the Post Induction Treatment AEs, i.e. occurring more than 30 days after last day of treatment during the Induction Phase (as defined in section 4.2.1), based on patients from the ITP population who has a study treatment discontinuation visit date. This table will present the following information for the non-randomized patients to MTP only:

- Number of AEs
- Number of patients with at least one AE
- Number of patients with at least one AE by CTC grade: 1, 2, 3, 4, 5, ≥3, missing
- Number of patients with at least one related AE
- Number of patients with at least one serious AE
- Number of patients with at least one related serious AE
- Number of patients with at least one AE with fatal outcome

An overview table will be produced for the maintenance phase based on the SAF and will present:

- Number of TEAEs
- Number of patients with at least one TEAE
- Number of patients with at least one TEAE by CTC grade: 1, 2, 3, 4, 5, ≥3, missing
- Number of patients with at least one related TEAE
    - Any study drug
    - Fluoropyrimidines
    - bevacizumab
    - cetuximab,
    - vemurafenib
    - FOLFOX
- Number of patients with at least one serious TEAE
- Number of patients with at least one related serious TEAE
    - Any study drug
    - Fluoropyrimidines
    - bevacizumab
    - cetuximab,
    - vemurafenib
    - FOLFOX
- Number of patients with at least one TEAE with fatal outcome
- Number of patients with at least one TEAEs leading to treatment discontinuation of:
    - Any study drug
    - bevacizumab
    - cetuximab,
    - vemurafenib
- Number of patients with at least one treatment emegent AESI (as reported on eCRF)
- Number of patients with at least one treatment emegent AESI (based on list of pre-defined terms)
    - bevacizumab,
    - vemurafenib
- Number of patients with at least one serious treatment emergent AESI (as reported on eCRF)

An overview table will be produced for the Post Maintenance Treatment AEs, i.e. AEs occurring more than 30 days after the last day of treatment during the Maintenance Phase (as defined in section 4.2.2), based on patients from the MTP population who have a study treatment discontinuation visit date. This table will present the following information:

- Number of AEs
- Number of patients with at least one AE
- Number of patients with at least one AE by CTC grade: 1, 2, 3, 4, 5, ≥3, missing
- Number of patients with at least one related AE
- Number of patients with at least one serious AE
- Number of patients with at least one related serious AE
- Number of patients with at least one AE with fatal outcome

In addition, the following tables (number and percentage of patients) will be presented for the ITP based on the ITP population and will display the number of patients (and corresponding number of TEAEs) and percentage with any:

- TEAEs by SOC and PT
- TEAEs by SOC and PT and by Worst Intensity
- Grade 3-5 TEAEs by SOC and PT
- Related TEAEs by SOC and PT: to any study drugs, FOLFOX, 5 FU/LV, bevacizumab
- Serious TEAEs by SOC and PT
- Related serious TEAEs by SOC and PT: to any study drugs, bevacizumab
- TEAEs leading to treatment discontinuation by SOC and PT: any study drug,
- TEAEs leading to dose reduction or interruption by SOC: any study drugs, bevacizumab
- Grade 5 TEAEs or TEAEs with fatal outcome by SOC and PT
- Treatment emergent AESI by AESI eCRF categories, SOC and PT
- Bevacizumab treatment emergent AESI based on pre-defined categories

The following tables will be presented for the MTP only and will display the number and percentage of patients (and corresponding number of TEAEs) with any:

- TEAEs by SOC and PT
- TEAEs by SOC and PT and by Worst Intensity
- Grade 3-5 TEAEs by SOC and PT
- Related TEAEs by SOC and PT: any study drugs, 5-FU/LV, FOLFOX, bevacizumab, cetuximab, vemurafenib,
- Serious TEAEs by SOC and PT
- Related Serious TEAEs by SOC and PT: any study drugs, 5-FU/LV, cetuximab, vemurafenib, bevacizumab, FOLFOX
- Grade 5 TEAEs or TEAEs with fatal outcome by SOC and PT
- TEAEs leading to treatment discontinuation by SOC and PT: any study drugs,
- TEAEs leading to dose reduction or interruption by SOC and PT: any study drugs, 5-FU/LV, cetuximab, vemurafenib, bevacizumab
- Treatment emergent AESI by AESI eCRF categories, SOC and PT and by Worst Intensity
- Serious Treatment emergent AESI by AESI eCRF categories, SOC and PT and by Worst Intensity
- Treatment emergent AESI by AESI eCRF categories, SOC and PT
- Serious Treatment emergent by AESI eCRF categories, SOC and PT
- Bevacizumab treatment emergent AESI based on pre-defined categories
- Vemurafenib treatment emergent AESI based on pre-defined categories

By-patient listings will be provided for AEs; they will include Post-treatment adverse events. Appropriate flagging of study phase (ITP/MTP) as well as TEAEs/Post-treatment AEs will be done. The following listings will be provided based on ITP population

- All adverse events
- All Grade 5 adverse events or any adverse events with fatal outcome
- All adverse events leading to treatment discontinuation
- All AESI (as reported on eCRF)

4.13.3 Death

The following summary tables will be provided and will present:

- The number of patients who died within 30 days from last day of treatment of the ITP (as defined in section 4.2.1) and the corresponding reason of death based on ITP population
- The number of patients who died more than 30 days from last day of treatment of ITP (as defined in section 4.2.1) and the corresponding reason of death based on ITP population who has a study treatment discontinuation visit date
- The number of patients who died within 30 days from last day of treatment of MTP for treated patients or within 30 days from randomization with the corresponding cause of death based on MTP population
- The number of patients who died within 30 days from last day of treatment of MTP (as defined in section 4.2.1) with the corresponding death reason using the SAF population
- The number of patients who died more than 30 days from last day of treatment of maintenance treatment and the corresponding reason of death based on patients from the MTP population who has a study treatment discontinuation visit date

One listing will be generated for deaths based on the ITP population and including appropriate flagging of study phase (ITP and MTP) and on-treatment/post-treatment deaths (i.e. within 30 days from last day of treatment/more than 30 days from last day of treatment).

All deaths information (including reason and date) will be retrieved from the Study Completion/Early Discontinuation eCRF page.

4.13.4 Laboratory Data

The following laboratory parameters will be considered as CTC gradable parameters.

Haematology

- Absolute Neutrophils Count (ANC)
- Hemoglobin (Hb)
- Leukocytes/White Blood Cells counts (WBC)
- Platelet Count

Blood chemistry

- Albumin
- Alkaline Phosphatase (ALP)
- Calcium
- Creatinine
- Glucose
- Potassium
- SGPT or alanine aminotransferase (ALT)
- SGOT or aspartate aminotransferase (AST)
- Sodium
- Total Bilirubin

- Magnesium
- Amylase
- Lipase

Coagulation
- international normalized ratio (INR)
- activated partial thromboplastin time (aPTT)

The following parameters will be considered as non CTC gradable parameters.

Hematology
- Red blood Cell (RBC)
- Hematocrit
- Lymphocytes
- Neutrophils
- Eosinophils
- Basophils
- Monocytes

Blood Chemistry
- Blood Urea Nitrogen
- Bicarbonate
- Chloride Lactate dehydrogenase (LDH)
- Phosphorus
- Total Protein

Urinalysis
- Urine Protein Dipstick
- 24-hour urine protein

All laboratory parameter information will be summarized for each phase separately. Laboratory information reported in tables will be restricted to the baseline and on-treatment measurements. The analysis population will be the ITP and the SAF population for the ITP and MTP, respectively.

Clinical laboratory values will be expressed using Système International (SI) units.

When applicable, laboratory tables will display their High (hyper)/Low (hypo) values of a specific parameter (e.g. calcium (high) and calcium (low) in separate tables.

In case of missing normal ranges for parameters that are not differential and have only grade 1 defined from normal ranges (e.g. Neutrophils, WBC, Albumin…) the worst case scenario will be applied, i.e. grade 1.

A “Missing” category will be reported for patients with missing grades or missing reference range indicators at baseline and/or on-treatment and patients with no laboratory assessments.

For hematology, blood chemistry and coagulation parameters which can be graded per CTCAE, the information will be summarized by means of a shift table summarizing the baseline grade versus the worst CTC grade per patient defined as the highest CTC grade among the on-

treatment evaluations. If there is no on-treatment evaluation, then the worst grade will be set to 'Missing'.

Hematology and blood chemistry parameters which cannot be graded per CTCAE, the information will be summarized by means of a shift table from baseline category to worst on-treatment category. The following categories will be used:

- Baseline: Low/Normal/High/Missing/Overall
- Worst on-treatment: Low/Normal/High/Missing/Overall

Patient with "High" and "Low" for the same laboratory test (at different visits) is counted for each direction in summary tables.

For urinalysis protein dipstick, all non-missing assessments excepted "0-absent" assessment will be considered "Present". A shift table presenting baseline category versus worst on-treatment category will be produced with the following categories:

- Baseline: Absent/Present/Missing/Overall
- Worst on-treatment: Absent/Present/Missing/Overall

For urinalysis, 24-hour urine protein values will not be tabulated but listed only.

All laboratory values will be listed along with CTC grade/category. Separate listings will be generated to include all abnormal laboratory values.

4.13.5 Vital Signs

Vital signs parameters include:

- Temperature (°C)
- Systolic blood pressure (SBP seated position) (mmHg)
- Diastolic blood pressure (DBP seated position) (mmHg)
- Weight (kg)
- BSA (m^2)
- Heart rate (beats/min)
- Respiratory rate (breaths/min)

Vital signs information will be summarized for each phase separately and by treatment group when applicable. Vital signs information reported in tables will be restricted to non-missing baseline and non-missing on-treatment measurements. The analysis population will be the ITP population for the ITP and the SAF population for the MTP.

Actual value and change from baseline for heart rate and systolic and diastolic blood pressure will be summarized by treatment group for each visit using descriptive statistics.

All vital signs data including change from baseline (and data reported at timepoints not included in the summary table) will be listed.

4.13.6 Other Safety Assessment - Applicable only for the experimental group

ECG data will be summarized on the SAF population for the MTP as follow:

- Summary of Qualitative ECG results over time presenting the number of patients by categories: Normal/Abnormal, not clinically significant/Abnormal, clinically significant/unable to Evaluate/Missing
- Summary of QTcF (in categories) over time presenting the number of patients with QTcF in categories: <=450 ms/ >450 ms - <=480 ms/>480 ms - <= 500 ms / >500 ms.

All ECG data will be listed on ITP population.

4.13.7 Other Safety Assessment

Pregnancy test data will be listed on the ITP population, ITP and MTP data will be flagged.

4.14 MISSING DATA

Imputation of partial/missing death date will be done as follows:

- If the date is completely missing, then the day of "Last known to be alive" +1 will be used
- If only day is missing and year and month are same as "Last known to be alive", then the day of "Last known to be alive"+1 will be used otherwise the 1st day of the month will be used
- If day and month are missing and year is same as "Last known to be alive", then the "Last known to be alive"+1 will be used, otherwise 1st of January will be used

Partially missing dates for adverse events (AEs) will be imputed as follows. Of note, imputation of missing/partial AE date will be done only to identify treatment emergent AEs.

AE onset dates

- Partially missing onset dates will be imputed as follows
  - When only Day is missing:
    - If Month & Year of the onset date are the same as Month & Year of the first day of treatment of the induction/maintenance treatment phase, the imputed onset date will be imputed as the minimum of the first day of treatment of the induction/maintenance treatment phase and the AE resolution date (imputed if needed).
    - Otherwise, the missing day will be replaced by "1".
  - When Day & Month are missing:
    - If Year of the onset date is the same as Year of the induction/maintenance treatment phase, the imputed onset date will be imputed as the minimum of the first day of treatment of the induction/maintenance treatment phase and the AE resolution date (imputed if needed).
    - Otherwise, the missing Day & Month will be replaced by "01JAN".

- Complete missing onset dates for AEs will be imputed by first day of treatment of the induction/maintenance treatment phase and the AE will be considered as treatment emergent, unless the end date of the AE (imputed if needed) or the end year of the AE (if day and month are missing) is entered and is before the year of the first treatment administration of the induction/maintenance treatment phase.

AE resolution dates

- Incomplete resolution dates will be replaced by the last day of the month (if day is missing only), if not resulting in a date later than the date of patient's death. In the latter case the date of death will be used to impute the incomplete resolution date
- In all other cases the incomplete resolution date will not be imputed

Of note, the above rules may allow allocation of an event to both the ITP and MTP treatment phase.

Partially missing dates for medications/therapies will be imputed as follows. Of note, imputation of missing/partial medicationstherapies date will be done only to identify concomitant medications/therapies.

Partial dates will be imputed as follow:

- Start dates
  - When only Day is missing: the missing day will be replaced by "1"
  - When Day & Month are missing: the missing Day & Month will be replaced by "01JAN".
- End dates
  - When only Day is missing: the missing day will be replaced by the last day of the month
  - When Day & Month are missing: the missing Day & Month will be replaced by "31DEC".

And rules described in section 4.10.3.2 and below will be applied using imputed dates.

In case of complete missing dates, the following will be applied:

- If the start date of the medication/therapy is unknown (i.e. complete missing date) and there is no end date, medication/therapy is flagged as taken prior to study but not as ongoing then the medication/therapy will be considered as a prior medication.
- If both the start date and end date of the medication/therapy is unknown (i.e. complete missing date), then the medication/therapy will be considered as a concomitant medication/therapy for both the induction and maintenance phase if the patient is treated in the phase of interest.
- If the start date of the medicationtherapy is unknown (i.e. complete missing date), but the end date is known and is prior to the first dosing date of the considered phase, then the medicationtherapy will not be considered as concomitant for the corresponding phase.
- If the start date of the medication/therapy is available and the end date is unknown, then the medication/therapy will not be considered as prior. Concomitance to ITP/MTP will be assessed using the available start date.

Partially missing dates for surgery will be imputed as follows. Of note, imputation of missing/partial surgeries date will be done only to identify concomitant surgeries.

Partial dates will be compared as follow:

- When only Day is missing: Month & Year of the surgery will be compared to Month & Year of the first dosing date of interest (either ITP or MTP). If on or after, the surgery will be considered as concomitant to the period of interest. If on or before the first doing date of ITP, the surgery will be considered as prior.
- When Day & Month are missing: Year of the surgery will be compared to Year of the dosing date of interest (either ITP or MTP). If on or after, the surgery will be considered as concomitant to the period of interest. If on or before the first doing date of ITP, the surgery will be considered as prior.

Of note, the above rules may allow a medication/procedure to be concomitant to both the ITP and MTP treatment phase.

For patients who discontinued study treatment but without any study treatment discontinuation visit date, this visit will be imputed as follows:

- If patient was treated in the MTP, the last dose will be retrieved from the treatment drug completion/early discontinuation page from the eCRF in the maintenance phase. The maximum date among the date mentioned for each treatment during MTP + 30 days will be considered.
- If patient was treated in the ITP, the last dose will be retrieved from the treatment drug completion/early discontinuation page from the eCRF in the induction phase. The maximum date among the date mentioned for each treatment during ITP + 30 days will be considered

with the following exception:

  - If a patient died within 30 days from last dose, the follow up phase does not exist for this patient

Partially missing dates for date of initial histological diagnosis or date of first diagnosis of metastatic disease or date of first diagnosis of locally recurrent disease will be imputed as follows:

Imputation of these partial dates will be done only to determine if the initial diagnosis is synchronous or metachronous and only in case the date day is missing. The imputation will consist in replacing the missing day by “1”. In case month and/or year are missing, no imputation will be done.

No other dates will be imputed, unless otherwise specified. The original incomplete, missing or partial dates will be presented in the listings, not the imputed dates.

4.15 INTERIM ANALYSES

No formal interim analyses on PFS or OS are planned.

5. REFERENCES

Di Nicolantonio F, Martini M, Molinari F, et al. Wild-type BRAF is required for response to panitumumab or cetuximab in metastatic colorectal cancer. J Clin Oncol. 2008 Dec 10;26(35):5705-12. doi: 10.1200/JCO.2008.18.0786. Epub 2008 Nov 10.

Ron Brookmeyer and John Crowley, A Confidence Interval for the Median Survival Time. Biometrics Vol. 38, No. 1 (Mar., 1982), 29-41

Appendix 1: Protocol Synopsis

Objectives

Efficacy Objectives

The primary efficacy objective of the study is to evaluate progression-free survival (PFS) within each maintenance treatment cohort.

Secondary efficacy objectives include the evaluation of efficacy through other endpoints:

- Overall survival (OS)
- Overall response rate (ORR)
- Disease control rate (DCR)
- Time to treatment response (TTR)
- Duration of response (DoR)
- Change in Eastern Cooperative Oncology Group (ECOG) performance status

Safety Objectives

Additional objectives for this study are to assess the safety of each treatment including:

- the 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

Adverse events (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 modified RECIST (mRECIST) in patients treated with atezolizumab

The exploratory biomarker objectives for 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)
- Explore and correlate microbiome with other biomarkers, baseline characteristics and clinical outcome

Study Design

Description of Study

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). The primary study endpoint is PFS according to RECIST 1.1 within each cohort. Secondary endpoints include other efficacy measurements and safety. In addition, exploratory outcomes will focus on the correlations between biomarkers and study outcomes.

Patients with mCRC who have not received any prior chemotherapy in the metastatic setting are eligible for entry. The study will enrol patients in Europe, Asia, Africa, and South America.

For an individual patient, the study will consist of a Screening Phase (≤ 28 days), a 4-month Induction Treatment Phase, a Maintenance Treatment Phase, and finally follow-up during the Post-Treatment Follow-up Phase.

Potential patients will undergo screening assessments to determine study eligibility within 28 days prior to starting study induction treatment. Results from routine assessments conducted prior to informed consent signature may be used as screening assessments as long as they were done within

7 days prior to informed consent signature. The primary tumour tissue block prepared at the time of the initial diagnosis will be used for biomarker assessment for maintenance treatment cohort assignment (see Appendix 17). If the tumour block is not available, ≥ 20 slides cut from the primary tumour sample will be accepted as an alternative. The sample (block or slides) must be shipped to the designated laboratory and confirmation of sample receipt by the laboratory must be obtained before the patient may be enrolled in the study.

All patients enrolled in the study will be asked to give written informed consent to provide blood samples for exploratory biomarker analyses and to allow all available residual samples of tumour, blood and plasma samples collected in the study be used for additional exploratory biomarker research using the Roche Clinical Sample Repository (RCR). No additional sampling is required for RCR samples. Prior to May 2018, an optional metastatic tumour sample was collected from all study patients. In addition, patients at selected centres were able to participate in an optional Supplemental Biomarker Program (described in Appendix 18). As of May 2018, collection of the optional baseline metastatic tumour sample has been discontinued and the Supplemental Biomarker Program has been closed. Baseline metastatic tumour samples and Supplemental Biomarker Program samples collected up to this time point may still be used for exploratory biomarker analyses.

Eligible patients will enter a 4-month Induction Treatment Phase. Treatment during this phase, based on Investigator's choice (see Appendix 6), 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

During the Induction Treatment Phase, patients will be assessed for AEs at every cycle. Clinical laboratory assessments will be conducted at each cycle, however results from tests conducted every second treatment cycle only will be collected in the case report form (CRF). Physical examinations and documentation of concomitant medications will be done every two treatment cycles. 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 prematurely discontinue study treatment for any reason during the Induction Treatment Phase, or who experience PD at any time during or at the end of the Induction Treatment Phase, or who refuse to proceed to the Maintenance Treatment Phase or who are not eligible for any study cohort will undergo a Study Treatment Discontinuation Visit within 30 days after the last dose of study treatment and will then enter the Post-Treatment Follow-up Phase. All patients need to be evaluated for potential resection of metastasis at completion of the induction period. This is of particular importance for patients with liver metastases. If the patient is found to be resectable they will undergo a Study Treatment Discontinuation Visit within 30 days after the last dose of study treatment and will then enter the Post-Treatment Follow-up Phase. Patients completing induction treatment who do not have progressive disease and whose disease has not become resectable can proceed to the Maintenance Treatment Phase. Informed consent based on the information specific to the assigned maintenance cohort will be obtained prior to the conduct of any cohort-specific screening assessments (unless the study site has chosen to conduct informed consent including information for induction regimens and all potential maintenance regimens prior to study entry).

Each maintenance treatment cohort will consist of a cohort-specific experimental treatment arm and a standard control arm of fluoropyrimidine (5-FU/LV or capecitabine) and bevacizumab. At completion of the Induction Treatment Phase of the study, patients continuing to the biomarker-driven Maintenance Treatment Phase will be assigned to a maintenance treatment cohort based on the biomarker profile determined from their primary tumour tissue. Biomarkers considered in maintenance

treatment assignment include presence or absence of HER2 overexpression (HER2+ or HER2- respectively), microsatellite stability status (microsatellite stable [MSS] or high microsatellite instability [MSI-H]), wild-type or mutated BRAF gene ($BRAF^{wt}$ or $BRAF^{mut}$ respectively), and presence or absence of RAS pathway mutation (RAS^{wt} or RAS^{mut} respectively; see Appendix 17 for the biomarker-based cohort assignment decision tree). Patients will be randomised within their assigned cohort on a 2:1 (experimental:control) basis to either the experimental treatment arm or the control arm of that cohort and will begin treatment within 3 weeks of completing induction treatment. Randomisation will be stratified according to specific biomarkers identified for each cohort, by geographical region, and/or by patient response after the Induction Treatment Phase (CR/PR vs. SD). Stratification variables applicable to each cohort are described in Section 4.2 of the protocol.

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 (see Figure 1).

Cohort 1

Biomarker profile (all patients screened prior to June 3, 2016): $BRAF^{mut}$

*Biomarker profile (all patients screened after June 3, 2016): **HER2-/MSS/$BRAF^{mut}$/RAS^{wt}***

5-FU/LV with cetuximab and vemurafenib

vs.

Fluoropyrimidine (5-FU/LV or capecitabine) and bevacizumab

Cohort 2 - CLOSED TO ENROLMENT

(No patients screened after June 3, 2016 will be assigned to this cohort)

*Biomarker profile: **$BRAF^{wt}$***

Fluoropyrimidine (5-FU/LV or capecitabine) with bevacizumab and atezolizumab

vs.

Fluoropyrimidine (5-FU/LV or capecitabine) and bevacizumab

Cohort 3

*Biomarker profile: **HER2+***

Capecitabine with trastuzumab and pertuzumab

vs.

Fluoropyrimidine (5-FU/LV or capecitabine) and bevacizumab

Cohort 4 - CLOSED TO ENROLMENT

(As of February 12, 2018, no further patients are assigned to this cohort. See protocol Section 3.1.2.4.)

*Biomarker profiles: **HER2-/MSI-H; HER2-/MSS/$BRAF^{wt}$; HER2-/MSS/$BRAF^{mut}$/RAS^{mut}***

Cobimetinib and atezolizumab

vs.

Fluoropyrimidine (5-FU/LV or capecitabine) and bevacizumab

See Appendix 17 for additional information on biomarker testing and biomarker-based cohort assignment.

Study Enrolment and Cohort Status Update:

- Accrual to Cohort 2 was completed in November 2016.

- Study enrolment and accrual into Cohort 4 were suspended in February 2018 as a result of an unfavourable benefit-risk evaluation of Cohort 4 by the independent Data Monitoring Committee (iDMC). Accrual to Cohort 4 was not re-opened after February 2018 due to iDMC recommendations. See protocol Section 3.1.2.4.
- Cohort assignment and randomization of any patients who were already enrolled and eligible for Cohorts 1 and 3 were continued following the February 2018 suspension of study enrolment.
- No new or modified cohorts have been identified for addition to the study. In the absence of a cohort with broad biomarker eligibility criteria (i.e. to replace Cohort 4), the majority of patients would not be eligible for maintenance cohort assignment. For this reason, study enrolment will not be re-opened following the February 2018 suspension.

All Cohorts

No other anti-cancer therapy is permitted during the study with the following exceptions:

- local ablation for liver metastases during Induction Treatment Phase only and only if there are other non-ablated sites of measurable disease that have been followed from baseline tumour assessment (i.e. prior to start of induction treatment)
- radiotherapy for pain control during the either Induction or Maintenance Treatment Phases

For all patients who are not receiving atezolizumab, study maintenance treatment will continue until disease progression (based on Investigator's assessment), unacceptable toxicity, initiation of another anti-cancer therapy, patient or physician decision to discontinue, or patient death, whichever occurs first.

For all patients who are receiving atezolizumab, study maintenance treatment may continue after the first tumour assessment showing progression per RECIST 1.1 as long as patients meet the following criteria as assessed by the Investigator:

- Evidence of clinical benefit
- Absence of symptoms and signs (including worsening of laboratory values, e.g. new or worsening hypercalcaemia) indicating unequivocal progression of disease
- No decline in ECOG performance status that can be attributed to disease progression
- Absence of tumour progression at critical anatomical sites (e.g. leptomeningeal disease) that cannot be managed by protocol-allowed medical interventions

Treatment should be discontinued if the next follow-up tumour assessment continues to demonstrate progression per RECIST 1.1 (as compared to the assessment at the end of induction treatment). If the next tumour assessment does not show progression per RECIST 1.1, the patient may continue maintenance treatment until such time as the treatment continuation criteria above are no longer met and/or two sequential tumour assessments show progression per RECIST 1.1.

Atezolizumab treated patients may be discontinued from study treatment for the following reasons other than loss of clinical benefit or persistent progression: unacceptable toxicity, initiation of another anti-cancer therapy, patient or physician decision to discontinue, or patient death, whichever occurs first.

Efficacy, safety and tolerability will be assessed during the entire Maintenance Treatment Phase. While receiving study treatment during the Maintenance Treatment Phase, patients will be assessed for AEs and concomitant medications at every treatment cycle. Clinical laboratory assessments will be conducted at every cycle. For regimens with two week treatment cycles, clinical laboratory results from every second treatment cycle only will be collected in the CRF. For regimens with three week treatment cycles (such as Cohort 3 experimental regimen), clinical laboratory results from every cycle will be collected in the CRF. Physical examinations will be done every treatment cycle (regimens with three week cycles) or every two treatment cycles (regimens with two week cycles). Additional safety

reviews (safety run-ins) will be conducted by the iDMC, when necessary, for a prespecified number of initial patients receiving experimental combinations with inadequate prior safety experience to assure appropriate dosing (e.g., as required for the initial patients treated with the experimental combination of '5-FU/LV + cetuximab + vemurafenib'). Up to and including May 31, 2019, disease status will be evaluated during the Maintenance Treatment Phase as compared to the tumour assessment at the end of induction treatment and in accordance with RECIST 1.1 (see Appendix 10) for all patients, and additionally according to mRECIST (see Appendix 11) for patients treated with atezolizumab. Tumour assessments will be conducted every eight weeks. After May 31, 2019, disease status will no longer be collected for study analyses and should be evaluated according to local practice. Schedules of Assessments for each cohort are provided in Appendices 2 to 5.

Patients who discontinue study treatment for any reason during the Maintenance Treatment Phase will undergo a Study Treatment Discontinuation Visit within 30 days after the last dose of study treatment and will then enter the Post-Treatment Follow-up Phase.

Patients who prematurely discontinue treatment during the Induction Treatment Phase, who did not proceed to the Maintenance Treatment Phase or who discontinue treatment during the Maintenance Treatment Phase, will be followed for new AEs for 28 days (patients discontinuing before maintenance treatment and patients treated in all maintenance cohort control arms and Cohort 1 experimental arm) or 90 days (patients treated in experimental arms of Cohorts 2, 3 and 4 only) following the discontinuation of study treatment. At the time of treatment discontinuation, any ongoing AE/SAE will be followed until the event resolves, the Investigator assesses the event as stable, or the patient is lost to follow-up, dies or withdraws consent. The Sponsor should be notified if the Investigator becomes aware of any SAE or AEs of special interest occurring after the end of the adverse event reporting period if the event is believed to be related to prior study treatment.

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. Before May 31, 2019, patients will be followed every 3 months during the Post-Treatment Follow-up Phase for subsequent anti-cancer therapies, survival, and AEs (as applicable) including therapy-specific safety assessments (e.g., investigations for squamous cell carcinoma in patients who received vemurafenib) (see Appendices 1 to 5). After May 31, 2019, patients in Cohorts 2 and 3 who have completed the adverse event reporting period and, if applicable, cohort-specific post-treatment follow-up safety assessments will be discontinued from the study. Cohorts 2 and 3 patients who have completed the adverse event reporting period (and cohort-specific post-treatment follow-up safety assessments if applicable) prior to May 31, 2019 will be discontinued at their Post-Treatment Follow-up visit within the 3 months prior to and including May 31, 2019. See protocol Section 5.3.1 for adverse event reporting periods and post-treatment follow-up safety assessments. All patients in Cohorts 1 and 4 will continue in the Post-Treatment Follow-up Phase until the end of the study. Refer to Appendix 19 for management of patients in each cohort based on their study status on May 31, 2019.

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 (patients discontinuing during the Induction Treatment Phase) or every eight weeks (patients discontinuing during the Maintenance Treatment Phase) until progression or May 31, 2019, whichever comes first. After May 31, 2019, disease status will no longer be collected for any study patient. Disease assessments in any patient who has not yet progressed as of May 31, 2019 should thereafter be conducted according to local practice.

Second-line treatment during the Post-Treatment Follow-up Phase is at the Investigator's discretion. However, patients who received atezolizumab should not receive other immunomodulatory agents for 10 weeks after maintenance treatment discontinuation.

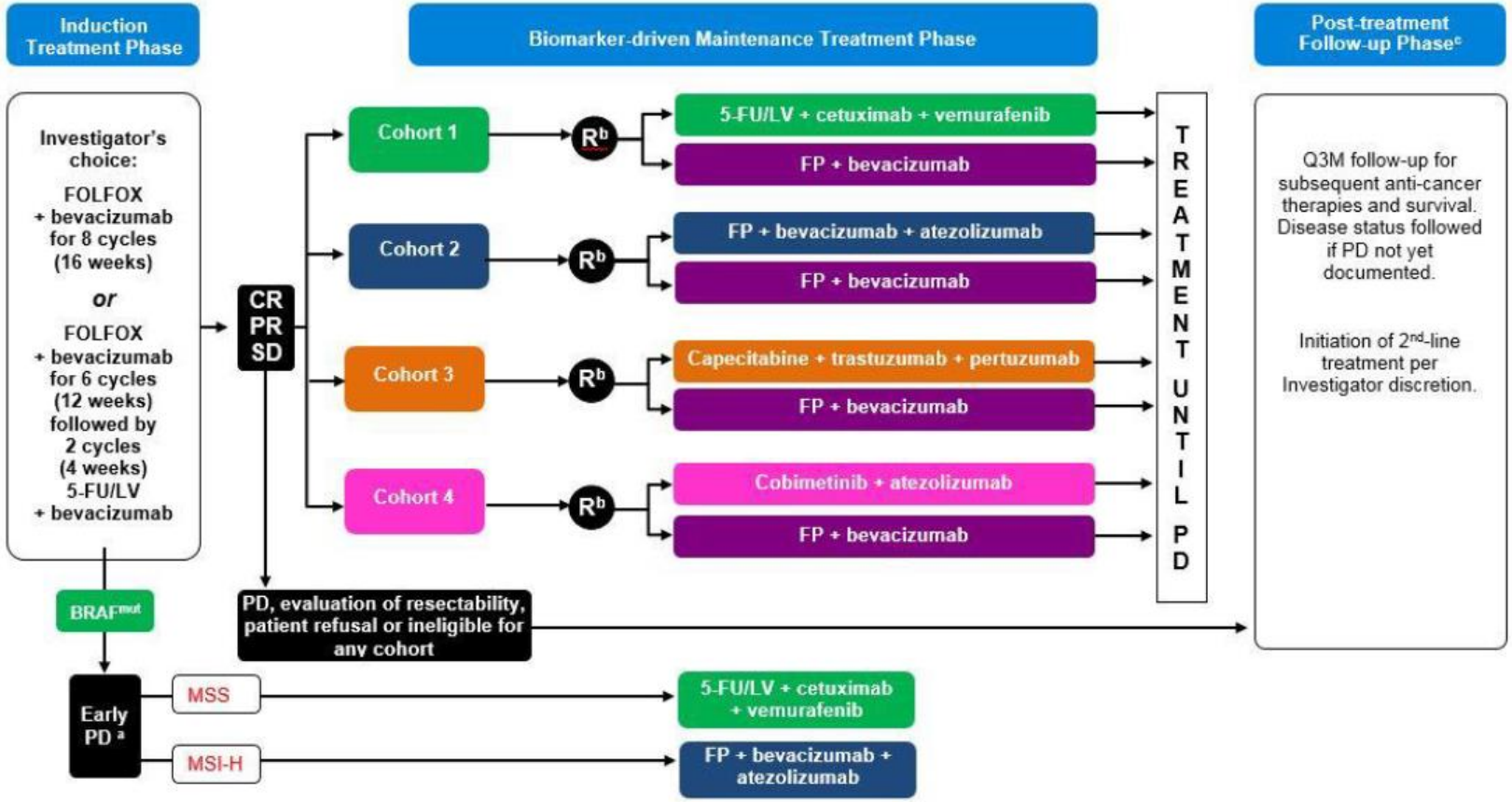
BRAF^{mut} Patients and Early Disease Progression

BRAF^{mut} patients experiencing early disease progression during induction treatment will have the option of proceeding immediately to receive second-line treatment with 5-FU/LV, cetuximab and vemurafenib if their primary tumour is MSS, or with a fluoropyrimidine (5-FU/LV or capecitabine), bevacizumab, and atezolizumab if their primary tumour is MSI-H.

If a patient previously indicated to have a BRAF^{mut} primary tumour (e.g. according to local testing) progresses prior to the availability of results from the study primary tumour biomarker testing, the Investigator may request an expedited biomarker report from the sponsor's Medical Monitor to confirm BRAF^{mut} status and to obtain MS status. Such patients will be allocated to the appropriate second-line treatment and may begin treatment following approval from the Medical Monitor.

Early progressing BRAF^{mut} patients receiving 5-FU/LV, cetuximab and vemurafenib as second-line treatment will be followed for safety and efficacy in accordance with the Maintenance Treatment Phase Schedule of Assessments (including eligibility, biomarker sampling and post-treatment follow-up) for Cohort 1 (see Appendix 2) and will be managed according to protocol recommendations and requirements for the experimental arm of Cohort 1. Early progressing BRAF^{mut} patients receiving a fluoropyrimidine (5-FU/LV or capecitabine), bevacizumab, and atezolizumab as second-line treatment will be followed for safety and efficacy in accordance with the Maintenance Treatment Phase Schedule of Assessments (including eligibility, biomarker sampling and post-treatment follow-up) for Cohort 2 (see Appendix 3) and will be managed according to protocol recommendations and requirements for the experimental arm of Cohort 2. This includes continuation of therapy beyond progression per RECIST 1.1 as described for Maintenance Treatment Phase patients receiving atezolizumab.

Figure 1: Study Design



FP = fluoropyrimidine (5-FU/LV or capecitabine); 5-FU/LV = 5-fluorouracil/leucovorin; MSI -H= high microsatellite instability; MSS = microsatellite stable

a. Patients who progress early and who are not BRAF^{mut} will enter the Post-treatment Follow-up Phase with initiation of 2nd-line treatment per Investigator discretion

b. Randomization stratified by: Cohorts 1 and 2- region (EU, Americas, Africa or Asia), induction treatment response (CR/PR vs. SD); Cohort 3- induction treatment response (CR/PR vs. SD), HER2 IHC (IHC0/ IHC1+/IHC2+ vs. IHC3+); Cohort 4- region (EU vs. rest of world), induction treatment response (CR/PR vs. SD), microsatellite stability (MSI-H vs. MSS), RAS status (wild-type KRAS and NRAS vs. mutant KRAS and/or NRAS)

c. Patients discontinuing study treatment for any reason during the Induction or Maintenance Treatment Phases will enter the Post-treatment Follow-up Phase.

Study Conduct

A Steering Committee (SC) will be responsible for overseeing the general conduct of the study. An iDMC will be responsible for evaluating the safety of the patients participating in the trial at regular intervals throughout the study. This includes ongoing evaluation of benefit-risk balance based on accumulating safety and, as warranted, efficacy data. The iDMC will make recommendations as to whether cohort recruitment should continue based on each interim evaluation. In addition, when necessary due to the nature of prior experience with a particular experimental regimen, the iDMC will conduct a safety run-in review of a pre-specified number of initial patients (e.g. as conducted for the initial patients treated with '5-FU/LV + cetuximab + vemurafenib'). Safety run-ins deemed necessary for additional cohorts will be specified in the protocol. The schedule of iDMC reviews will be determined by the iDMC and described in the iDMC Charter. Additional data are provided in the respective SC and iDMC Charters.

Number of Patients

Before study enrolment was closed prematurely, approximately 1,820 patients were expected to be screened and approximately 1,400 patients were expected to be enrolled in the Induction Treatment Phase of the study in order to randomise the target sample size in each maintenance cohort. This included 405 patients in Cohort 2. Accrual into Cohort 4 was terminated prior to reaching the target sample size. Due to early closure of study enrolment, target sample sizes will not be reached for Cohorts 1 and 3.

Screening procedures

For comparability reasons, only the archival primary tumour sample from the original diagnosis will be used for the biomarker assessment which determines treatment assignment during the Maintenance Treatment Phase, as this material will be available for all patients. To be eligible for the study, patients must have an archival primary tumour sample for biomarker assessment for cohort assignment. If the tumour block is not available, ≥ 20 slides cut from the primary tumour sample will be accepted as an alternative. The sample (block or slides) must be shipped to the designated lab with confirmation of sample receipt provided by the laboratory prior to study enrolment. Biomarker analyses for cohort assignment will be conducted during the Induction Treatment Phase and these results will only be available during the Induction Treatment Phase and not during Screening. Patients with an adequate tumour sample but with unknown biomarker status due to lack of determinant result (e.g. due to technical issues) may still be included in the study depending on the addition of future cohorts.

For enrolment into the study, patients who do not meet the study eligibility criteria (screen failures) may be re-screened within 7 days of the date they are determined to be screen failures. Re-screening of a patient > 7 days after screen failure is allowed only with prior approval from the Medical Monitor. Patients cannot be re-screened for the study more than once.

Target Population

The target study population consists of patients with mCRC who have not received any prior chemotherapy in the metastatic setting. Cohort-specific target populations are further defined by specific biomarker profiles.

The "All Cohort" eligibility criteria are evaluated prior to initiating the first cycle of study treatment during the Induction Treatment Phase. Cohort-specific exclusion criteria must be assessed within 3 weeks of completing Induction Treatment Phase. Biomarker assessments will be completed prior to randomisation, as the results of the biomarker assessments are required to identify the intended cohort in order to complete the appropriate cohort-specific eligibility assessments.

Inclusion Criteria

Patients must meet the following criteria for study entry:

All Cohorts

Patient Status

1. Have provided written informed consent prior to any study specific procedures
2. Willing and able to comply with the protocol
3. ≥ 18 years of age
4. ECOG status of ≤ 2 (see Appendix 8)
5. At least 16 weeks of life expectancy at time of entry into the study

Disease-related

6. Histologically confirmed CRC with mCRC confirmed radiologically
7. Measurable, unresectable disease according to RECIST 1.1
8. No prior chemotherapy for CRC in the metastatic setting
9. Archival tumour formalin-fixed paraffin-embedded tissue (FFPET) block from the primary tumour obtained at the time of the initial diagnosis must be shipped to the Sponsor's designated laboratory with sample receipt confirmed by the laboratory. If the tumour block is not available, ≥ 20 slides cut from the primary tumour sample will be accepted as an alternative (see Appendix 17). The slides must be shipped with receipt confirmed by the Sponsor's designated laboratory prior to study enrolment.

Exclusion Criteria

Patients who meet any of the following criteria will be excluded from study entry:

All Cohorts

Other Prior or Current Treatments

1. Less than 6 months from completion of any prior neoadjuvant or adjuvant chemotherapy or radiotherapy
2. Prior or current treatment with bevacizumab or any other anti-angiogenic drug (i.e. anti-VEGF or vascular endothelial growth factor receptor [VEGFR] therapies or tyrosine kinase inhibitors)
3. Current or recent (within 10 days of start of study induction treatment) use of aspirin (> 325 mg/day), clopidogrel (> 75 mg/day), therapeutic oral or parenteral anticoagulants, or thrombolytic agents for therapeutic purposes.

   Note: The use of full-dose oral or parenteral anticoagulants is permitted as long as the international normalised ratio (INR) or activated partial thromboplastin time (aPTT) is within therapeutic limits (according to the medical standard of the institution) and the patient has been on a stable dose of anticoagulants for at least two weeks prior to the start of study induction treatment. Prophylactic use of anticoagulants is allowed.
4. Requirement for treatment with any medicinal product that contraindicates the use of any of the study medications, may interfere with the planned treatment, affects patient compliance or puts the patient at high risk for treatment-related complications
5. Treatment with any other investigational agent within 28 days or 5 investigational agent half-lives (whichever is longer) prior to the start of study induction treatment

Haematological, Biochemical and Organ Function

6. Inadequate haematological function indicated by one or more of the following:
   - Absolute neutrophil count (ANC) < 1.5 x 10^9/L
   - Platelet count < 100 x 10^9/L
   - Haemoglobin < 9 g/dL (patients may have transfusions and/or growth factors to attain adequate haemoglobin)
7. Inadequate liver function indicated by one or more of the following:
   - Total bilirubin ≥ 1.5 x upper limit of normal (ULN)
   - Aspartate transaminase (AST) or alanine aminotransferase (ALT) ≥ 2.5 x ULN (≥ 5 x ULN in patients with known liver metastases)
   - Alkaline phosphatase (ALP) ≥ 2 x ULN (≥ 5 x ULN in patients with known liver metastases)
8. Inadequate renal function indicated by one or more of the following:
   - Serum creatinine > 1.25 x ULN or calculated creatinine clearance < 50 ml/min
   - Urine dipstick for proteinuria ≥ 2+ unless a 24-hour urine protein < 1 g of protein is demonstrated
9. INR > 1.5 or aPTT > 1.5 x ULN within 7 days prior to the start of study induction treatment for patients not receiving anti-coagulation. For patients, receiving anticoagulants INR and aPTT must be within the medical standard of enrolling institution.

   The use of full-dose oral or parenteral anticoagulants is permitted as long as the INR or aPTT is within therapeutic limits (according to the medical standard of the enrolling institution) and the patient has been on a stable dose of anticoagulants for at least two weeks prior to the start of study induction treatment.

General Criteria

10. Active infection requiring intravenous antibiotics at the start of study induction treatment
11. Previous or concurrent malignancy, except for adequately treated basal or squamous cell skin cancer, *in situ* cervical cancer, or other cancer for which the patient has been disease-free for five years prior to study entry
12. Evidence of any other disease, neurologic or metabolic dysfunction, physical examination finding or laboratory finding giving reasonable suspicion of a disease or condition that contraindicates the use of any of the study medications, puts the patient at higher risk for treatment-related complications or may affect the interpretation of study results
13. Inadequately controlled hypertension (defined as systolic blood pressure > 150 mmHg and/or diastolic blood pressure > 100 mmHg)
14. Prior history of hypertensive crisis or hypertensive encephalopathy
15. Clinically significant (i.e. active) cardiovascular disease, for example cerebrovascular accidents ≤ 6 months prior to start of study induction treatment, myocardial infarction ≤ 6 months prior to study enrolment, unstable angina, New York Heart Association (NYHA) Functional Classification Grade 2 or greater congestive heart failure, or serious cardiac arrhythmia uncontrolled by medication or potentially interfering with protocol treatment
16. History or evidence upon physical or neurological examination of central nervous system (CNS) disease (e.g. seizures) unrelated to cancer unless adequately treated with standard medical therapy
17. Significant vascular disease (e.g. aortic aneurysm requiring surgical repair or recent arterial thrombosis) within 6 months of start of study induction treatment
18. Any previous venous thromboembolism > National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) Grade 3 within 12 months prior to start of study induction treatment

19. Active, symptomatic or untreated CNS metastases; CNS disease other than supratentorial or cerebellar metastases (i.e. patients with metastases to midbrain, pons, medulla or spinal cord are excluded); history of or known carcinomatous meningitis.

    Note: Treatment of brain metastases, either by surgical or radiation techniques, must have been completed > 4 weeks prior to start of study induction treatment. Patients requiring anticonvulsants or corticosteroids for symptom control and patients with evidence of interim progression between the completion of CNS-directed therapy and study baseline disease assessments are excluded from the study.

    Note: Patients without measurable disease outside the CNS are excluded from the study.

20. History of haemoptysis ≥ Grade 2 (defined as ≥ 2.5 mL bright red blood per episode) within 1 month of start of study induction treatment
21. History or evidence of inherited bleeding diathesis or significant coagulopathy at risk of bleeding (i.e. in the absence of therapeutic anticoagulation)
22. Surgical procedure (including open biopsy, surgical resection, wound revision, or any other major surgery involving entry into a body cavity) or significant traumatic injury within 28 days prior to start of study induction treatment, or anticipation of need for major surgical procedure during the course of the study
23. Minor surgical procedure including placement of a vascular access device, within 2 days of start of study induction treatment
24. History of abdominal fistula, gastrointestinal (GI) perforation, intra-abdominal abscess or active GI bleeding within 6 months prior to start of study induction treatment
25. Serious, non-healing wound, active ulcer, or untreated bone fracture
26. Known hypersensitivity to any component of any of the study induction or maintenance treatment medications
27. History of severe allergic, anaphylactic, or other hypersensitivity reactions to chimeric or humanised antibodies or fusion proteins
28. Known dihydropyrimidine dehydrogenase (DPD) deficiency
29. Pregnancy or lactation. A serum pregnancy test is required within 7 days prior to start of study induction treatment, or within 14 days with a confirmatory urine pregnancy test within 7 days prior start of study induction treatment
30. For women who are not post-menopausal (< 12 months of non-therapy-induced amenorrhea) or surgically sterile (absence of ovaries and/or uterus): refusal to use a highly effective contraceptive method (i.e. with a failure rate of < 1% per year such as sexual abstinence, hormonal implants, combined oral contraceptives, vasectomised partner), during both the Induction and Maintenance Treatment Phases and for at least 7 months after the last dose of study medication. Periodic abstinence [e.g., calendar, ovulation, symptothermal, postovulation methods] and withdrawal are not acceptable methods of contraception. A combination of male condom with cap, diaphragm or sponge with spermicide (double barrier methods) is not considered highly effective, birth control methods. Acceptable methods of contraception may include total abstinence in cases where the lifestyle of the patient ensures compliance. A vasectomised partner is a highly effective birth control method provided that partner is the sole sexual partner of the MODUL trial participant and that the vasectomised partner has received medical assessment of the surgical success. Some of the study-related medication, such as vemurafenib may decrease the plasma exposure of those hormonal contraceptives predominantly metabolised by CYP3A4. In these cases, the use of an alternate highly effective method of contraception must be considered.
31. For men: refusal to use a highly effective contraceptive method (i.e. with a failure rate of < 1% per year such as vasectomy, sexual abstinence or female partner use of hormonal implants or combined oral contraceptives) during both the Induction and Maintenance Treatment Phases and for a period of at least 6 months after the last dose of study medication. Periodic abstinence [e.g., calendar, ovulation, symptothermal, postovulation methods] and withdrawal are not acceptable

methods of contraception. A combination of male condom with either cap, diaphragm or sponge with spermicide (double barrier methods) is not considered highly effective, birth control methods. Acceptable methods of contraception may include total abstinence in cases where the lifestyle of the patient ensures compliance. A vasectomised MODUL trial participant is a highly effective birth control method provided that the MODUL trial participant has received medical assessment of the surgical success. Men must also agree not to donate sperm for at least 6 months after their last dose of study drug.

Cohort-Specific Exclusion Criteria

The following criteria will be assessed following biomarker-based cohort assignment:

Additional criteria for Cohort 1

1. Have not provided informed consent to participate in Cohort 1.

   Note: At study centers where a single informed consent form is used, informed consent to participate in any maintenance cohort will have already been provided at study entry. Patients enrolled at centers using two informed consent forms must provide maintenance cohort-specific consent after cohort assignment and prior to cohort-specific eligibility assessments other than eligibility assessments already conducted as part of routine care.

2. Inability to swallow pills.
3. Refractory nausea and vomiting, malabsorption, external biliary shunt or significant bowel resection that would preclude adequate absorption.
4. History or presence of clinically significant ventricular or atrial dysrhythmias ≥ NCI CTCAE Grade 2
5. Corrected QT (QTc) interval ≥ 450 msec as assessed within 3 weeks prior to randomization, long QT syndrome, uncorrectable electrolyte abnormalities (including magnesium) or requirement for medicinal products known to prolong the QT interval
6. For women who are not post-menopausal (< 12 months of non-therapy-induced amenorrhea) or surgically sterile (absence of ovaries and/or uterus): refusal to use an alternate highly effective contraceptive method (i.e. with a failure rate of < 1% per year such as sexual abstinence, vasectomised partner) other than hormonal contraceptives, during both the Induction and Maintenance Treatment Phases and for at least 7 months after the last dose of study medication. Vemurafenib may decrease the plasma exposure of those hormonal contraceptives predominantly metabolised by CYP3A4.
7. ECOG PS > 2.

   Note: Due to the potential risks associated with treatment in the experimental arm of Cohort 1, patients with ECOG PS = 2 and a low body mass index (BMI) must be judged by the Investigator as adequately physically fit to receive treatment with 5-FU/LV + cetuximab + vemurafenib to be considered eligible. See protocol Section 4.3.2.2.2.

Additional criteria for Cohort 2

1. Have not provided informed consent to participate in Cohort 2

   Note: At study centers where a single informed consent form is used, informed consent to participate in any maintenance cohort will have already been provided at study entry. Patients enrolled at centers using two informed consent forms must provide maintenance cohort-specific consent after cohort assignment and prior to cohort-specific eligibility assessments other than eligibility assessments already conducted as part of routine care.

2. Known hypersensitivity or allergy to Chinese hamster ovary cell products
3. History of autoimmune disease including but not limited to myasthenia gravis, myositis, autoimmune hepatitis, systemic lupus erythematosus, rheumatoid arthritis, inflammatory bowel

disease, vascular thrombosis associated with antiphospholipid syndrome, Wegener's granulomatosis, Sjögren's syndrome, Guillain-Barré syndrome, multiple sclerosis, vasculitis, or glomerulonephritis (see Appendix 9 for a more comprehensive list of autoimmune diseases)

Patients with the following are eligible:

- a history of autoimmune-related hypothyroidism on a stable dose of thyroid replacement hormone
- controlled Type 1 diabetes mellitus on a stable insulin regimen
- eczema, psoriasis, lichen simplex chronicus, or vitiligo with dermatologic manifestations only (e.g. patients with psoriatic arthritis would be excluded) are permitted provided that they meet the following conditions:
  - rash must cover less than 10% of body surface area (BSA)
  - disease is well controlled prior to randomization and only requires low potency topical steroids
  - no acute exacerbations of underlying condition within the previous 12 months (not requiring PUVA [psoralen plus ultraviolet A radiation], methotrexate, retinoids, biologic agents, oral calcineurin inhibitors, high potency or oral steroids)

4. Prior allogeneic bone marrow transplantation or prior solid organ transplantation
5. History of idiopathic pulmonary fibrosis (including pneumonitis), drug-induced pneumonitis, organizing pneumonia (i.e., bronchiolitis obliterans, cryptogenic organizing pneumonia), or evidence of active pneumonitis on most recent chest imaging (CT scan or MRI)

   Note: History of radiation pneumonitis in the radiation field (fibrosis) is permitted.
6. Positive test for human immunodeficiency virus (HIV)
7. Active hepatitis B (defined as having a positive hepatitis B surface antigen [HBsAg] test prior to randomization) or hepatitis C

   Note: Patients with past hepatitis B virus (HBV) infection or resolved HBV infection (defined as having a negative HBsAg test and a positive antibody to hepatitis B core antigen [anti-HBc] antibody test) are eligible.

   Patients positive for hepatitis C virus (HCV) antibody are eligible only if polymerase chain reaction (PCR) is negative for HCV RNA.
8. Active tuberculosis
9. Severe infection within 4 weeks prior to start of maintenance treatment including, but not limited to, hospitalization for complications of infection, bacteremia, or severe pneumonia; has signs or symptoms of significant infection or has received oral or IV antibiotics within 2 weeks prior to start of maintenance treatment.

   Note: Patients receiving prophylactic antibiotics (e.g. for prevention of a urinary tract infection or chronic obstructive pulmonary disease) are eligible.
10. Administration of a live, attenuated vaccine within 4 weeks prior to start of study maintenance treatment or anticipation that such a live attenuated vaccine will be required during the study
11. Prior treatment with CD137 agonists, anti-CTLA4, anti-PD-1, or anti-PD-L1 therapeutic antibody or pathway-targeting agents
12. Treatment with systemic immunostimulatory agents (including but not limited to interferons or interleukin-2) within 4 weeks or five half-lives of the drug, whichever is longer, prior to start of study maintenance treatment
13. Treatment with systemic corticosteroids or other systemic immunosuppressive medications (including but not limited to prednisone, dexamethasone, cyclophosphamide, azathioprine, methotrexate, thalidomide, and anti-tumour necrosis factor [TNF] agents) within 2 weeks prior to

start of study maintenance treatment, or requirement for systemic immunosuppressive medications during the trial.

Note: The use of inhaled corticosteroids for chronic obstructive pulmonary disease (≤ 10 mg oral prednisone or equivalent), mineralocorticoids (e.g., fludrocortisone) for patients with orthostatic hypotension, and low-dose supplemental corticosteroids for adrenocortical insufficiency are allowed.

Patients who have received acute, low-dose (≤ 10 mg oral prednisone or equivalent), systemic immunosuppressant medications may be enrolled in the study after discussion with and approval by the Medical Monitor.

14. If receiving a RANKL inhibitor (e.g. denosumab), unwilling to adopt alternative treatment such as (but not limited to) bisphosphonates, while receiving atezolizumab.

Additional criteria for Cohort 3

1. Have not provided informed consent to participate in Cohort 3

   Note: At study centers where a single informed consent form is used, informed consent to participate in any maintenance cohort will have already been provided at study entry. Patients enrolled at centers using two informed consent forms must provide maintenance cohort-specific consent after cohort assignment and prior to cohort-specific eligibility assessments other than eligibility assessments already conducted as part of routine care.

2. Inability to swallow pills
3. Left ventricular ejection fraction (LVEF) < 50% as assessed after completion of induction treatment by either 2D echocardiogram (ECHO) or multiple-gated acquisition (MUGA) (ECHO is the preferred method).
4. Clinically significant cardiovascular disease, including unstable angina, history of or active congestive heart failure of ≥ NYHA Grade 2, history of or ongoing serious cardiac arrhythmia requiring treatment (except for controlled atrial fibrillation and/or paroxysmal supraventricular tachycardia).
5. Current uncontrolled hypertension (systolic > 150 mmHg and/or diastolic > 100 mmHg) with or without medication
6. Current dyspnoea at rest due to complications of advanced malignancy or other disease requiring continuous oxygen therapy
7. Insulin-dependent diabetes
8. Current known infection with HIV, HBV, or HCV (active infection or carriers)
9. Requirement for concurrent use of the antiviral agent sorivudine (antiviral) or chemically related analogues, such as brivudine
10. Malabsorption syndrome, disease significantly affecting gastrointestinal function, resection of the stomach or small bowel, or ulcerative colitis
11. Known hypersensitivity to murine proteins

Additional Criteria for Cohort 4

1. Have not provided informed consent to participate in Cohort 4

   Note: At study centers where a single informed consent form is used, informed consent to participate in any maintenance cohort will have already been provided at study entry. Patients enrolled at centers using two informed consent forms must provide maintenance cohort-specific consent after cohort assignment and prior to cohort-specific eligibility assessments other than eligibility assessments already conducted as part of routine care.

2. Inability to swallow medications
3. Known hypersensitivity or allergy to Chinese hamster ovary cell products

4. History of autoimmune disease including but not limited to myasthenia gravis, myositis, autoimmune hepatitis, systemic lupus erythematosus, rheumatoid arthritis, inflammatory bowel disease, vascular thrombosis associated with antiphospholipid syndrome, Wegener's granulomatosis, Sjögren's syndrome, Guillain-Barré syndrome, multiple sclerosis, vasculitis, or glomerulonephritis (see Appendix 9 for a more comprehensive list of autoimmune diseases)

   Patients with the following are eligible:

   - a history of autoimmune-related hypothyroidism on a stable dose of thyroid replacement hormone
   - controlled Type 1 diabetes mellitus on a stable insulin regimen
   - eczema, psoriasis, lichen simplex chronicus, or vitiligo with dermatologic manifestations only (e.g. patients with psoriatic arthritis would be excluded) are permitted provided that they meet the following conditions:
     - rash must cover less than 10% of body surface area (BSA)
     - disease is well controlled prior to randomization and only requires low potency topical steroids
     - no acute exacerbations of underlying condition within the previous 12 months (not requiring PUVA [psoralen plus ultraviolet A radiation], methotrexate, retinoids, biologic agents, oral calcineurin inhibitors, high potency or oral steroids)
5. History of idiopathic pulmonary fibrosis (including pneumonitis), drug-induced pneumonitis, organizing pneumonia (i.e., bronchiolitis obliterans, cryptogenic organizing pneumonia), or evidence of active pneumonitis on most recent chest imaging (CT scan or MRI)

   Note: History of radiation pneumonitis in the radiation field (fibrosis) is permitted.
6. Malabsorption condition that would alter the absorption of orally administered medications
7. Amylase or lipase ≥ 1.5 × ULN within 14 days prior to maintenance treatment initiation
8. Serum albumin < 2.5 g/dL
9. LVEF < institutional lower limit of normal or < 50%, whichever is lower.
10. Poorly controlled hypertension, defined as a blood pressure consistently above 150/90 mmHg despite optimal medical management.
11. Uncontrolled pleural effusion, pericardial effusion or ascites requiring repeated drainage more than once every 28 days. Indwelling drainage catheters (e.g. PleurX®) are allowed.
12. Unstable angina, new onset angina within last 3 months, myocardial infarction within last 6 months and current congestive heart failure ≥ NYHA Grade 2
13. History of stroke, reversible ischemic neurological defect, or transient ischemic attack within 6 months prior to initiation of maintenance treatment
14. History or evidence of intracranial hemorrhage or spinal cord hemorrhage
15. Evidence of clinically significant vasogenic edema
16. Any hemorrhage or bleeding event ≥ NCI CTCAE Grade 3 within 28 days prior to initiation of maintenance treatment
17. History or evidence of retinal pathology on ophthalmologic examination that is considered a risk factor for central serous retinopathy, retinal vein occlusion, or neovascular macular degeneration

    Patients will be excluded if they currently have any of the following risk factors for retinal vein occlusion:

    - Uncontrolled glaucoma with intra ocular pressure ≥ 21 mmHg
    - Uncontrolled hypercholesterolemia > 300 mg/dL or 7.75 mmol/L
    - Uncontrolled hypertriglyceridemia > 300 mg/dL or 3.42 mmol/L
    - Fasting hyperglycemia > 160 mg/dL or 8.9 mmol/L

18. Positive HIV test
19. Active hepatitis B (defined as having a positive HBsAg test prior to randomization) or hepatitis C

    Note: Patients with past HBV infection or resolved HBV infection (defined as having a negative HBsAg test and a positive anti-HBc antibody test) are eligible.

    Patients positive for HCV antibody are eligible only if PCR is negative for HCV RNA.
20. Active tuberculosis
21. Severe infection within 4 weeks prior to start of maintenance treatment including, but not limited to, hospitalization for complications of infection, bacteremia, or severe pneumonia; has signs or symptoms of significant infection or has received oral or IV antibiotics within 2 weeks prior to start of maintenance treatment.

    Note: Patients receiving prophylactic antibiotics (e.g. for prevention of a urinary tract infection or chronic obstructive pulmonary disease) are eligible.
22. Prior allogeneic bone marrow transplantation or prior solid organ transplantation
23. Administration of a live, attenuated vaccine within 4 weeks prior to start of study maintenance treatment or anticipation that such a live attenuated vaccine will be required during the study
24. Prior treatment with CD137 agonists, anti-CTLA4, anti-PD-1, or anti-PD-L1 therapeutic antibody or pathway-targeting agents
25. Prior treatment with a MEK or ERK inhibitor
26. Treatment with systemic immunostimulatory agents (including but not limited to interferons or interleukin-2) within 4 weeks or five half-lives of the drug, whichever is longer, prior to start of study maintenance treatment
27. Treatment with systemic corticosteroids or other systemic immunosuppressive medications (including but not limited to prednisone, dexamethasone, cyclophosphamide, azathioprine, methotrexate, thalidomide, and anti-TNF agents) within 2 weeks prior to start of study maintenance treatment, or requirement for systemic immunosuppressive medications during the trial.

    Note: The use of inhaled corticosteroids for chronic obstructive pulmonary disease (≤ 10 mg oral prednisone or equivalent), and mineralocorticoids (e.g., fludrocortisone) for patients with orthostatic hypotension, and low-dose supplemental corticosteroids for adrenocortical insufficiency are allowed.

    Note: Patients who have received acute, low-dose (≤ 10 mg oral prednisone or equivalent), systemic immunosuppressant medications (e.g. a one-time dose of dexamethasone for nausea) may be enrolled in the study after discussion with and approval by the Medical Monitor.
28. If receiving a RANKL inhibitor (e.g. denosumab), unwilling to adopt alternative treatment such as (but not limited to) bisphosphonates, while receiving atezolizumab.
29. Consumption of foods, supplements or drugs that are potent CYP3A4 enzyme inducers or inhibitors ≤ 7 days before initiation of study maintenance treatment or expected concomitant use during maintenance treatment. These include St. John's wort or hyperforin (potent CYP3A4 enzyme inducer) and grapefruit juice (potent cytochrome P450 CYP3A4 enzyme inhibitor).

Length of Study

Study recruitment started in April 2015. Patient screening was temporarily suspended beginning in June 2016 for the addition of maintenance Cohorts 3 and 4. Screening and enrolment were again suspended in February 2018 to accommodate closure of accrual to Cohort 4. Study enrolment will not be re-opened. The entire study duration is estimated to be approximately 5 years.

End of Study

The end of the study is defined as the date when all study patients have discontinued study treatment and completed the adverse event reporting period and, if applicable, cohort-specific post-treatment follow-up safety assessments (see protocol Section 5.3.1 for adverse event reporting periods and post-treatment follow-up safety assessments). After this, the trial will end and no further data will be collected in the clinical database for this study.

Continued access to Roche investigational medicinal products (IMPs) used in the study will be in accordance with the Roche Global Policy on Continued Access to Investigational Medicinal Product.

Efficacy Outcome Measures

All Cohorts

Efficacy outcome measures will be assessed within each cohort (experimental arm vs. control arm) during the Maintenance Treatment Phase.

Primary

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

Secondary

- 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. Response will be determined by the Investigator according to RECIST 1.1 based on comparisons to the tumour assessment done at the end of the Induction Treatment Phase.
- DCR (defined as CR, PR or SD) during the Maintenance Treatment Phase. Response will be determined by the Investigator according to RECIST 1.1 based on comparisons to the tumour assessment done at the end 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

Safety Outcome Measures

All Cohorts

The safety outcome measures for this study are as follows:

- Incidence, nature and severity of all adverse events (graded according to NCI CTCAE v4.0)
- Incidence and nature of all Grade 3 – 5 AEs
- Grade 5 AEs or AEs leading to death on study treatment
- All SAEs
- Incidence and reasons for any premature discontinuation of any component of study treatment

- Incidence and reasons for any dose reductions or interruptions of any component of study treatment
- AEs of special interest
- Clinically significant changes in laboratory values

Adverse events 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 Outcome Measures

Cohorts 2 and 4- Experimental Arms Only

PFS in patients treated with atezolizumab defined as the time from randomisation into the Maintenance Treatment Phase until disease progression per Investigator assessment using mRECIST or death from any cause, whichever occurs first.

All Cohorts

The exploratory biomarker and microbiome outcome measures for this study include molecular markers/marker profiles and efficacy and/or safety outcomes. Efficacy outcomes considered for this analysis may include, but are not limited to, ORR, PFS and OS, as appropriate. Biomarkers, biomarker profiles and microbiomes may be assessed using various methodologies including, but not limited to, immunohistochemistry (single and multiplex), RNA and DNA analysis (e.g polymerase chain reaction; next generation sequencing; and mutation, expression and microsatellite instability analyses) of tumour and blood samples collected from all study patients as well as additional tumour samples and stool samples collected from patients participating in the Supplemental Biomarker Program.

Study Treatment

Induction Treatment Phase

All Cohorts

All patients will receive 4 months of study treatment in the Induction Treatment Phase. Treatment during this phase, based on Investigator's choice, will be either:

- eight 2-week cycles of 5-FU/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

and should be in accordance with locally approved prescribing information including any recommendations for pre-treatment (i.e. antiemetic therapies). The Investigator will select the FOLFOX regimen (e.g. FOLFOX-4, FOLFOX-6, modified FOLFOX-6, FOLFOX-7 or modified FOLFOX-7; see Appendix 6) also in accordance with local standards.

Maintenance Treatment Phase

All Cohorts

Each cohort will contain an experimental treatment arm based specifically on the patient's biomarker status based on the patient's archival tumour sample from the initial diagnosis (see Appendix 17 for additional details on cohort assignment). Patients with an adequate tumour sample but with unknown

biomarker status due to lack of determinant result (e.g. due to technical issues) may still be eligible depending on the addition of future cohorts. Each cohort will also include a control treatment arm containing a fluoropyrimidine and bevacizumab. Maintenance treatment will begin within 3 weeks of completing induction treatment.

For patients in Cohorts 1 and 3, and the control arms of Cohorts 2 and 4, study treatment during the Maintenance Treatment Phase will continue until disease progression (based on Investigator's assessment according to RECIST 1.1), unacceptable toxicity, initiation of another anti-cancer therapy, patient or physician decision to discontinue, or patient death, whichever occurs first.

For patients randomised to the experimental arms of Cohorts 2 and 4 (i.e. patients who are receiving atezolizumab), study treatment during the Maintenance Treatment Phase may continue after the first tumour assessment showing progression per RECIST 1.1 as long as they meet the following criteria as assessed by the Investigator:

- Evidence of clinical benefit
- Absence of symptoms and signs (including worsening of laboratory values, e.g. new or worsening hypercalcaemia) indicating unequivocal progression of disease
- No decline in ECOG performance status that can be attributed to disease progression
- Absence of tumour progression at critical anatomical sites (e.g. leptomeningeal disease) that cannot be managed by protocol-allowed medical interventions

Treatment should be discontinued if the next follow-up tumour assessment continues to demonstrate progression per RECIST 1.1 (as compared to the assessment at the end of induction treatment). If the next tumour assessment does not show progression per RECIST 1.1, the patient may continue maintenance treatment until such time as the treatment continuation criteria above are no longer met and/or two sequential tumour assessments show progression per RECIST 1.1.

Atezolizumab treated patients may be discontinued from study treatment during the Maintenance Phase for the following reasons other than loss of clinical benefit or persistent progression: unacceptable toxicity, initiation of another anti-cancer therapy, patient or physician decision to discontinue, or patient death, whichever occurs first.

Dose reductions or interruptions of IMPs are only allowed as recommended in the applicable Investigator's Brochure. If any drug of any study treatment regimen in either the Induction or Maintenance Treatment Phase is discontinued or held for > 21 days, approval from the Medical Monitor will be required before treatment can be re-initiated. If Medical Monitor approval is not obtained, the patient will come off all study treatment and will enter the Post-Treatment Follow-up Phase.

All Cohorts - Control Arms

The maintenance treatment regimen is the same for the control arms of all cohorts.

Fluoropyrimidine (5-FU/LV or capecitabine): dose and schedule will be according to local label, where applicable, or otherwise will be determined per the Investigator's discretion. Administration should be according to local prescribing information.

Bevacizumab: 5 mg/kg via 15 – 30 minute IV infusion on Day 1 of every 2-week cycle. Bevacizumab should be prepared and administered in accordance with local prescribing information.

Cohort 1 – Experimental Arm

Patients assigned to the experimental arm of Cohort 1 with an ECOG PS = 2 and a low BMI must be carefully assessed by the Investigator for physical fitness adequate for receipt of this regimen prior to initiating treatment. Such patients must be closely monitored through the maintenance treatment period.

5-FU: The first six patients in this cohort received 1,600 mg/m² 5-FU administered via 46-hour IV infusion, in combination with LV 400 mg/m² administered via 2-hour infusion, on Day 1 of every 2-week cycle. Subsequent patients in this cohort will receive 1,600 – 2,400 mg/m² 5-FU administered via 46-hour IV infusion (IV bolus is not permitted), in combination with LV 400 mg/m² administered via 2-hour infusion, on Day 1 of every 2-week cycle.

Cetuximab: The dose and scheduling of cetuximab is 500 mg/m² via IV infusion on Day 1 of every 2-week cycle. Cetuximab must be administered in hospital under the supervision of a physician experienced in the use of antineoplastic medicinal products. Cetuximab must be administered via infusion pump or syringe pump at a rate not exceeding 5 mg/min for the first administration and 10 mg/min for subsequent administrations. Close monitoring is required during the infusion and for at least 1 hour after the end of the infusion. Availability of resuscitation equipment must be ensured. Prior to the first infusion of cetuximab, patients must receive premedication with an antihistamine and a corticosteroid. This premedication is recommended prior to all subsequent infusions. Refer to cetuximab Package Insert (Appendix 14).

Vemurafenib: The dose and scheduling of vemurafenib is 960 mg b.i.d by mouth. Vemurafenib should be taken at approximately the same times each day, the first dose is to be taken in the morning and the second dose is to be taken approximately 12 hours later in the evening. Each dose should always be taken in the same manner i.e. either with or without a meal. Missed doses will not be made up.

Note: A safety run-in review of the first six patients treated with the experimental combination of '5-FU/LV + cetuximab + vemurafenib' was conducted in February 2016. The iDMC recommended that patients allocated to this regimen may now receive 5-FU at doses up to 2,400 mg/m². The iDMC will continue to monitor initial patients in this regimen treated with 5-FU doses ≥ 1,600 mg/m² and have also recommended that patients with ECOG PS = 2 and a low BMI be carefully assessed by the Investigator for physical fitness adequate for receipt of this regimen.

Cohort 2 - Experimental Arm

Fluoropyrimidine (5-FU/LV or capecitabine): 1,600 – 2,400 mg/m² 5-FU administered via 46-hour IV infusion (IV bolus is not permitted) on Day 1 of every 2-week cycle, and LV 400 mg/m² administered via a 2-hour infusion on day 1 every 2 weeks; or 1000 mg/m² twice-daily capecitabine (b.i.d.) by mouth given days 1-14 every 2 weeks followed by a one-week treatment break.

Bevacizumab: The dose and schedule of bevacizumab is 5 mg/kg via 15 – 30 minute IV infusion on Day 1 of every 2-week cycle. Bevacizumab should be prepared and administered in accordance with local prescribing information. Patients may be at risk of developing infusion / hypersensitivity reactions with bevacizumab. Close observation of the patient during and following the administration of bevacizumab is recommended as expected for any infusion of a therapeutic humanised monoclonal antibody. If a reaction occurs, the infusion should be discontinued and appropriate medical therapies should be administered. A systematic premedication is not warranted.

Atezolizumab: Atezolizumab is administered at a fixed dose of 800 mg via 60-minute IV infusion on Day 1 of every 2-week cycle. Atezolizumab must be administered in hospital under the supervision of a physician experienced in the use of antineoplastic medicinal products. For the first infusion, the patient's vital signs (heart rate, respiratory rate, blood pressures, and temperature) should be determined within 60 minutes before the infusion, every 15 ± 5 minutes during the infusion, and 30 ± 10 minutes after the infusion. For subsequent infusions, vital signs will be collected within 60 minutes before the infusion and should be collected during or after the infusion if clinically indicated or if symptoms occurred in the prior infusion. If the initial infusion is well tolerated, subsequent infusions will be done over a 30-minute time period. No premedication is indicated for the first dose of atezolizumab. Patients who experience an infusion-related reaction with Cycle 1 of atezolizumab may receive premedication with antihistamines or

antipyretics/analgesics (e.g. acetaminophen) for subsequent infusions. The rate of atezolizumab infusion should be modified in the event of an infusion-related reaction.

Cohort 3 - Experimental Arm

Capecitabine, trastuzumab and pertuzumab will be administered according to the doses and schedules described below. For the first treatment cycle, pertuzumab should be administered on Day 1, followed by the first dose of trastuzumab and capecitabine on Day 2. If the administration of all three agents is well tolerated in the first treatment cycle, they may be given sequentially on Day 1 (pertuzumab and trastuzumab should not be mixed in the same infusion bag) in subsequent cycles thereafter. If a patient cannot tolerate all three drugs given on the same day, pertuzumab should continue to be delivered on Day 1, with trastuzumab and capecitabine delivered on Day 2 for subsequent treatment cycles.

Capecitabine: 1000 mg/m^2 twice-daily capecitabine (b.i.d.; for a total daily dose of 2000 mg/m^2) by mouth given days 1-14 every 2 weeks followed by a one-week treatment break administered in accordance with local prescribing information. See Appendix 7 for capecitabine dose calculations by body surface area with corresponding tablet counts.

Trastuzumab: Trastuzumab is administered by IV infusion on Day 1 of every 3-week treatment cycle at an initial loading dose of 8 mg/kg followed by 6 mg/kg for subsequent doses. Trastuzumab must be administered in hospital under the supervision of a physician experienced in the use of antineoplastic medicinal products. The first infusion should be delivered over 90 minutes followed by a 60 minute observation period. If the first infusion is well tolerated without infusion-associated AEs, the second and subsequent infusions may be delivered over 30 minutes with an observation period of 30 minutes. Longer infusion and/or observation times can be maintained if there is any doubt about tolerability. No premedication will be allowed for the first dose of trastuzumab. Premedication may be administered for subsequent cycles at the discretion of the treating physician. The rate of trastuzumab infusion should be modified in the event of an infusion-related reaction.

Pertuzumab: Pertuzumab is administered by IV infusion on Day 1 of each 3-week treatment cycle at an initial fixed loading dose of 840 mg followed by 420 mg for subsequent doses. Pertuzumab must be administered in hospital under the supervision of a physician experienced in the use of antineoplastic medicinal products. The first infusion should be delivered over 60 minutes followed by a 60 minute observation period. The observation period for subsequent infusions may be between 30 and 60 minutes if the first infusion is well tolerated without infusion-associated AEs. No premedication will be allowed for the first dose of pertuzumab. Premedication may be administered for subsequent cycles at the discretion of the treating physician. The rate of pertuzumab infusion should be modified in the event of an infusion-related reaction.

Cohort 4 - Experimental Arm

In an Urgent Safety Measure Letter dated July 25, 2018, the Sponsor advised investigators to strongly consider discontinuing treatment in any Cohort 4 patients receiving experimental treatment. Investigators were advised to discuss appropriate next treatment options, including combination treatment with a fluoropyrimidine plus bevacizumab, with patients discontinuing experimental treatment. Please refer to protocol Section 3.1.2.4 for further details of the basis for Sponsor decisions for Cohort 4 and management of ongoing patients randomized to the experimental arm.

Cobimetinib: Cobimetinib is administered orally at a dose of 60 mg for 3 weeks followed by a 1 week treatment break (21/7 schedule). Treatment cycle length in this arm is 2 weeks. Cobimetinib will be administered daily every day of each odd numbered 2-week treatment cycle, and for the first 7 days only of each even numbered 2-week treatment cycle. Cobimetinib should be taken at the same time every day with or without food. If a dose is missed or vomiting occurs when a dose is taken, dosing should be resumed at the next scheduled dose.

Atezolizumab: Atezolizumab is administered at a fixed dose of 840 mg via 60-minute IV infusion on Day 1 of every 2-week cycle. Atezolizumab must be administered in hospital under the supervision of a physician experienced in the use of antineoplastic medicinal products. For anaphylaxis precautions, see Appendix 16. For the first infusion, the patient's vital signs (heart rate, respiratory rate, blood pressures, and temperature) should be determined within 60 minutes before the infusion, every 15 ± 5 minutes during the infusion, and 30 ± 10 minutes after the infusion. For subsequent infusions, vital signs will be collected within 60 minutes before the infusion and should be collected during or after the infusion if clinically indicated or if symptoms occurred in the prior infusion. If the initial infusion is well tolerated, subsequent infusions will be done over a 30-minute time period. No premedication is indicated for the first dose of atezolizumab. Patients who experience an infusion-related reaction with Cycle 1 of atezolizumab may receive premedication with antihistamines or antipyretics/analgesics (e.g. acetaminophen) for subsequent infusions. The rate of atezolizumab infusion should be modified in the event of an infusion-related reaction.

Post-Treatment Follow-up Phase

All Cohorts

Second-line treatment during the Post-Treatment Follow-up Phase is at the Investigator's discretion. However, patients who received atezolizumab should not receive other immunomodulatory agents for 10 weeks after maintenance treatment discontinuation.

$BRAF^{mut}$ Patients and Early Disease Progression

Exceptionally, $BRAF^{mut}$/MSS patients experiencing early disease progression during the induction treatment will have the option of proceeding immediately to receive second-line treatment with 5-FU/LV, cetuximab and vemurafenib. These patients will be followed for safety and efficacy in accordance with the Maintenance Treatment Phase Schedule of Assessments (including eligibility, biomarker sampling and post-treatment follow-up) for Cohort 1 (see Appendix 2) and will be managed according to protocol recommendations and requirements for the experimental arm of Cohort 1.

Similarly, $BRAF^{mut}$/MSI-H patients experiencing early disease progression during induction treatment will have the option of proceeding immediately to receive second-line treatment with a fluoropyrimidine (5-FU/LV or capecitabine), bevacizumab, and atezolizumab. These patients will be followed for safety and efficacy in accordance with the Maintenance Treatment Phase Schedule of Assessments (including eligibility, biomarker sampling and post-treatment follow-up) for Cohort 2 (see Appendix 3) and will be managed according to protocol recommendations and requirements for the experimental arm of Cohort 2.

Investigational Medicinal Products

The IMPs used in this study include:

- all non-fluoropyrimidine agents comprising the experimental arms of each maintenance treatment cohort (i.e. cetuximab and vemurafenib in Cohort 1, bevacizumab and atezolizumab in Cohort 2, trastuzumab and pertuzumab in Cohort 3, cobimetinib and atezolizumab in Cohort 4)
- bevacizumab in the Induction Treatment Phase
- bevacizumab in the control arms of each maintenance treatment cohort
- cetuximab, vemurafenib, bevacizumab and atezolizumab administered as optional second-line treatments to early progressing $BRAF^{mut}$ patients

Non-Investigational Medicinal Products

Non-IMPs used in this study include all fluoropyrimidine agents (i.e. 5-FU and capecitabine) and leucovorin administered during the Induction and Maintenance Treatment Phases and as optional

second-line treatment to early progressing BRAF^{mut} patients. Oxaliplatin administered as part of induction treatment is also considered a non-IMP.

Statistical Methods

All Cohorts

The cohorts will be based on different biomarkers (see Appendix 17), with each cohort consisting of an experimental treatment arm and a control arm. The inclusion of a control group allows discrimination of patient outcomes caused by the experimental treatment from outcomes caused by other factors. Randomisation avoids systematic differences (bias) between the groups with respect to known or unknown baseline variables that could affect outcome. The treatment for patients in the control arms represents standard of care.

The primary objective of the study is to evaluate PFS per RECIST 1.1 within each cohort.

Provided the iDMC does not recommend discontinuation of enrolment to a cohort or enrolment is not otherwise discontinued prior to a cohort reaching its target sample size, the primary analysis will occur for each cohort when the target number of PFS events has been reached. Secondary endpoints will also be summarised at this time. Analyses of any cohort closed to accrual before its target sample size is reached will be described in an SAP and will depend on accrual at the time of closure.

Update on statistical analysis plans and cohort status following premature closure of study enrolment: Accrual to Cohort 2 was completed in November 2016. Accrual to Cohort 4 was closed in February 2018 due to iDMC recommendations as a result of an unfavourable benefit-risk evaluation (see protocol Section 3.1.2.4). Study enrolment was suspended at the time of discontinuation of accrual to Cohort 4 (February 2018) and will remain permanently closed to further enrolment. Cohorts 1, 3 and 4 will not reach their target sample size. As originally planned for cohorts reaching their target number of PFS events (applies to Cohort 2 only), an update analysis of efficacy and safety parameters will be conducted based on 24 months survival follow-up after the clinical cut-off date (CCOD) for the primary analysis. The CCOD for the Cohort 2 primary analysis was May 31, 2017. The Cohort 2 update analysis will be conducted based on a CCOD of May 31, 2019. The primary analysis for cohorts 1, 3 and 4 will be conducted at the same time as the Cohort 2 update analysis (i.e. based on the same CCOD of May 31, 2019).

The final study analysis for all cohorts will be conducted after all patients in the study have discontinued study treatment and completed the adverse event reporting period and any applicable post-treatment follow-up safety assessments (see protocol Section 5.3.1 for adverse event reporting periods and post-treatment follow-up safety assessments). Data will be summarised using appropriate summary statistics: mean, standard deviation, median, quartiles and range (minimum and maximum) for continuous variables, and number and percentage for categorical variables.

Analysis Populations

For each cohort, the Intent-To-Treat (ITT) Population will include patients entered into the Maintenance Treatment Phase of the study, irrespective of whether or not they received study medication. In this population, patients will be allocated to the study maintenance treatment into which they were randomised. The ITT Population will be used for all efficacy analyses.

The Per Protocol Population will not be defined for this study but major protocol violations will be listed.

The Safety Population will include all patients who received at least one dose of study medication during the Induction or Maintenance Treatment Phases. Patients will be allocated to the treatment regimen that they actually received. The Safety Population will be used for all safety analyses.

Statistical Hypotheses

Cohorts 1 and 3

The null and alternative hypotheses when comparing PFS between the two randomised treatments in Cohort 1 (Arm A: 5-FU/LV with cetuximab and vemurafenib vs. Arm B: fluoropyrimidine and bevacizumab) and in Cohort 3 (Arm A: capecitabine with trastuzumab and pertuzumab vs. Arm B: fluoropyrimidine and bevacizumab) are:

H_0: the distribution of the PFS time is the same in the two treatment groups

PFS (Arm A) = PFS (Arm B)

H_1: the distribution of the PFS time is different in the two treatment groups

specifically PFS (Arm A) > PFS (Arm B)

If the hazard ratio (HR) of Arm A compared to Arm B is assumed to be constant over time, then the null and alternative hypotheses are:

H_0: HR = 1 vs. H_1: HR < 1

Due to the relatively low prevalence of mCRC patients with HER2+ or $BRAF^{mut}$ disease, the formal statistical tests for Cohorts 1 and 3 will be one-sided and performed at an alpha level (type I error rate) of 10%.

Cohorts 2 and 4

The null and alternative hypotheses when comparing PFS between the two randomised treatments in Cohort 2 (Arm A: fluoropyrimidine with bevacizumab and atezolizumab vs. Arm B: fluoropyrimidine and bevacizumab) and in Cohort 4 (Arm A: cobimetinib with atezolizumab vs. Arm B: fluoropyrimidine and bevacizumab) are:

H_0: the distribution of the PFS time is the same in the two treatment groups

PFS (Arm A) = PFS (Arm B)

H_1: the distribution of the PFS time is different in the two treatment groups

PFS (Arm A) ≠ PFS (Arm B)

If the HR of Arm A compared to Arm B is assumed to be constant over time, then the null and alternative hypotheses are:

H_0: HR = 1 vs. H_1: HR ≠ 1

The formal statistical tests for Cohorts 2 and 4 will be two-sided and performed at an alpha level (type I error rate) of 5%.

Primary Endpoint

All Cohorts

The primary efficacy endpoint of PFS is defined as the time from randomisation into the Maintenance Treatment Phase until disease progression per Investigator assessment using RECIST 1.1 or death from any cause, whichever occurs first. Tumour size will be calculated using the sum of the longest diameters of all target lesions, and reduction will be based on comparisons to the tumour assessment done at the end of the Induction Treatment Phase.

Patients without an event will be censored at the date of their last evaluable tumour assessment or, if this is not available, at the date of randomisation. For each cohort, the primary analysis of PFS will occur when the target number of PFS events has been reached.

Within each cohort, PFS will be presented graphically for each treatment group using the Kaplan-Meier method. Estimates and the corresponding 95% confidence interval will be reported by treatment group for median survival time, and for the 4-, 6- and 12-month PFS rates.

Within each cohort, the comparison of PFS between the treatment groups will be performed using an unstratified log-rank test. In addition, a Cox regression will be performed with treatment and applicable stratification variables (biomarkers, geographic region and/or response after induction treatment) as terms in the model. The estimated hazard ratio and its corresponding 95% confidence interval will be presented.

The timing and methods of the primary efficacy endpoint analyses for any cohort closed to accrual before its target sample size is reached may differ from above. These will be described in the SAP applicable to the cohort and will depend on accrual at the time of early closure.

Secondary Efficacy Endpoints

All Cohorts

The secondary efficacy endpoints for each cohort are OS, ORR, DCR, TTR, DoR and ECOG performance status.

OS is defined as the time from randomisation until death from any cause. Patients who are still alive at the time of analysis (clinical cut-off) and patients who are lost to follow-up will be censored at their last clinical assessment date.

Best overall response will be assessed for all patients after randomisation until disease progression. ORR will be calculated as the proportion of patients with a best overall response of CR or PR determined according to RECIST 1.1. ORR will be summarised and presented along with the 95% Clopper-Pearson confidence interval.

DCR will be calculated as the proportion of patients with a best overall response of CR, PR or SD as determined according to RECIST 1.1. DCR will be summarised and presented along with the 95% Clopper-Pearson confidence interval.

TTR will be calculated as the time from randomisation to the first occurrence of a documented objective response (CR or PR) determined according to RECIST 1.1.

DoR will be assessed for all patients after randomisation until PD. Only patients with a best overall response of CR or PR per RECIST 1.1 are considered responders. The duration of response is the time from the first assessment of CR or PR until disease progression or death from any cause, whichever occurs first.

The secondary time-to-event endpoints will be analysed by the same methods and at the same time as the primary endpoint.

ECOG performance status will be summarised over time.

Safety Endpoints

All Cohorts

Verbatim adverse event (AE) data will be mapped to Medical Dictionary for Regulatory Activities (MedDRA) thesaurus terms.

All treatment-emergent AEs occurring during or after the first dose of study medication will be summarised by treatment group in frequency tables, as follows:

- By preferred term and system organ class
- By severity of all adverse events (graded according to NCI CTCAE v4.0)
- Grade 3 – 5 AEs
- Grade 5 AEs or AEs leading to death on study treatment

- All SAEs
- AEs leading to premature discontinuation of any component of study treatment
- AEs leading to dose reduction or interruption of any component of study treatment
- AEs of special interest

The above safety data will be summarised separately for the Induction and Maintenance Treatment Phases overall and by individual maintenance treatment cohort.

Deaths reported during the study treatment period and those reported during follow-up after treatment completion/discontinuation will be summarised.

Study medication exposure will be separately summarised by number of cycles, duration, dose and dose intensity.

Vital signs data, clinical laboratory parameters, concomitant medication and subsequent anti-cancer therapy will also be summarised.

Analysis for Exploratory Outcome Measures

Cohorts 2 and 4 - Experimental Arms Only

The exploratory efficacy endpoint of PFS in patients treated with atezolizumab is defined as the time from randomisation into the Maintenance Treatment Phase until disease progression per Investigator assessment using mRECIST or death from any cause, whichever occurs first. Patients without an event will be censored at the date of their last evaluable tumour assessment or, if this is not available, at the date of randomisation. PFS may be presented graphically using the Kaplan-Meier method. Estimates and the corresponding 95% confidence interval may be reported for the 4-, 6- and 12-month PFS rates.

All Cohorts

Biomarker analyses will be of exploratory nature only, utilizing all available data obtained from archival tumour samples from initial diagnoses, all tumour and blood samples collected during the study (including additional tumour samples collected from Supplemental Biomarker Program participants), and stool samples collected during the study from Supplemental Biomarker Program participants. These analyses will be of exploratory nature only, using descriptive methods with no fixed hypotheses testing.

With the ongoing analyses of the study's various biomarker-based cohorts, more information on the concordance of different biomarkers will be collected and summarised. Relevant findings will be discussed with the study's SC in order to conduct further exploratory biomarker analyses accordingly.

Interim Analyses

The iDMC will evaluate accumulating safety and efficacy data within each cohort to assure these data continue to support an early positive benefit-risk ratio and to confirm that continued enrolment into each cohort is appropriate. The amount of efficacy data to be assessed in a given cohort will be determined by the iDMC at a preceding iDMC meeting. Details of this process are described in the iDMC charter. Decisions on what efficacy data have to be evaluated for each cohort will be documented in the iDMC meeting minutes. In addition, the iDMC will review data from any safety run-in patients required for an experimental regimen (e.g. as conducted for the initial patients treated with the experimental combination of '5-FU/LV + cetuximab + vemurafenib'). These safety run-ins will be specified in the protocol.

Determination of Sample Size

Before study enrolment was closed prematurely, approximately 1,820 patients were expected to be screened and approximately 1,400 patients were expected to be enrolled in the Induction Treatment Phase of the study in order to randomise the planned number of patients in each of the maintenance

cohorts (see Table 1). Cohort 2 reached its target sample size and was closed to further accrual. Cohort 4 was closed to accrual with 99 patients randomized (i.e. prior to reaching the target sample size per Table 1). Due to early closure of study enrolment, target sample sizes will not be reached in Cohort 1 (final n=60) or Cohort 3 (final n=5).

Within each cohort, the required sample size is based on the comparison of PFS between the treatment groups and an assumed recruitment period of 11 months for Cohorts 2 and 4. Median PFS assumed for each cohort and treatment arm are shown in Table 1.

Table 1: PFS and Sample Size Estimates per Cohort

Cohort	Median PFS (months)		Target Sample Size
	Experimental treatment group	Control group (FP and bevacizumab)	
Cohort 1	7	4.9	126
Cohort 2	11.5	7.5	405
Cohort 3	11.5	7.5	90
Cohort 4	11.5	7.5	405

Additional details of the sample size calculation inputs are found in the statistical section of the protocol.

Appendix 2: Schedule of Assessments for All Patients (Screening / Baseline and Induction Treatment Phase)

					Patients who have PD during or at end of Induction Treatment Phase or who refuse Maintenance Treatment or who are not eligible for any study cohort	
	Screening / Baseline		Induction Treatment Phase [a]		Study Treatment Discontinuation Visit [b]	Post-Treatment Follow-Up Phase [c]
	≤ 28 days	≤ 7 days	Day 1 Cycle 1	Every 2 cycles (every 4 weeks)	(≤ 30 days after last dose of study treatment)	Every 3 months *until May 31, 2019 (see Appendix 19)*
Informed consent [d]	x					
Confirmation of general eligibility [e]	x	x		As required		
Demographics and medical history [f]	x					
Vital signs and weight [g]	x	x	x	x	x	
Physical examination[h]	x		x	x	x	
ECOG performance status [i]		x	x	x	x	
Concomitant medications [j]	x	x	x	x	x	
Haematology and blood chemistry [k]		x		x	x	
INR, aPTT (select patients) [l]		x		x		
Urinalysis (dipstick) [m]		x		x	x	
Pregnancy test [n]		x		If clinically indicated		
Tumour assessments [o]	x			Mandatory at end of Induction Treatment Phase		According to local standard of care until disease progression

					Patients who have PD during or at end of Induction Treatment Phase or who refuse Maintenance Treatment or who are not eligible for any study cohort	
	Screening / Baseline		Induction Treatment Phase [a]		Study Treatment Discontinuation Visit [b]	Post-Treatment Follow-Up Phase [c]
	≤ 28 days	≤ 7 days	Day 1 Cycle 1	Every 2 cycles (every 4 weeks)	(≤ 30 days after last dose of study treatment)	Every 3 months *until May 31, 2019 (see Appendix 19)*
Archival primary tumour tissue for biomarker assessment [p]	x					
Metastatic tumour tissue for exploratory biomarker assessment [q] Collection of these samples discontinued as of May 2018	No sample collection			No sample collection Supplemental Biomarker Program CLOSED		
Whole blood sample [r]			x			
Plasma samples [r]			x	Cycles 4, 6 and 8		At time of progression (if patient has not yet progressed)
Stool sample Supplemental Biomarker Program closed as of May 2018. Collection of these samples has been discontinued.	No sample collection Supplemental Biomarker Program CLOSED				No sample collection Supplemental Biomarker Program CLOSED	
Adverse events (including SAEs) [s]	x	x	x	Every cycle	x	x (as applicable)
Study medication administration [t]			x Administered every 2 weeks			

					Patients who have PD during or at end of Induction Treatment Phase or who refuse Maintenance Treatment or who are not eligible for any study cohort	
	Screening / Baseline		Induction Treatment Phase [a]		Study Treatment Discontinuation Visit [b]	Post-Treatment Follow-Up Phase [c]
	≤ 28 days	≤ 7 days	Day 1 Cycle 1	Every 2 cycles (every 4 weeks)	(≤ 30 days after last dose of study treatment)	Every 3 months *until May 31, 2019 (see Appendix 19)*
Subsequent anti-cancer therapies (see [c])						x
Patient survival (see [c])					x	x

a. With the exception of Cycle 1, all other study visits and assessments should be performed within ± 7 days of the scheduled date.

b. Patients who experience PD during or at the end of the Induction Treatment Phase, or who refuse to go into the Maintenance Treatment Phase or who are not eligible for any study cohort, will undergo a Study Treatment Discontinuation Visit within 30 days after the last dose of study medication. These patients will then enter the Post-Treatment Follow-up Phase. All patients need to be evaluated for potential resection of metastasis at completion of the induction period. This is of particular importance for patients with liver metastases. If the patient is found to be resectable they will undergo a Study Treatment Discontinuation Visit within 30 days after the last dose of study treatment and will then enter the Post-Treatment Follow-up Phase.

c. Patients in the Post-Treatment Follow-up Phase will be followed up every 3 months after their Study Treatment Discontinuation Visit. During post-treatment follow-up subsequent anti-cancer therapies will be recorded and survival assessed up to May 31, 2019 only. Refer to Appendix 19 for management of patients based on their study status on May 31, 2019. Treatment during the Post-Treatment Follow-up Phase is at the Investigator's discretion; $BRAF^{mut}$/MSS patients experiencing early disease progression during induction treatment will have the option of proceeding immediately to receive second-line treatment with 5-FU/LV, cetuximab and vemurafenib; $BRAF^{mut}$/MSI-H patients experiencing early disease progression during induction treatment will have the option of proceeding immediately to receive second-line treatment with a fluoropyrimidine (5-FU/LV or capecitabine), bevacizumab and atezolizumab. See Section 3.1.1.1 for further details including if disease progression occurs prior to availability of study biomarker test results in a patient with a previous BRAF mutation-positive result (e.g. by local test). Patients who discontinue study treatment during the Induction Treatment Phase prior to disease progression will also continue to be followed for PFS, with disease status followed according to local practice until progression or May 31, 2019, whichever comes first. Disease status will not be collected for the study after May 31, 2019.

d. Written informed consent for participation in the study must be obtained before performing any study-specific screening tests or evaluations and before shipping primary tumour blocks or slides to the Sponsor-designated laboratory. However, results from routine assessments conducted

prior to informed consent signature may be used as screening assessments as long as they were done within 7 days prior to informed consent signature.

e. The "All Cohort" eligibility criteria are evaluated prior to initiating the first cycle of study treatment during the Induction Treatment Phase.

f. Medical history includes clinically significant diseases, surgeries, cancer history (including prior cancer therapies and procedures), reproductive status, smoking history, use of alcohol and drugs of abuse, and all medications (e.g., prescription drugs, over-the-counter drugs, herbal or homeopathic remedies, nutritional supplements) used by the patient within 7 days prior to the Screening visit. Demographic data will include age, sex, and self-reported race/ethnicity (where permitted by federal regulations).

g. Vital signs include measurements of systolic and diastolic blood pressure while the patient is in a seated position, and temperature. During Screening, weight only required ≤ 7 days.

h. Baseline assessment requires a complete physical exam. A complete physical examination should include an evaluation of the head, eyes, ears, nose, and throat, and the cardiovascular, dermatological, musculoskeletal, respiratory, gastrointestinal, genitourinary, and neurological systems. Abnormalities identified at Screening / Baseline will be recorded as baseline conditions. At subsequent visits (or as clinically indicated), limited, symptom-directed physical examinations should be performed. Changes from Baseline, with new or worsened clinically significant abnormalities, should be reported as AEs if appropriate.

i. ECOG status assessed within 7 days prior to Day 1 of Cycle 1 (Induction Treatment Phase) for eligibility determination. See Appendix 8.

j. Concomitant medication includes any prescription medications or over-the-counter preparations used by a patient between the 7 days prior to the date of informed consent up until the date of study discontinuation. Only concomitant medications used for supportive care, to alleviate symptoms of mCRC, or to treat adverse drug reactions should be recorded on the Concomitant Medications eCRF. At subsequent visits, only changes to current medications or medications used since the last documentation of medications will be recorded. Concomitant medications for treatment of AEs related to study medication will continue to be recorded while the AE is being followed. For permitted and prohibited concomitant medications, see Section 4.4.

k. Haematology includes haemoglobin, haematocrit, platelet count, red blood cell count, white blood cell count, and differential. Blood chemistry includes ALT, AST, alkaline phosphatase, total bilirubin, total protein, albumin, blood urea nitrogen or urea, LDH, creatinine, glucose, calcium, phosphorus, sodium, potassium, chloride, and bicarbonate. Hematology and blood chemistry tests must be conducted prior to each treatment cycle, with the results available for review prior to start of treatment according to local standards for treatment management. However, only tests conducted every second treatment cycle will be recorded in the eCRF. Clinical laboratory results constituting a clinically significant AE should be recorded as such.

l. INR and aPTT are required for all patients at screening but only for patients receiving anticoagulants while on protocol-specified treatment.

m. Urinalysis must be performed by dipstick at Baseline and within 48 hours prior to every cycle. A 24-hour urine collection is needed in the event of proteinuria ≥ ± 2 by dipstick test.

n. Urine or blood pregnancy test, only for women of childbearing potential (i.e. not post-menopausal as indicated by < 12 months of non-therapy-induced amenorrhea, nor surgically sterile [absence of ovaries and/or uterus]), including those who have had a tubal ligation. A serum pregnancy test is required within 7 days prior to start of study induction treatment, or within 14 days with a confirmatory urine pregnancy test within 7 days prior start of study induction treatment

o. Will include radiology, chest and abdominal CT or MRI, and other scans to document all sites of disease. Include upper abdomen at Baseline. A CT or MRI scan of the brain is required if there is clinical suspicion of CNS metastases at screening/Baseline or at any time during the Induction Treatment Phase. Subsequent tumour assessments will be done according to standard of care at each study centre, with the exception that all patients must have a tumour assessment at the end of the Induction Treatment Phase. Tumour assessments are not required for study purposes after disease progression has been documented. Patients who discontinue study treatment during the Induction Treatment Phase prior to disease progression will also continue to be followed for progressive disease, with disease status followed according to local practice until progression or May 31, 2019, whichever comes first. After May 31, 2019, disease status will not be collected for the study.

p. Archival tumour tissue (FFPET) block from the primary tumour obtained at the time of the initial diagnosis. If the tumour block is not available, ≥ 20 slides cut from the primary tumour sample will be accepted as an alternative. Before a patient can be enrolled, the sample (block or slides) must be shipped to the designated laboratory with the corresponding pathology report and receipt of the shipment must be confirmed by the laboratory. See Appendix 17.

q. Collection of the optional core biopsy of metastatic tumours was discontinued as of May 2018 (See Appendix 18).

r. Whole blood and plasma samples will be collected from all study patients for exploratory biomarker analyses unless genomic analysis is not allowed per local regulations. In such instances, only plasma samples will be collected. All samples will be sent to a designated laboratory. Samples during treatment should be taken within 48 hours prior to study treatment Day 1 of each cycle indicated, unless otherwise specified (see Appendix 17 and Laboratory Manual).

s. After the signing of the informed consent form, and prior to Day 1 of Cycle 1 (Induction Treatment Phase), any SAEs thought to be related to a protocol-mandated intervention should be reported. Adverse events will be documented at every cycle during treatment. All patients will be followed for new AEs for 28 days following the discontinuation of study treatment. At the time of treatment discontinuation, any ongoing AE/SAE will be followed until the event resolves, the Investigator assesses the event as stable, the patient is lost to follow-up, dies or withdraws consent. Death related to disease progression is not considered to be an SAE. The Sponsor should be notified if the Investigator becomes aware of any SAE or AEs of special interest occurring after the end of the adverse event reporting period if the event is believed to be related to prior study treatment.

t. 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-FU, 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.

Appendix 3: Schedule of Assessments During Maintenance Phase (Cohort 1)

	Prior to randomization	Maintenance Treatment Phase [a]	Study Treatment Discontinuation Visit [b]	Post-Treatment Follow-Up Phase [c]
	Within 3 weeks of completing Induction Treatment Phase	Every 2 cycles (approximately every 4 weeks)	(≤ 30 days after last dose of study treatment)	Every 3 months
Assignment of cohort [d]	x			
Cohort- specific informed consent	x (sites using 2 consent forms only)			
Confirmation of cohort-specific eligibility [e]	x			
Randomisation [f]	x			
Vital signs and weight [g]		x	x	
Physical examination [h]		x	x	
Head and neck assessment for SCC [i] *(Experimental Arm only)*		Prior to Cycles 1, 4, 7, 10, 13, 16, 19, 22 and every 3 cycles thereafter	x	At 6 months
Chest CT assessment for SCC [j] *(Experimental Arm only)*		Prior to Cycles 1, 7, 13, 19, 25, 31 and every 6 cycles thereafter	x	At 6 months
Dermatology evaluation [k] *(Experimental Arm only)*		Prior to Cycles 1, 3, 5, 7, 9, 11, 13, 15 and every 2 cycles thereafter	x	At 6 months
Anal and pelvic exam [l] *(Experimental Arm only)*		Prior to Cycle 1	x	
ECOG performance status [m]		x	x	
12-lead ECG [n]	x	*Experimental arm only*	*Experimental arm only*	
Concomitant medications [o]		Every cycle	x	

	Prior to randomization	Maintenance Treatment Phase [a]	Study Treatment Discontinuation Visit [b]	Post-Treatment Follow-Up Phase [c]
	Within 3 weeks of completing Induction Treatment Phase	Every 2 cycles (approximately every 4 weeks)	(≤ 30 days after last dose of study treatment)	Every 3 months
Haematology and blood chemistry [p]		Every cycle	x	
INR, aPTT (select patients) [q]		According to local standard of care		
Urinalysis (dipstick) [r]		Every cycle	x	
Pregnancy test [s]		If clinically indicated		
Tumour assessments [t]		Up to and including May 31, 2019: Every 8 weeks regardless of treatment delays After May 31, 2019: per local practice		Up to and including May 31, 2019: Every 8 weeks until disease progression After May 31, 2019: per local practice
Metastatic tumour tissue for exploratory biomarker assessment [u] Supplemental Biomarker Program closed as of May 2018. Collection of these samples has been discontinued.	No sample collection Supplemental Biomarker Program CLOSED	No sample collection Supplemental Biomarker Program CLOSED		
Plasma samples [v]		Cycles 1, 2, 4, 6, 8, 10, 12,14 and every 2 cycles thereafter And at time of PD		At time of progression (if patient has not yet progressed)
Stool sample Supplemental Biomarker Program closed as of May 2018. Collection of these samples has been discontinued.	No sample collection Supplemental Biomarker Program CLOSED		No sample collection Supplemental Biomarker Program CLOSED	
Adverse events (including SAEs) [w]		Every cycle	x	x (as applicable)

	Prior to randomization	Maintenance Treatment Phase [a]	Study Treatment Discontinuation Visit [b]	Post-Treatment Follow-Up Phase [c]
	Within 3 weeks of completing Induction Treatment Phase	Every 2 cycles (approximately every 4 weeks)	(≤ 30 days after last dose of study treatment)	Every 3 months
Study medication administration [x]		Every cycle		
Subsequent anti-cancer therapies (see [c])				x
Patient survival (see [c])			x	x

a. With the exception of Cycle 1, all other study visits and assessments should be performed within ± 7 days of the scheduled date. If a control arm patient receives capecitabine administered according to a 3- week cycle, timing of all study procedures and assessments scheduled according to 2-week treatment cycles (e.g. ECOG performance status) will be defined by the treatment cycles of concurrently administered bevacizumab.

b. Patients who experience PD at any time during the Maintenance Treatment Phase, or who need to permanently discontinue study medication for any reason, will undergo a Study Treatment Discontinuation Visit within 30 days after the last dose of study medication. These patients will then enter the Post-Treatment Follow-up.

c. After discontinuation of study treatment and the Study Discontinuation Visit, patients will enter the Post-Treatment Follow-up Phase. Beginning after the Study Treatment Discontinuation visit, patients will be followed up every 3 months. Up to and including May 31, 2019, follow-up will include disease status (patients discontinuing study treatment prior to disease progression only) in addition to safety evaluations and recording of subsequent anti-cancer therapies and survival. After May 31, 2019, disease status will not be documented for study purposes. Treatment during the Post-Treatment Follow-up Phase is at the Investigator's discretion. Patients who discontinue study treatment prior to disease progression will be followed for PFS, with disease status followed every 8 weeks until progression or May 31, 2019, whichever comes first.

d. Patients completing the Induction Treatment Phase, and who have not experienced PD can then proceed to the Maintenance Treatment Phase. Depending on the patient's biomarker status (based on the archival sample from initial diagnosis), these patients will be assigned to a maintenance treatment cohort. Cohorts 2 and 4 are closed to further enrolment. Patients with an adequate tumour sample but with unknown biomarker status due to lack of determinant result (e.g. due to technical issues) may still be included in the study depending on the addition of future cohorts.

e. The cohort-specific exclusion criteria must be assessed prior to randomization to study maintenance treatment but assessment of cohort-specific eligibility can only be completed after the biomarker analysis results from the patient's archival tumour tissue from initial diagnosis are known. Patients found ineligible for any cohort will undergo a Study Treatment Discontinuation Visit and enter the Post-Treatment Follow-up Phase.

f. Each cohort will consist of an experimental treatment arm and a control arm. Randomised on a 2:1 (experimental:control) basis to either the experimental treatment arm or the control arm of that cohort. See Section 4.2.

g. Vital signs include measurements of systolic and diastolic blood pressure while the patient is in a seated position, and temperature.

h. Physical examinations will be symptom-directed, and will include changes from Baseline (pre-Induction) with new or worsened clinically significant abnormalities being reported as AEs if appropriate.

i. To be performed by the Investigator or other qualified physician as part of the evaluation for SCC. The head and neck examination will consist of at least a visual inspection of the oral mucosa and lymph node palpation. Any suspicious findings will be referred to an appropriate specialist.

j. The routinely scheduled radiographic assessment for tumour burden may be used (if available) as the chest CT for the evaluation of non-cutaneous SCC. MRI may be used if a CT scan is contra-indicated for the patient.

k. Evaluation to be performed by a dermatologist, the Investigator or other qualified physician.

l. Pelvic examinations for women (with special attention to cervix) and anal examinations for all patients will be performed by the Investigator or other qualified physician prior to start of Experimental Therapy and at the Study Treatment Discontinuation Visit for the evaluation of SCC. The pelvic examination should include a complete external and internal examination (internal examination of uterine cervix may include a Pap smear, which would be a decision of the Investigator). The anal examination should include external examination, digital anorectal examination and anoscopy or proctoscopy. However, if in opinion of the Investigator the presence of “abnormal lesions including SCC” can be excluded by the external inspection and the manual examination, this is acceptable. However, if the presence of a lesion is suspected, an anoscopy or proctoscopy are recommended.

m. See Appendix 8.

n. ECG to determine Cohort 1 eligibility must conducted within 3 weeks of randomization. During maintenance treatment, ECGs will be required in experimental arm patients only. Measurements include heart rate, PR interval, QRS duration, and QT and QTc intervals.

o. Concomitant medication includes any prescription medications or over-the-counter preparations used by a patient between the 7 days prior to the date of informed consent up until the Study Treatment Discontinuation visit. Only concomitant medications used for supportive care, to alleviate symptoms of mCRC, or to treat adverse drug reactions should be recorded on the Concomitant Medications eCRF. At subsequent visits, only changes to current medications or medications used since the last documentation of medications will be recorded. Concomitant medications for treatment of AEs related to study medication will continue to be recorded while the AE is being followed. For permitted and prohibited concomitant medications, see Section 4.4.

p. Haematology includes haemoglobin, haematocrit, platelet count, red blood cell count, white blood cell count, and differential. Blood chemistry includes ALT, AST, alkaline phosphatase, total bilirubin, total protein, albumin, blood urea nitrogen or urea, LDH, creatinine, glucose, calcium, phosphorus, sodium, potassium, chloride and bicarbonate. Patients in the experimental arm will also have magnesium, amylase and lipase tested. Haematology and blood chemistry tests must be conducted prior to each treatment cycle, with the results available for review prior to start of treatment according to local standards for treatment management. However, only tests conducted every second treatment cycle will be recorded in the eCRF. Clinical laboratory results constituting a clinically significant AE should be recorded as such.

q. INR and aPTT only for patients receiving anticoagulants while on protocol-specified treatment.

r. Urinalysis must be performed by dipstick within 48 hours prior to every cycle. A 24-hour urine collection is needed in the event of proteinuria ≥ ± 2 by dipstick test. Urinalysis results from every second cycle only will be recorded in the CRF.

s. Urine or blood pregnancy test, only for women of childbearing potential (i.e. not post-menopausal as indicated by < 12 months of non-therapy-induced amenorrhea, nor surgically sterile [absence of ovaries and/or uterus]), including those who have had a tubal ligation. If urine pregnancy test is positive, it must be confirmed by a serum pregnancy test.

t. Up to and including May 31, 2019, tumour assessments will be conducted according to RECIST 1.1 for Cohort 1 with disease status during maintenance treatment determined based on comparison with the tumour assessment done at the end of induction treatment. Assessments will include radiology, chest and abdominal CT or MRI, and other scans to document all sites of disease. A CT or MRI scan of the brain is required if there is a clinical suspicion of CNS metastases. Up to and including May 31, 2019, tumour assessments will be conducted every eight weeks from the start of maintenance treatment regardless of treatment delays. After May 31, 2019, disease status will not be collected for the study and tumour assessments may be conducted per local practice. Patients who discontinue study treatment during the Maintenance Treatment Phase prior to disease progression will also continue to be followed for progressive disease, with disease assessments *per RECIST 1.1* conducted every eight weeks until progression or May 31, 2019, whichever comes first.

u. Supplemental Biomarker Program closed as of May 2018. Collection of these samples has been discontinued (see Appendix 18).

v. Plasma samples will be collected from all patients for exploratory biomarker analyses. These samples will be sent to a designated laboratory. Samples during treatment should be taken within 48 hours prior to study treatment Day 1 of each cycle indicated, unless otherwise specified (see Appendix 17 and the Laboratory Manual).

w. Adverse events will be documented at every cycle during treatment. All patients will be followed for new AEs for 28 days following the discontinuation of study treatment. At the time of treatment discontinuation, any ongoing AE/SAE will be followed until the event resolves, the Investigator assesses the event as stable, the patient is lost to follow-up, dies or withdraws consent. Death related to disease progression is not considered to be an SAE. The Sponsor should be notified if the Investigator becomes aware of any SAE or AEs of special interest occurring after the end of the adverse event reporting period if the event is believed to be related to prior study treatment.

Appendix 4: SAS code

The following SAS code will be used to obtain the log-rank p-value from the unstratified log-rank test mentioned in section 4.11.1:

```
PROC LIFETEST data=dataset METHOD=KM CONFTYPE=LOGLOG;
TIME pfstime*censor(1);
STRATA treat / test=logrank;
RUN;
* pfstime represents variable containing event/censor times;
* censor represents censoring variable (1=censored, 0=event);
* treat represents treatment group variable;
Further options to control the output may be added.
```

The following SAS code will be used for the logistic regression mentioned in section 4.11.2.2:

```
PROC LOGISTIC DATA= dataset;
CLASS treat (ref='FP+Bev')strate1 / param=ref;
MODEL response (event='1') = treat strate1 / alpha=0.05;
RUN;
* response represents the response variable;
* treat represents the treatment group;
* strate1 represents the categorical covariate related to stratification
factors as per eCRF data for tumor response;
Further options to control the output may be added.
```

The following SAS code will be used to obtain the hazard ratio and corresponding confidence interval from the Cox Model with treatment as single covariate mentioned in section 4.11.4:

```
PROC PHREG data=dataset;
CLASS treat;
MODEL pfstime*censor(1)=treat /RL TIES=EXACT;
RUN;
* pfstime represents variable containing event/censor times;
* censor represents censoring variable (1=censored, 0=event);
* treat represents treatment group variable;
Further options to control the output may be added.
```

The following SAS code will be used to obtain the hazard ratio and corresponding confidence interval from the adjusted Cox Model mentioned in section 4.11.4:

```
PROC PHREG data=dataset;
CLASS treat strate1;
MODEL pfstime*censor(1)=treat stratum1 /RL TIES=EXACT;
RUN;
* pfstime represents variable containing event/censor times;
* censor represents censoring variable (1=censored, 0=event);
* treat represents treatment group variable;
* strate1 represents the categorical covariates related to stratification
factors;
Further options to control the output may be added.
```

The following SAS code will be used for the logistic regression with treatment as single covariate mentioned in section 4.11.4:

```
PROC LOGISTIC DATA= dataset;
CLASS treat (ref='FP+Bev') / param=ref;
MODEL response (event='1') = treat / alpha=0.05;
RUN;
* response represents the response variable;
* treat represents the treatment group;
Further options to control the output may be added.
```

Appendix 5 : List of Outputs

List of Outputs: Tables

Table Number	Table Title	Phase	Population	Primary analysis	Final Analysis
	Patient Disposition				
14.1.1.1	Patient Disposition For Induction Treatment Phase	ITP	ALL	X	
14.1.1.2	Patient Disposition For Maintenance Treatment Phase	MTP	MTP	X	**X**
14.1.1.3	Duration of Follow-up	MTP	MTP	X	**X**
14.1.2.1	Major Protocol Deviations For Induction Treatment Phase	ITP	ITP	X	
14.1.2.2	Major Protocol Deviations For Maintenance Treatment Phase	MTP	MTP	X	**X**
	Demographics and Baseline Characteristics				
14.1.3.1	Summary of Baseline and Demographic Characteristics	ITP	ITP	X	
14.1.3.2	Summary of Baseline and Demographic Characteristics	MTP	MTP	X	
14.1.3.3	Summary of Baseline Biomarker Status	MTP	MTP	X	
14.1.3.4	Summary of Baseline Biomarker Status	ITP	ITP	X	
14.1.4.1	Tumor Response Status (RECIST 1.1) at End of Induction (eCRF data)	ITP	ITP	X	
14.1.5	Randomization by Country and Study Center	MTP	MTP	X	
14.1.6	Stratification Factors as per IxRS	MTP	MTP	X	
14.1.7.1	Tumor Response Status (RECIST 1.1) at End of Induction (eCRF data)	MTP	MTP	X	
14.1.7.2	Tumor Response (RECIST 1.1) at End of Induction as per IxRS versus eCRF Data	MTP	MTP	X	
14.1.8.1	Summary of Colorectal Cancer History	ITP	ITP	X	
14.1.8.2	Summary of Colorectal Cancer History	ITP	MTP	X	
14.1.9	RECIST Tumor-Specific Characteristics at Baseline	MTP	MTP	X	
14.1.10.1	Medical History	ITP	ITP	X	
14.1.10.2	Medical History	ITP	MTP	X	
14.1.11.1	Summary of Prior Anti-Cancer Treatments/Procedures	ITP	ITP	X	
14.1.11.2	Summary of Prior Anti-Cancer Treatments/Procedures	ITP	MTP	X	
14.1.12	Prior Medications	ITP	ITP	X	

Table Number	Table Title	Phase	Population	Primary analysis	Final Analysis
14.1.13.1	Concomitant Medications during the Induction Phase	ITP	ITP	X	
14.1.13.2	Concomitant Medications during the Maintenance Phase	MTP	SAF	X	
14.1.14.1	Concomitant Radiotherapy during the Induction Phase	ITP	ITP	X	
14.1.14.2	Concomitant Radiotherapy during the Maintenance Phase	MTP	SAF	X	
14.1.15.1	Concomitant Colorectal Cancer Surgery during the Induction Phase	ITP	ITP	X	
14.1.15.2	Concomitant Colorectal Cancer Surgery during the Maintenance Phase	MTP	SAF	X	
	Exposure				
14.1.16.1	Summary of Total Number of Cycles Initiated during ITP	ITP	ITP	X	
14.1.16.2	Summary of Drug Exposure during ITP	ITP	ITP	X	
14.1.17.1	Summary of Overall Duration of Treatment and Number of Cycles Initiated during MTP	MTP	SAF	X	**X**
14.1.17.2	Summary of Drug Exposure during MTP	MTP	SAF	X	**X**
14.1.17.3	Summary of Cycles Delayed during MTP	MTP	SAF	X	**X**
14.1.17.4	Summary of Cycles Delayed (at the Cycle Level) during MTP	MTP	SAF	X	**X**
	Efficacy				
14.2.1.1	Summary of Progression Free Survival - Primary Analysis (Surgery Censored)	MTP	MTP	X	
14.2.1.2	Progression Free Survival: Hazard Ratio	MTP	MTP	X	
14.2.1.3.2	Summary of Progression Free Survival by Tumor Response at end of ITP (based on eCRF data)	MTP	MTP	X	
14.2.1.3.3	Summary of Progression Free Survival by Tumor Colon Location	MTP	MTP	X	
14.2.2.1	Summary of Progression Free Survival - Sensitivity Analyses (Surgery not Censored)	MTP	MTP	X	
14.2.2.2	Progression Free Survival: Hazard Ratio - Sensitivity Analyses (Surgery not Censored)	MTP	MTP	X	
14.2.7.1	Summary of Overall Survival	MTP	MTP	X	**X**
14.2.7.2	Overall Survival: Hazard Ratio	MTP	MTP	X	**X**
14.2.7.3.2	Summary of Overall Survival by Tumor Response at end of ITP (based on eCRF data)	MTP	MTP	X	**X**
14.2.7.3.3	Summary of Overall Survival by Tumor Colon Location	MTP	MTP	X	**X**
14.2.8.1	Summary of Overall Response Rate (Main Definition)	MTP	MTP	X	

Table Number	Table Title	Phase	Population	Primary analysis	Final Analysis
14.2.8.2.2	Summary of Overall Response Rate (Main Definition) by Tumor Response at End of ITP (Based on eCRF Data)	MTP	MTP	X	
14.2.8.2.3	Summary of Overall Response Rate (Main Definition) by Tumor Colon Location	MTP	MTP	X	
14.2.8.3	Summary of Overall Response Rate (Secondary Definition)	MTP	MTP	X	
14.2.8.4.2	Summary of Overall Response Rate (Secondary Definition) by Tumor Response at End of ITP (Based on eCRF Data)	MTP	MTP	X	
14.2.8.4.3	Summary of Overall Response Rate (Secondary Definition) by Tumor Colon Location	MTP	MTP	X	
14.2.8.5	Overall Response Rate (ORR): Odds Ratio	MTP	MTP	X	
14.2.9.1	Summary of Disease Control Rate (Main Definition)	MTP	MTP	X	
14.2.9.2	Summary of Disease Control Rate (Secondary Definition)	MTP	MTP	X	
14.2.9.3	Disease Control Rate (DCR): Odds Ratio	MTP	MTP	X	
14.2.10.1	Summary of Duration of Response and Time to Response (Main Definition)	MTP	MTP	X	
14.2.10.2	Summary of Duration of Response and Time to Response (Secondary Definition)	MTP	MTP	X	
14.2.12.1	Summary of ECOG Performance Status over Time	MTP	MTP	X	
14.2.12.2	Shift from Baseline to ECOG Performance Status at End of MTP	MTP	MTP	X	
	Adverse Events				
14.3.1.1.1	Treatment Emergent Adverse Events (TEAEs) during ITP: Overall Summary	ITP	ITP	X	
14.3.1.1.2	Treatment Emergent Adverse Events (TEAEs) during MTP: Overall Summary	MTP	SAF	X	**X**
14.3.1.1.3	Post Induction Treatment Adverse Events (AEs): Overall Summary	Post-Treatment	ITP	X	
14.3.1.1.4	Post Maintenance Treatment Adverse Events (AEs): Overall Summary	Post-Treatment	SAF	X	**X**
14.3.1.2.1	Treatment Emergent Adverse Events by SOC and PT and by Worst Intensity during ITP	ITP	ITP	X	
14.3.1.2.2	Treatment Emergent Adverse Events by SOC and PT and by Worst Intensity during MTP	MTP	SAF	X	
14.3.1.2.3	Treatment Emergent AESI as reported on eCRF by SOC and PT and by Worst Intensity during MTP	MTP	SAF	X	

Table Number	Table Title	Phase	Population	Primary analysis	Final Analysis
14.3.1.2.4	Serious Treatment Emergent AESI as reported on eCRF by SOC and PT and by Worst Intensity during MTP	MTP	SAF	X	
14.3.1.2.5	Treatment Emergent Adverse Events by SOC and PT during MTP	MTP	SAF	X	**X**
14.3.1.2.6	Treatment Emergent Adverse Events by SOC and PT during ITP	ITP	SAF	X	
14.3.1.3.1	Treatment Emergent Adverse Events Related to Any Study Drug by SOC and PT during ITP	ITP	ITP	X	
14.3.1.3.2	Treatment Emergent Adverse Events Related to FOLFOX by SOC and PT during ITP	ITP	ITP	X	
14.3.1.3.3	Treatment Emergent Adverse Events Related to 5-FU/LV by SOC and PT during ITP	ITP	ITP	X	
14.3.1.3.4	Treatment Emergent Adverse Events Related to Bevacizumab by SOC and PT during ITP	ITP	ITP	X	
14.3.1.3.5	Treatment Emergent Adverse Events Related to Any Study Drug by SOC and PT during MTP	MTP	SAF	X	**X**
14.3.1.3.6	Treatment Emergent Adverse Events Related to Fluoropyrimidines by SOC and PT during MTP	MTP	SAF	X	
14.3.1.3.7	Treatment Emergent Adverse Events Related to FOLFOX by SOC and PT during MTP	MTP	SAF	X	
14.3.1.3.9	Treatment Emergent Adverse Events Related to Bevacizumab by SOC and PT during MTP	MTP	SAF	X	
14.3.1.3.10	Treatment Emergent Adverse Events Related to Cetuximab by SOC and PT during MTP	MTP	SAF	X	
14.3.1.3.11	Treatment Emergent Adverse Events Related to Vemurafenib by SOC and PT during MTP	MTP	SAF	X	
14.3.1.4.1	Treatment Emergent Adverse Events Leading to Discontinuation of Any Study Drug by SOC and PT during ITP	ITP	ITP	X	
14.3.1.4.5	Treatment Emergent Adverse Events Leading to Discontinuation of Any Study Drug by SOC and PT during MTP	MTP	SAF	X	**X**
14.3.1.5.1	Treatment Emergent Adverse Events Leading to Dose Reduction or Interruption of Any Study Drug by SOC and PT during ITP	ITP	ITP	X	
14.3.1.5.4	Treatment Emergent Adverse Events Leading to Dose Reduction or Interruption of Bevacizumab by SOC and PT during ITP	ITP	ITP	X	
14.3.1.5.5	Treatment Emergent Adverse Events Leading to Dose Reduction or Interruption of Any Study Drug by SOC and PT during MTP	MTP	SAF	X	**X**

Table Number	Table Title	Phase	Population	Primary analysis	Final Analysis
14.3.1.5.6	Treatment Emergent Adverse Events Leading to Dose Reduction or Interruption of Fluoropyrimidines by SOC and PT during MTP	MTP	SAF	X	
14.3.1.5.8	Treatment Emergent Adverse Events Leading to Dose Reduction or Interruption of Bevacizumab by SOC and PT during MTP	MTP	SAF	X	
14.3.1.5.9	Treatment Emergent Adverse Events Leading to Dose Reduction or Interruption of Vemurafenib by SOC and PT during MTP	MTP	SAF	X	
14.3.1.5.10	Treatment Emergent Adverse Events Leading to Dose Reduction or Interruption of Cetuximab by SOC and PT during MTP	MTP	SAF	X	
14.3.1.6.1	Treatment Emergent Adverse Events of Grade 3 or More by SOC and PT during ITP	ITP	ITP	X	
14.3.1.6.2	Treatment Emergent Adverse Events of Grade 3 or More by SOC and PT during MTP	MTP	SAF	X	**X**
14.3.1.7.1	Serious Treatment Emergent Adverse Events by SOC and PT during ITP	ITP	ITP	X	
14.3.1.7.2	Serious Treatment Emergent Adverse Events by SOC and PT during MTP	MTP	SAF	X	**X**
14.3.1.8.1	Serious Treatment Emergent Adverse Events Related to Any Study Drug by SOC and PT during ITP	ITP	ITP	X	
14.3.1.8.4	Serious Treatment Emergent Adverse Events Related to Bevacizumab by SOC and PT during ITP	ITP	ITP	X	
14.3.1.8.5	Serious Treatment Emergent Adverse Events Related to Any Study Drug by SOC and PT during MTP	MTP	SAF	X	**X**
14.3.1.8.6	Serious Treatment Emergent Adverse Events Related to Fluoropyrimidines by SOC and PT during MTP	MTP	SAF	X	
14.3.1.8.7	Serious Treatment Emergent Adverse Events Related to FOLFOX by SOC and PT during MTP	MTP	SAF	X	
14.3.1.8.9	Serious Treatment Emergent Adverse Events Related to Bevacizumab by SOC and PT during MTP	MTP	SAF	X	
14.3.1.8.10	Serious Treatment Emergent Adverse Events Related to Vemurafenib by SOC and PT during MTP	MTP	SAF	X	
14.3.1.8.111	Serious Treatment-Emergent Adverse Events Related to Cetuximab by SOC and PT during MTP	MTP	SAF	X	
14.3.1.9.1	Treatment Emergent Adverse Events with Fatal Outcome by SOC and PT during ITP	ITP	ITP	X	
14.3.1.9.2	Treatment Emergent Adverse Events with Fatal Outcome by SOC and PT during MTP	MTP	SAF	X	**X**

Table Number	Table Title	Phase	Population	Primary analysis	Final Analysis
14.3.1.10.1	Treatment Emergent AESI Based on eCRF Categories during MTP	MTP	SAF	X	**X**
14.3.1.10.2	Treatment Emergent AESI Based on eCRF Categories during ITP	ITP	ITP	X	
14.3.1.10.3	Bevacizumab Treatment Emergent AESI Based on Pre-Defined Categories during MTP	MTP	SAF	**X**	**X**
14.3.1.10.4	Bevacizumab Treatment Emergent AESI Based on Pre-Defined Categories during ITP	ITP	ITP	**X**	
14.3.1.10.6	Vemurafenib Treatment Emergent AESI Based on Pre-Defined Categories during MTP	MTP	SAF	**X**	**X**
14.3.1.11	Serious Treatment Emergent AESI Based on eCRF Categories during MTP	MTP	SAF	X	**X**
	Deaths				
14.3.1.12.1	Deaths within 30 days from Last Day of Treatment of ITP and Reason	ITP	ITP	X	
14.3.1.12.2	Deaths within 30 days from Last Day of Treatment of MTP and Reason	MTP	MTP	X	**X**
14.3.1.12.3	Deaths within 30 Days from Last Day of Treatment of MTP and Reason	MTP	SAF	X	**X**
14.3.1.12.4	Post Induction Treatment Deaths and Reason	Post-Treatment	ITP	X	
14.3.1.12.5	Post Maintenance Treatment Deaths and Reason	Post-Treatment	SAF	X	**X**
	Laboratory Parameters				
14.3.4.1.1	Shift Table (Baseline versus Worst On-Treatment) during ITP for CTC Gradable Hematology Parameters	ITP	ITP	X	
14.3.4.1.2	Shift Table (Baseline versus Worst On-Treatment) during MTP for CTC Gradable Hematology Parameters	MTP	SAF	X	
14.3.4.2.1	Shift Table (Baseline versus Worst On-Treatment) during ITP for CTC Gradable Blood Chemistry Parameters	ITP	ITP	X	
14.3.4.2.2	Shift Table (Baseline versus Worst On-Treatment) during MTP for CTC Gradable Blood Chemistry Parameters	MTP	SAF	X	
14.3.4.3.1	Shift Table (Baseline versus Worst On-Treatment) during ITP for CTC Gradable Coagulation Parameters	ITP	ITP	X	
14.3.4.3.2	Shift Table (Baseline versus Worst On-Treatment) during MTP for CTC Gradable Coagulation Parameters	MTP	SAF	X	
14.3.4.4.1	Shift Table (Baseline versus Worst On-Treatment) during ITP for Non CTC Gradable Hematology Parameters	ITP	ITP	X	

Table Number	Table Title	Phase	Population	Primary analysis	Final Analysis
14.3.4.4.2	Shift Table (Baseline versus Worst On-Treatment) during MTP for Non CTC Gradable Hematology Parameters	MTP	SAF	X	
14.3.4.5.1	Shift Table (Baseline versus Worst On-Treatment) during ITP for Non CTC Gradable Blood Chemistry Parameters	ITP	ITP	X	
14.3.4.5.2	Shift Table (Baseline versus Worst On-Treatment) during MTP for Non CTC Gradable Blood Chemistry Parameters	MTP	SAF	X	
14.3.4.7.1	Shift Table (Baseline versus Worst On-Treatment) during ITP for Urinalysis Protein Dipstick	ITP	ITP	X	
14.3.4.7.2	Shift Table (Baseline versus Worst On-Treatment) during MTP for Urinalysis Protein Dipstick	MTP	SAF	X	
	Other Safety Data				
14.3.5.1	Summary of Vital Signs Over Time during ITP	ITP	ITP	X	
14.3.5.2	Summary of Vital Signs Over Time during MTP	MTP	SAF	X	
14.3.7	Summary of Qualitative ECG Assessment over Time	MTP	SAF	X	
14.3.8	Summary of QTcF (in Categories) over Time	MTP	SAF	X	

List of Outputs: Figures

Figure Number	Figure Title	Phase	Population	Primary analysis	Final Analysis
	Disposition				
14.1.1	CONSORT Flow Diagram for All Screened Patients	All	Screened	X	
14.1.2	CONSORT Flow Diagram for Patients Randomized in Cohort 1	All	MTP	X	**X**
	Efficacy				
14.2.1.1	Kaplan Meier Plot of Progression Free Survival - Primary Analysis	MTP	MTP	X	
14.2.1.2	Kaplan Meier Plot of Progression Free Survival - Sensitivity Analysis (Surgery not Censored)	MTP	MTP	X	

Figure Number	Figure Title	Phase	Population	Primary analysis	Final Analysis
14.2.1.7.2	Kaplan Meier Plot of Progression Free Survival by Tumor Response at End of ITP (Based on eCRF Data)	MTP	MTP	X	
14.2.1.7.3	Kaplan Meier Plot of Progression Free Survival by Tumor Colon Location	MTP	MTP	X	
14.2.1.8	PFS: Proportional Hazard Assumption - Model Checking	MTP	MTP	X	
14.2.1.9.1	Forest Plot of Hazard Ratio for Progression Free Survival by Demographic Characteristics Subgroup	MTP	MTP	X	
14.2.1.9.2	Forest Plot of Hazard Ratio for Progression Free Survival by Baseline Disease Characteristics Subgroup	MTP	MTP	X	
14.2.1.10	Kaplan Meier Plot with Reverse Censoring of PFS	MTP	MTP	X	
14.2.2.1	Kaplan Meier Plot of Overall Survival	MTP	MTP	X	**X**
14.2.2.2.2	Kaplan Meier Plot of Overall Survival by Tumor Response at End of ITP (Based on eCRF Data)	MTP	MTP	X	**X**
14.2.2.2.3	Kaplan Meier Plot of Overall Survival by Tumor Colon Location	MTP	MTP	X	**X**
14.2.2.3.1	Forest Plot of Hazard Ratio for Overall Survival by Demographic Characteristics Subgroup	MTP	MTP	X	**X**
14.2.2.3.2	Forest Plot of Hazard Ratio for Overall Survival by Baseline Disease Characteristics Subgroup	MTP	MTP	X	**X**
14.2.3	Waterfall Plot of Best Percentage Change from Baseline in Sum of Diameters	MTP	MTP	X	
14.2.4.1	Forest Plot of Odds Ratio for Overall Response Rate (Main Definition) by Demographic Characteristics Subgroup	MTP	MTP	X	
14.2.4.2	Forest Plot of Odds Ratio for Overall Response Rate (Main Definition) by Baseline Disease Characteristics Subgroup	MTP	MTP	X	

List of Outputs: Listings

Listing Number	Listing Title	Phase	Population	Primary analysis	Final Analysis
	Disposition				
16.2.1.1	Patient Disposition and Study Termination Information	ITP	ITP	X	**X**
16.2.1.2	Patient Who Discontinue Treatment due to Adverse Event	ITP	ITP	X	**X**

Listing Number	Listing Title	Phase	Population	Primary analysis	Final Analysis
16.2.2	Major Protocol Deviations from PDMS	ITP/MTP	ITP	X	**X**
16.2.3	Analysis Population	ITP/MTP	ALL	X	
	Demographics and Baseline Characteristics				
16.2.4.1	Demographics and Baseline Characteristics	ITP/MTP	ITP	X	
16.2.4.4	Baseline Biomarker Status	MTP	MTP	X	
16.2.4.5	Randomization Stratification Factors as per IxRS and eCRF	MTP	MTP	X	
16.2.4.6	Colorectal Cancer History	ITP	ITP	X	
16.2.4.7	Medical History	ITP	ITP	X	
16.2.4.8	Prior Anti-Cancer Therapy	ITP	ITP	X	
16.2.4.9	Cancer Radiotherapy: Prior and On-study	ITP/MTP	ITP	X	**X**
16.2.4.10	Colorectal Cancer Surgery : Prior and On-Study	ITP/MTP	ITP	X	**X**
16.2.4.11	Prior and Concomitant Medications	ITP/MTP	ITP	X	**X**
16.2.4.12	Subsequent Anti-cancer Therapies	Post-Treatment	ITP	X	**X**
	Drug Administration				
16.2.5.1	Study Drug Administration for 5-FU	ITP/MTP	ITP	X	
16.2.5.2	Study Drug Administration for Leucovorin	ITP/MTP	ITP	X	
16.2.5.3	Study Drug Administration for Oxaliplatin during ITP	ITP	ITP	X	
16.2.5.4	Study Drug Administration for Bevacizumab	ITP/MTP	ITP	X	**X**
16.2.5.5	Drug Exposure during ITP	ITP	ITP	X	
16.2.5.6	Study Drug Administration for Cetuximab during MTP	MTP	SAF	X	**X**
16.2.5.7	Study Drug Administration for Vemurafenib during MTP	MTP	SAF	X	**X**
16.2.5.8	Drug Exposure during MTP	MTP	SAF	X	**X**
	Efficacy				
16.2.6.1	Progression Free Survival - Primary Analysis (Surgery Censored)	MTP	MTP	X	
16.2.6.2	Progression Free Survival - Sensitivity Analysis (Surgery not Censored)	MTP	MTP	X	
16.2.6.3	Individual Tumor Assessment and Overall Response as per RECIST v1.1	ITP/MTP	ITP	X	

Listing Number	Listing Title	Phase	Population	Primary analysis	Final Analysis
16.2.6.8	Best Overall Response, Time to Response and Duration of Response	MTP	MTP	X	
16.2.6.9	Overall Survival	MTP	MTP	X	**X**
16.2.6.11	ECOG performance status	ITP/MTP	ITP	X	
16.2.6.12	Head and Neck Assessment for SCC	MTP	MTP	X	
16.2.6.13	Chest CT Assessment for SCC	MTP	MTP	X	
16.2.6.14	Dermatology Evaluation	MTP	MTP	X	
16.2.6.15	Anal and Pelvic Exam	MTP	MTP	X	
	Safety				
16.2.7.1	Adverse Events	ITP/MTP/ Post-treatment	ITP	X	**X**
16.2.7.2	Grade 5 Adverse Events or any Adverse Events with Fatal Outcome	ITP/MTP/ Post-treatment	ITP	X	**X**
16.2.7.3	Adverse Events Leading to Treatment Discontinuation	ITP/MTP/ Post-treatment	ITP	X	**X**
16.2.7.4	Adverse Events of Special Interest as Reported on eCRF	MTP/ Post-treatment	ITP	X	**X**
16.2.7.5	Deaths	ITP/MTP/ Post-treatment	ITP	X	**X**
16.2.8.1	Laboratory Values - Hematology	ITP/MTP	ITP	X	
16.2.8.1	Laboratory Values – Blood Chemistry	ITP/MTP	ITP	X	
16.2.8.1	Laboratory Values - Coagulation	ITP/MTP	ITP	X	
16.2.8.2	Laboratory Abnormalities	ITP/MTP	ITP	X	
16.2.8.3	Urinalysis: Urine Protein Dipstick	ITP/MTP	ITP	X	
16.2.8.4	Urinalysis: 24 Hour Urine Protein	ITP/MTP	ITP	X	
16.2.8.5	Pregnancy Test	ITP/MTP	ITP	X	

Listing Number	Listing Title	Phase	Population	Primary analysis	Final Analysis
16.2.9.1	Vital Signs	ITP/MTP	ITP	X	
16.2.9.2	ECG	ITP/MTP	ITP	X	

ADDENDUM TO STATISTICAL ANALYSIS PLAN

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

COHORT 2

PROTOCOL NUMBER: MO29112

COHORT 2 STUDY DRUGS: atezolizumb (MPDL3280A, RO5541267)
bevacizumab (RO4876646)

VERSION NUMBER: 2.0

IND NUMBER: N/A

EUDRACT NUMBER: 2014-001017-61

SPONSOR: F. Hoffmann-La Roche Ltd

PLAN PREPARED BY: [redacted]
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1215 Geneva 15
Switzerland

DATE FINAL: 02 August 2018

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HISTORY CHANGE

Version	Date	Changes
Final 1.0	22-Jan-2018	N/A
Final 2.0	02-Aug-2018	• Additional analysis on protocol deviations • Additional analysis on PFS considering first 330 patients randomized • Additional analysis to summarize median follow-up

LIST OF ABBREVIATIONS

Abbreviation	Definition
CSR	Clinical Study Report
ECOG	Eastern Cooperative Oncology Group
ITP	Induction Treatment Phase
MTP	Maintenance Treatment Phase
PFS	progression free survival
SAP	statistical analysis plan

1. INTRODUCTION

The purpose of this addendum is to revise the Statistical Analysis Plan (SAP). The rational is based on the Sponsor's decision to add complementary analyses to the version 2.0 of the SAP following the review of the SREP outputs or further analysis required for Clinical Study Report (CSR). No changes are applied on analyses that were already described in the SAP version 2.0 (15-Sep-2017).

The changes to be made to the SAP are described in the section 2.

2. LIST OF CHANGES COMPARED TO STATISTICAL ANALYSIS PLAN V2.0

2.1 SECTION 4.8.1 (MODIFICATION)

During Data Review on 14-Nov-2017, it was identified that one patient without BRAF mutation had ICF signed on 28-June-2016, but should be included in the ALL Population.

SMT decided to change the definition of the ALL population as follow: 'ALL population consists of all patients without a confirmed BRAF mutation result who signed an Inform consent form until ~~June 3, 2016~~ June 28, 2016.'

2.2 SECTION 4.10.1 (ADDITION)

Baseline biomarker status will be summarized also on the ITP population to compare characteristics for patients randomized in MTP versus patients not randomized

2.3 SECTION 4.11.5 (ADDITION)

Some subgroups of interest were included in the forest plot for the progression-free survival analysis by subgroups. Kaplan Meier curves will be added for the following subgroups:

- Gender
- Baseline ECOG performance status
- Initial diagnosis

2.4 SECTION 4.13.2 (ADDITION)

Treatment emergent adverse events occuring during MTP will also be summarized by SOC/PT (regardless of the grades) on the safety population. All summaries planned in the SAP were by highest grade.

2.5 SECTION 4.9.2 (ADDITION)

Major protocol deviations will be summarized separately for deviations occuring: 1) prior start of ITP, 2) prior or during ITP.

2.6 SECTION 4.11.4 (ADDITION)

An additional sensitivity analysis will be performed for PFS, considering the first 330 patients randomized.

2.7 SECTION 4.9.1 (ADDITION)

Duration of follow-up (in months) will be summarized on the MTP population using descriptive statistics. Duration of follow-up will be defined as time from randomization to death for patients who died, or last known alive date, for patients who were censored.

3. LIST OF ADDITIONAL OUTPUTS

Output Number	Title	Population
Adhoc Table 1	Treatment Emergent Adverse Events by SOC and PT during MTP	SAF Population
Adhoc Figure 2	Kaplan Meier Plot of Progression Free Survival by Gender	MTP Population
Adhoc Figure 3	Kaplan Meier Plot of Progression Free Survival by Baseline ECOG Performance Status	MTP Population
Adhoc Figure 4	Kaplan Meier Plot of Progression Free Survival by Initial Diagnosis	MTP Population
Adhoc Table 5	Summary of Baseline Biomarker Status	ITP Population
Adhoc Table 6	Major Protocol Deviations Prior Start of ITP	ITP Population
Adhoc Table 7	Major Protocol Deviations Prior or During ITP	ITP Population
Adhoc Table 8	Summary of PFS Considering the First 330 Patients Randomized	MTP Population
Adhoc Table 9	PFS: Hazard Ratio Considering the First 330 Patients Randomized	MTP Population
Adhoc Figure 10	Kaplan Meier Plot of PFS Considering the First 330 Patients Randomized	MTP Population
Adhoc Table 11	Duration of Follow-up	MTP Population

STATISTICAL ANALYSIS PLAN

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

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SPONSOR: F. Hoffmann-La Roche Ltd

PLAN PREPARED BY: [redacted]
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DATE FINAL: 15th September 2017

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LIST OF APPENDICES

HISTORY CHANGE

Version	Date	Changes
Final 1.0	17-Feb-2017	N/A
Final 2.0	15-Sep-2017	• Change in primary analysis to only consider surgery with palliative or curative intent to censor the patients for PFS. Indeed, if the patient had a surgery with diagnostic intent between baseline tumor assessment for MTP and a disease progression, then the PFS event will be taken into account in the primary analysis. • Addition of a sensitivity analysis for PFS that is considering all PFS events reported during MTP regardless of any surgery. • Following CHMP request, addition of Progression-Free Survival 2 analysis. • Following regular monitoring of PFS events all groups pooled, the cut-off date has been revised from 31-Jul-2017 to 31-May-2017. • Modification of the best overall response to consider the tumor assessments from randomization date (instead of start of treatment date), and regardless of a surgery. • Addition of clarification to handle AE related to FOLFOX starting in MTP phase: Those AEs could not be reported as such in current CRF as it was not envisioned at the start of the study. A unique text has been reported in a comment field, to identify those AEs. This unique text will be used to select any AE related to FOLFOX during MTP. • Revision of the list of AE tables to be produced by replacing some tables by SOC/PT and worst grade by tables by SOC/PT only. • Revision of the general section to focus on Cohort 2, by removing the information related to the other cohorts. • Harmonization of the definitions related to exposure (eg. dose intensity, relative dose intensity). • Clarifications of some sections.

LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	adverse event
AESI	adverse events of special interest
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANC	absolute neutrophils count
aPTT	activated partial thromboplastin time
AST	aspartate aminotransferase
BMI	body mass index
BOR	best overall response
$BRAF^{mut}$	BRAF mutation
BSA	body surface area
CI	confidence interval
CR	complete response
CSR	clinical study report
DCR	disease control ate
DoR	duration of response
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic Case Report Form
EU	European Union
FP	fluoropyrimidine
Hb	hemoglobin
HER2	human epidermal growth factor receptor 2
HER2+	human epidermal growth factor receptor 2 positive
HR	hazard ratio
IC	informed consent
ICH	International Conference on Harmonization
iDMC	Independent Data Monitoring Committee
IHC	immunohistochemistry
INR	international normalized ratio
ITP	Induction Treatment Phase
IxRS	interactive voice or web-based response system
KM	Kaplan Meier
LDH	lactate dehydrogenase
mCRC	metastatic Colorectal Cancer
MedDRA	Medical Dictionary for Regulatory Activities
mRECIST	modified Response Evalution Criteria in Solid Tumors

Abbreviation	Definition
MSI-H	high microsatellite instability
MSS	microsatellite stable
MTP	Maintenance Treatment Phase
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NE	not evaluable
NGS	next generation sequencing
ORR	objective response rate
OS	overall survival
PD	progressive disease
PDMS	protocol deviation management system
PFS	progression free survival
PK	pharmacokinetic
PP	Per protocol
PR	partial response
PS	performance status
PT	preferred term
PTFUP	Post-treatment follow-up phase
RBC	red blood cell
RDI	relative dose intensity
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	serious adverse event
SAF	safety population
SAP	statistical analysis plan
SC	Steering Committee
SD	stable disease
SI	Système International
SOC	System Organ Class
SOD	sum of target lesions diameter
TEAE	treatment emergent adverse event
TSH	thyroid-stimulating hormone
TTR	time to treatment response
WBC	white blood cells counts or leukocytes

1. BACKGROUND

The study is a randomized, multi-center, active-controlled, open-label, parallel-group clinical study of biomarker-driven maintenance treatment for first-line metastatic colorectal cancer (mCRC) patients. All patients will receive induction treatment with FOLFOX and bevacizumab. Induction treatment will be followed by maintenance treatment with chemotherapy combined with targeted therapy within one of several maintenance treatment cohorts. Only those patients who experience disease response or disease control during induction and who are not assessed as resectable at completion of induction will proceed to further treatment in the Maintenance Treatment Phase (MTP) of the study. Patients will be assigned to a maintenance treatment cohort based on their primary tumour biomarker results. The primary study objective within each cohort is to evaluate progression-free survival (PFS).

Maintenance treatment cohorts may be added or modified over the course of the study. This SAP describes planned analyses of patients who were assigned, or would have been assigned, to maintenance treatment Cohort 2 based on their primary tumour biomarker profile. Analyses of patients assigned to all other MODUL cohorts will be described in SAPs applicable to each specific cohort.

A Steering Committee (SC) is responsible for overseeing the general conduct of the study.

In addition, an independent Data Monitoring Committee (iDMC) is responsible for evaluating the safety of the patients participating in the trial at regular intervals throughout the study. The iDMC makes recommendations as to whether cohort recruitment should continue based on benefit-risk evaluations that include efficacy as well as safety data. To minimize the impact of such reviews on efficacy endpoint analyses, efficacy data included in these reviews has to be specified by the iDMC at a preceding iDMC meeting and has to be documented in the iDMC meeting minutes. In addition, the iDMC evaluates the safety data from a prespecified number of initial patients for experimental combinations with inadequate prior safety experience to assure appropriate dosing (e.g. as required for the initial patients treated with the Cohort 1 experimental combination of '5-FU/LV + cetuximab + vemurafenib')

Of note, a preliminary assessment of efficacy of Cohort 2 (according to protocol version 5) was conducted by the iDMC on April, 4th 2016. Based on recommendations from the study SC and iDMC, the preliminary assessment of efficacy has been removed in protocol version 6 as well as the early efficacy assessment as co-primary objective. PFS remained as the primary endpoint. Analysis of a co-primary objective is no more mentioned in the Statistical Analysis Plan (SAP) that focuses only on the description of the analysis required for Cohort 2.

2. STUDY DESIGN

Patients continuing from the Induction Treatment Phase (ITP) to the Maintenance Treatment Phase are assigned to a maintenance treatment cohort based on their primary tumour biomarker status. Following eligibility assessment for their assigned cohort, eligible patients are randomized to the experimental or control arm within their cohort.

The study was initiated with 2 maintenance treatment cohorts, Cohorts 1 and 2. Two additional cohorts, Cohorts 3 and 4, were added with protocol amendment 5 (protocol version 6). Enrolment into the study was stopped temporarily as of June 3, 2016 since patients enrolled in

the study at that time were estimated as adequate to fulfil accrual to Cohort 2. Patients enrolled in the study after June 2016 cannot be enrolled into Cohort 2. The study restarted with amendment 5 that includes additional Cohorts 3 and 4. Further cohorts can be added and/or existing cohorts be changed over the course of the study via protocol amendments.

In this open-label study, all patients will receive 8 cycles induction treatment that is considered standard in many countries and that has been shown to improve outcomes in the first-line setting. Treatment during the ITP, 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

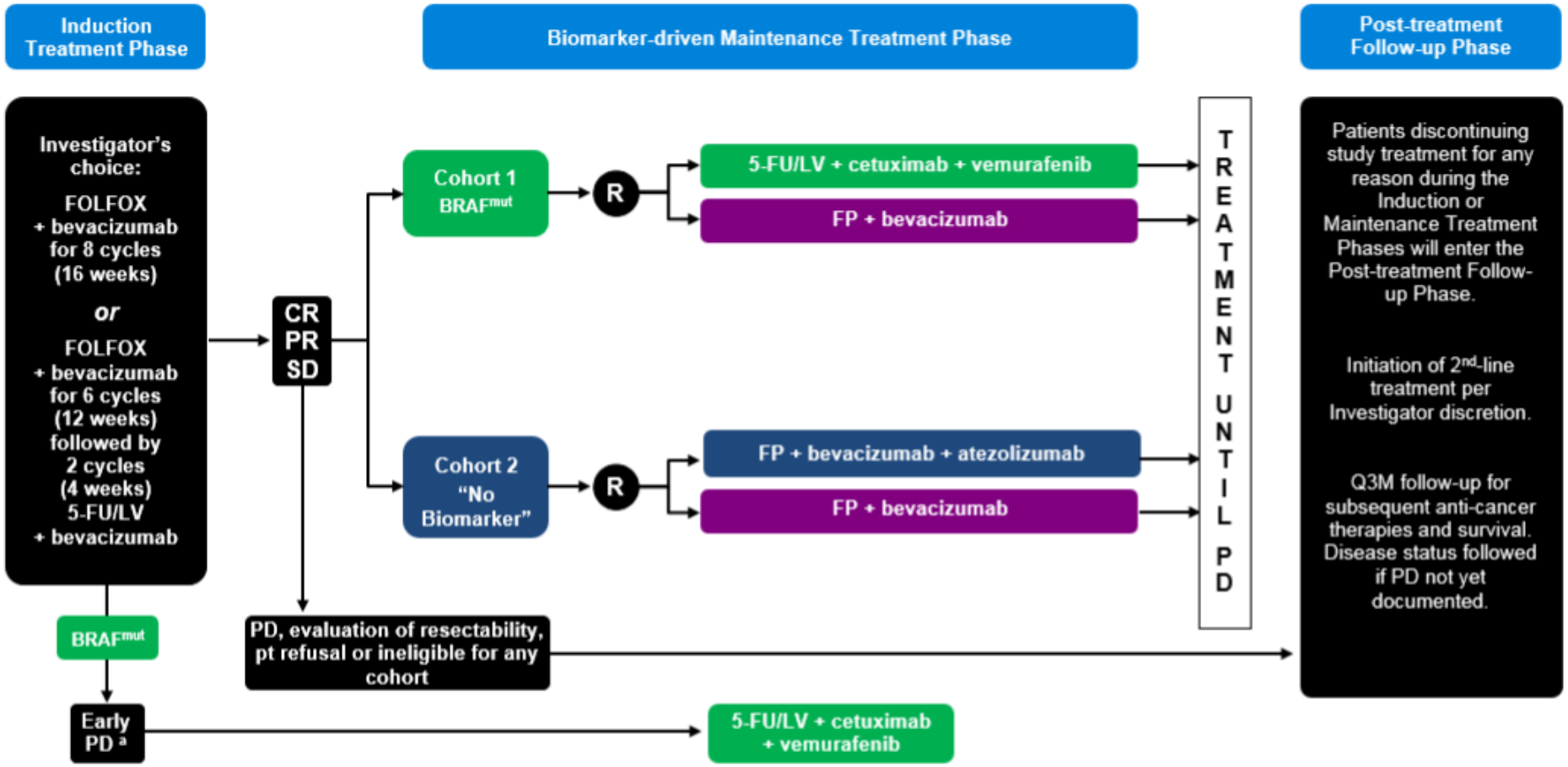
- Six 2-week cycles of FOLFOX in combination with bevacizumab, followed by two 2-week cycles of 5-FU/LV with bevacizumab

Patients who prematurely discontinue study treatment for any reason during ITP, who experience progressive disease (PD) at any time during or at the end of the ITP, who are evaluated as resectable at the end of ITP, who refuse to proceed to the MTP or who are not eligible for any maintenance cohort will undergo a study treatment discontinuation visit and enter post-treatment follow-up. Patients who experience disease control or tumor response to induction treatment will continue to the randomized MTP of the study wherein the effects of experimental and control groups will be compared. Patients enrolled in the study before June 3, 2016 (i.e. prior to study amendment 5) who do not have BRAFmut disease or whose primary tumour biomarker status is unknown for technical reasons are assigned to Cohort 2. Patients with BRAFmut disease enrolled prior to study amendment 5 are assigned to Cohort 1. Treatment in each cohort is shown in Figure 1.

BRAFmut patients enrolled prior to study amendment 5 experiencing early disease progression during the ITP will have the option of proceeding immediately to receive second-line treatment with 5-FU/LV+ cetuximab + vemurafenib according to treatment administration and management applicable to Cohort 1.

The study design applicable to patients enrolled in the study before June 3, 2016 (i.e. prior to study amendment 5, protocol version 6) is summarized in Figure 1.

Figure 1: Study Design as per protocol version 5



FP = fluoropyrimidine (5-FU/LV or capecitabine)

a. Patients who progress early and who are not BRAF^{mut} will enter the Post-treatment Follow-up Phase with initiation of 2nd-line treatment per Investigator discretion

Primary objective of this study:

The primary study objective within each cohort is to evaluate PFS.

An iDMC is responsible for regularly reviewing safety data.

2.1 PROTOCOL SYNOPSIS

The Protocol version 5 synopsis is provided in Appendix 1. For additional details, see the Schedule of Assessments in Appendix 2.

2.2 OUTCOME MEASURES

As mentioned in the protocol, each cohort will be analysed separately and therefore this SAP focuses on the description of the analysis required for cohort 2 data only.

2.2.1 Primary Efficacy Outcome Measures

PFS is defined as the time from randomization into the MTP until documented disease progression as per investigator assessment using Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 or death from any cause, whichever occurs first. If no progression / death is observed at the time of clinical cut-off or by the date of any on-study colorectal anti-cancer surgery with palliative or curative intent, patients will be censored at the date of the last evaluable tumor assessment or date of randomization, whichever comes last.

(Of note: (i) Progressive disease are identified by the Overalll Response='PD', even if solely based on symptomatic deterioration, (ii) Only surgery occurring between baseline tumor assessment for MTP and PFS events are considered for censoring PFS)

Sensitivity Analysis

PFS is defined as the time from randomization into the MTP until documented disease progression as per investigator assessment using Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 or death from any cause, whichever occurs first. If no progression / death is observed at the time of clinical cut-off, patients will be censored at the date of the last evaluable tumor assessment or date of randomization, whichever comes last.

2.2.2 Secondary Efficacy Outcome Measures

2.2.2.1 Overall Survival (OS)

OS is defined as the time from randomization into the MTP to time of death from any cause. Patients still alive at time of clinical cut-off will be censored at their last date known to be alive as defined in section 4.3. For imputation of "Partial Death Date", please refer to section 4.14.

2.2.2.2 Best Overall Response (BOR)

Main definition

BOR (e.g. complete response [CR], partial response [PR], stable disease [SD], progressive disease [PD], not evaluable [NE]) for the MTP will defined as the best response recorded from the randomization date until progressive disease (taking as reference for progressive disease the smallest measurements recorded since randomization date). For patients under maintenance treatment at time of primary analysis, the BOR will be defined based on available tumor assessment at time of clinical cut-off. The overall response per time point reported on the electronic Case Report Form (eCRF) by the investigator (as per RECIST v1.1) will be used for the derivation of the BOR. No confirmation of response is required as per protocol.

A minimum interval of 28 days will be considered for SD to be assigned as best overall response, i.e. in the case the single response is SD, SD must have been assessed no less than 28 days after randomization date of the MTP, otherwise the best overall response will be NE.
If the patient has missing baseline tumor assessment, best overall response will be NE.
Patients without tumor assessment after randomization will be assigned a tumor response of NA (Not applicable).
Patients with only non-target lesions classified as having an eCRF tumor response status of "Non-CR/Non-PD" are classified as SD.

Secondary/Sensitivity definition

BOR (e.g. CR, PR, SD, PD, NE) for the MTP will defined as the best response recorded from the randomization date until end of maintenance treatment or progressive disease whichever comes first (taking as reference for progressive disease the smallest measurements recorded since randomization date).

The derivation of the BOR will be the same as for the main definition, the only change being the time window during which the best overall response is observed. In other words, the main definition for BOR considers all tumor assessments collected on study (i.e. including post-treatment tumor assessments phase for patients withdrawing maintenance treatment for other reason than PD) whereas the secondary/sensitivity definition considers only tumor assessments collected on maintenance treatment phase (i.e within 30 days from last day of treatment of MTP, up to the day before the start of further anti-cancer therapy, whichever comes first). Therefore the secondary/sensitivity analysis regarding BOR is an on-treatment analysis.

2.2.2.3 Objective Response Rate (ORR)

ORR is defined as the number of patients with a BOR of CR or PR during the MTP phase divided by the number of patients in the studied population.

2.2.2.4 Disease Control Rate (DCR)

DCR is defined as the number of patients with a BOR during the MTP of CR, PR or SD divided by the number of patients in the studied population.

2.2.2.5 Time to Treatment Response (TTR)

TTR will be calculated for responders (i.e. patients with a MTP BOR of CR or PR) only. It will be defined as the time from randomisation to the first occurrence of a documented objective response (CR or PR).

2.2.2.6 Duration of Response (DoR)

DoR will be calculated for responders only. It will be defined as the time from the first assessment of CR or PR until disease progression or death from any cause, whichever occurs first. Patients who do not progress or die after they have had a response are censored at the date of their last tumor measurement.

2.2.2.7 Progression Free Survival 2 (PFS2)

PFS2 is defined as the time from randomisation to second objective disease progression, or death from any cause, whichever first. Patients alive and for whom a second objective disease progression has not been observed should be censored at the last time known to be alive and without second objective disease progression.

Of note: Date of second objective disease progression is the first date of progressive disease as reported on the 'Subsequent Anti-Cancer Therapies' eCRF page.

2.2.2.8 Other

- Change from baseline in tumor size during MTP

The change from baseline in tumor size at a specific assessment occurring during the maintenance treatment phase will be defined as:

100*((SOD at visit x– baseline SOD) / baseline SOD)

with:

- SOD at visit x corresponding to the Sum Of target lesions Diameter (SOD) at visit
- Baseline SOD is the last SOD recorded on or prior to the randomization date in the MTP. This baseline assessment should correspond to the tumor assessment performed at the end of ITP as defined in section 4.10.1.

- Eastern Cooperative Oncology Group (ECOG) Performance Status (PS) during and after MTP

2.2.3 Exploratory Efficacy Outcome Measures

2.2.3.1 PFS in Patients Randomized to Atezolizumab according to Modified RECIST (mRECIST) (applicable to experimental group only of Cohort 2)

This endpoint is only applicable to patients randomized to atezolizumab. It is defined as the time from randomisation into the MTP until disease progression per Investigator assessment using mRECIST (refer to Appendix 8 in protocol version 5) or death from any cause, whichever

occurs first. Patients without an event at the time of clinical cut-off or by the date of any on-study colorectal anti-cancer surgery with palliative or curative intent will be censored at the date of the last evaluable tumour assessment or date of randomization, whichever comes last.

2.2.4 Safety Outcome Measures

The safety outcome measures for this study are as follows

- Incidence, nature and severity of all adverse events (graded according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) v4.0)
- All serious adverse events (SAEs)
- Incidence and reasons for any dose reductions, interruptions or premature discontinuation of any component of study treatment
- Adverse events of special interest (AESI)*
- Clinically significant changes in laboratory values
- Vital signs

*AESI for cohort 2 are only reported for the maintenance phase, since no AESIs are defined for the induction phase in protocol version 5.

2.2.5 Pharmacokinetic (PK) Outcome Measures

There are no PK outcome measures for this study.

2.2.6 Exploratory Biomarker Outcome Measures

The exploratory biomarker outcome measures for this study include molecular markers/marker profiles and efficacy and/or safety outcomes. Efficacy outcomes considered for this analysis may include, but are not limited to ORR, PFS and OS, as appropriate. Biomarkers, biomarker profiles and microbiomes may be assessed using various methodologies including, but not limited to, immunohistochemistry (IHC) (single and multiplex), RNA and DNA analysis (e.g. polymerase chain reaction, next generation sequencing [NGS], mutation expression and microsatellite instability [MSI] analyses) of tumour and/or blood samples collected from all study patients.

Next-generation sequencing was introduced with protocol amendment 5. Retrospective NGS will be conducted on samples collected provided appropriate consent has been obtained. Statistical analysis will be covered in a separate SAP.

2.3 DETERMINATION OF SAMPLE SIZE

Estimates of overall study screening and enrolment will vary with the addition of new maintenance treatment cohorts over the course of the study. Approximately 700 patients were planned for enrolment in the Induction Treatment Phase of the study as described in protocol version 5.0 in order to randomise 126 patients in Cohort 1 and 405 patients in Cohort 2.

The calculated sample size for each study cohort has been based on an estimated recruitment period for 11 months for Cohorts 2 and on the comparison between PFS in the experimental and control groups of that cohort. Estimated proportions of the patients enrolled into the study that are eligible for each cohort are based on published reports (*di Nicolantonio et al. 2008)* Approximately 25% of all patients enrolled are expected to have disease progression prior to randomisation into the Maintenance Treatment Phase (Roche, data on file). Inputs used in cohort-specific sample size calculations are provided in Table 1.

Table 1: Sample Size Determination per Cohort

	Cohort 1	Cohort 2
Percent of study population eligible for cohort based on biomarker status	10%	90%
Percent of patients eligible for cohort based on biomarker status expected to have disease progression prior to randomization	25%	25%
Average randomization rate (pts/month) [a]	3.5	31.5
Estimated median PFS [b] (months) - Experimental group	7	11.5
Estimated median PFS [b] (months) - Control group	4.9	7.5
Hazard ratio (HR)	0.70	0.65
Number of expected PFS events	96	259
Statistical test	1-sided	2-sided
Alpha level	10%	5%
Power	65%	90%
Randomized patients	126	405
Randomization ratio (experimental vs control)	2:1	2:1
Recruitment period (months)	36	11
Time to primary analysis of PFS (months) [c]	36	22

a. Based on 1,680 patients screened over a 3-year recruitment period
b. Per RECIST 1.1
c. Time from first patient randomized in cohort

2.4 ANALYSIS TIMING

The primary analysis for each cohort will be performed based on data collected until the analysis cut-off date, defined as the time when the target number of PFS events has been reached for that cohort, as shown in Table 1 in the number of expected PFS row. The primary analysis for cohort 2 will occur when 259 PFS events have been observed i.e. approximately 22 months after first patient was randomized.

Tracking of events will be performed based on the clinical database data to predict the time when the number of targeted events is reached. Tracking of events started once accrual of the cohort was complete and is done on a monthly basis. As the targeted number of events is approached the more frequently the tracking of events might occur. As per prediction at the date of signature of the version 1.0 of the SAP and as per Roche Global Medical Team meeting on February, 13th 2017, the cut-off date for cohort 2 was initially defined to be 31 July 2017. Following regular tracking of events, the cut-off date was revised and set to 31 May 2017.

The final analysis, which will consist of updating main time-to-event and safety endpoints, will take place once the 24-month survival follow-up from the primary cut-off date (i.e. from the date when 259 PFS events are reached) is complete. Final results of efficacy and safety parameters will be reported in a separate clinical study report (CSR).

The outputs to be provided for each analysis (primary or final) are listed in Appendix 5.

Analysis for cohorts other than cohort 2 is not covered in this SAP and will be documented in separate SAPs.

3. STUDY CONDUCT

3.1 RANDOMIZATION ISSUES

Patients will be assigned to a cohort based on the results of biomarker assessments conducted on archival primary tumour tissue obtained during their initial CRC diagnosis. Once assigned to a cohort, patients will be randomized on a 2:1 basis to either the experimental treatment group or the control group of that cohort. Randomization in Cohort 2 will be stratified by geographical region (EU, Americas, Africa or Asia), and by patient response after the Induction Treatment Phase (CR/PR vs. SD).

3.2 INDEPENDENT REVIEW FACILITY

Not applicable.

3.3 DATA MONITORING

An iDMC is responsible for:

- evaluating the safety of the patients participating in the trial at regular intervals throughout the study,
- making recommendations as to whether cohort recruitment should continue based on benefit-risk evaluations that include efficacy as well as safety data. To minimize the impact of such reviews on efficacy endpoint analyses, efficacy data included in these reviews has to be specified by the iDMC at a preceding iDMC meeting and has to be documented in the iDMC meeting minutes,
- performing a review of the safety data from a prespecified number of initial patients for experimental combinations with inadequate prior safety experience to assure appropriate dosing (e.g. as required for the experimental combination of '5-FU/LV + cetuximab + vemurafenib').

4. STATISTICAL METHODS

4.1 GENERAL DESCRIPTIVE METHODS

Categorical variables

For categorical variables, summary tabulations of the number and missing observations as well as the number and percentage within each category of the parameter will be presented. Missing will not be considered as a separate category and thus missing observations will not be part of the denominator to compute the percentages. Percentages will be rounded to one decimal place. Therefore, there may be cases where for instance the total of the percentages does not exactly equal 100%. If number of patients is '0' then 0 will be reported instead of '0 (0.0%)'

Continuous variables

For continuous variables, N, the mean, median, standard deviation, 25th and 75th percentile. minimum and maximum values will be presented.

Time-to-event efficacy variables

Time-to-event efficacy variables (e.g. PFS and OS) summaries will include number of patients in the population (N), number of patients with the event of interest, number of patients censored, median and two-sided 95% confidence interval (CI) computed according to Brookmeyer and Crowley (1982) method. Kaplan-Meier (KM) estimates and median survival times are calculated with the PROC LIFETEST procedure in SAS. KM curves (product-limit method) will be presented as well as the event rates at certain time points with the relevant CIs calculated via log-log transformation method (default option CONFTYPE=LOGLOG in SAS) based on standard errors computed using the Greenwood's formula.

Cox proportional hazards models

Cox proportional hazards model will be implemented using PHREG procedure with option TIES=EXACT. It assumes that there is a true but unknown ordering for the tied event times as contrasted to option TIES=DISCRETE which assumes that the events occurred at exactly the same time.

Missing values

For categorical variables, summary tabulations of the number and missing observations as well as the number and percentage within each category of the parameter will be presented. For continuous variable, number of missing is displayed between brackets next to 'n', unless otherwise specified.

Decimals

Mean, standard deviation, and median (Q1 and Q3 if applicable) will be presented with one more decimal place compared to the raw data, minimum and maximum will be presented with same number of decimal places as the raw data. Hazard ratio, odds ratio will be provided with

two decimals. P-value will be provided with three decimals. If <0.001, then '<0.001' will be displayed.

4.2 DEFINITION OF TREATMENT PHASE

In this study, there are 3 treatment phases:

1. Patients are treated first in the Induction Treatment Phase (ITP) for a planned duration of 8 cycles, i.e. 16 weeks.

2. If they do not experience any progressive disease before or at the end of the ITP, are not considered resectable at the end of the ITP and do not withdraw from the study and are still eligible for any cohort, they are randomized and treated in the Maintenance Treatment Phase (MTP).

3. If they discontinue study treatment for any reason during the Induction or Maintenance Treatment Phases, do not withdraw from the study and are still alive, they enter the Post-Treatment Follow-up Phase.

4.2.1 Induction Treatment Phase (ITP)

ITP is defined as the time from first study drug administration until

- the day before the randomization for patients continuing treatment in the MTP
- the last assessment date otherwise

The first day of treatment in the ITP is defined as the earliest day of a non-null administration of any induction phase treatment.

The last day of treatment in the ITP is defined as the last day of the last initiated cycle of the induction phase, or as the death day if the patient died in between. A two-week cycle duration is assumed.

Baseline evaluations for the ITP will be those performed not earlier than 28 days prior to the first day of treatment in the induction phase, unless otherwise stated. The latest available assessment up to start of the first day of treatment in the induction phase will be considered as baseline. For laboratory examinations, weight, vital signs and ECOG PS, assessments performed on the first day of treatment of the ITP will be assumed to have been performed before drug was given and, thus, will be considered as baseline evaluations.

On-treatment evaluations for the ITP will be post baseline evaluations performed until

- the day before the randomization for patients continuing treatment in the MTP
- (including) the study treatment discontinuation visit within 30 days after last day of treatment of the ITP (as defined above), for patients not randomized in the MTP.

4.2.2 Maintenance Treatment Phase (MTP)

MTP is defined as the time from randomization into MTP until (including) the study treatment discontinuation visit in the MTP.

The first day of treatment in the MTP is defined as the earliest day of a non-null administration of any maintenance phase treatments.

The last day of treatment in the MTP is defined as the last day of the last initiated cycle of the maintenance phase, or as the death day if the patient died in between. A two-week cycle duration is assumed.

Baseline evaluations for the MTP will be those performed prior to the first day of treatment in the maintenance, unless otherwise stated. The latest available assessment prior to the first day of treatment in the maintenance phase will be considered as baseline for safety assessments. For laboratory examinations, weight and vital signs, assessments performed on the first day of treatment of the MTP will be assumed to have been performed before drug was given and, thus, will be considered as baseline evaluations. For subjects randomized but not treated in the MTP, the latest available assessment before or on randomization date (including assessments from ITP) will be considered as baseline for the MTP.

For efficacy assessments, the latest available assessment prior or on the randomization date will be considered as baseline.

On-Treatment evaluations for the MTP will be evaluations performed on or after the first day of treatment in the MTP within 30 days from last day of treatment in the maintenance phase. On-treatment laboratory will be all values collected after the first day of treatment in the maintenance phase and within 30 days from last day of treatment in the maintenance phase (as defined above). For adverse events, treatment emergent adverse events (TEAEs) will be events occurring on or after the first day of treatment in the MTP within 30 days (for patients in control group, i.e. not treated with atezolizumab) and 90 days (for patients in experimental group, i.e. treated with atezolizumab) from last day of treatment in the maintenance phase (as defined above).

4.2.3 Post-Treatment Follow-up Phase

Post treatment Follow-up Phase is defined as the time from (excluding) the study treatment discontinuation visit until the last available assessment date before clinical cut-off date. For patients who discontinue study treatment but without any study treatment discontinuation visit date, please refer to 4.14 for imputation of this missing visit date.

Post-Treatment Follow-up evaluations will be evaluations performed according to the protocol after the study treatment discontinuation visit.

4.3 DATA CONVENTION

All data will be listed (e.g. pre-treatment serious adverse events), whereas only baseline and on-treatment assessments will be considered for summary tables.

Baseline and on-treatment data will be flagged in the data listings as well as the different phases of the study.

The overall column will not be displayed in any summary tables.

The following conversion factors will be used to convert days to months or years, where applicable:

- 1 week= 7 days
- 1 month = 30.4375 days
- 1 year = 365.25 days

Age at informed consent (IC) {in years} = (date of informed consent – date of birth) / 365.25

To calculate **duration / time between** two dates the following convention will be used:

[later date] – [earlier date] + 1 day

Durations and times between two dates will be calculated only when both start and end dates are available (imputed dates cannot be used for computation), apart for overall survival when date of death has only day as missing)..

Body surface area (BSA) will be recalculated based on the height and weight of the patient using the following formula:

BSA (m^2) = ([Height {cm} x Weight {kg}] / 3600)^{½}

Body mass index (BMI) will be calculated using the following formula:

BMI (kg/m^2) = Weight {kg} / Height^2 {m}

The last known date to be alive will be the latest date among all dates specified in the eCRF except the following:

- Survival Follow-up date when status is either dead (in this case the date of death is specified on the Adverse events or Study Completion/Early Discontinuation or SAE reporting summary form) or lost to follow-up (in this case last date known to be alive is specified on the Survival follow-up form)
- Study Completion/Early Discontinuation date when reason is neither death or lost to follow-up.
- A sample / record with test 'Not Done'.

4.4 COMPUTING ENVIRONMENT

All statistical analyses will be performed using SAS statistical software (Version 9.2 or newer version), unless otherwise noted.

4.5 GRADING AND CODING OF ADVERSE EVENTS, LABORATORY PARAMETERS AND MEDICATIONS

Laboratory results, adverse events, and other symptoms will be graded using the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Event (CTCAE), version 4.0, except where CTC grades are not available.

Adverse events and relevant Medical History data fields (i.e. prior symptoms / AEs) will be coded using the most recent version of Medical Dictionary for Regulatory Activities (MedDRA) dictionary available at the time of analysis.

Prior and concomitant anti-cancer therapy / other medications will be coded using the most up-to-date version of the in house Genentech Drug Thesaurus Dictionary.

Dictionary versions used will be displayed in analysis outputs.

4.6 ADUSTMENTS FOR COVARIATES

When indicated, efficacy analysis will be adjusted i.e. the covariates will be incorporated in the model used to assess the treatment effect upon the efficacy endpoints. The covariates below will be considered:

- Geographical region as per clinical database: EU, Americas, Africa or Asia. For inferential analysis, “EU” will be used as reference. Note: if the number of patients in a region is small, the region will be pooled (e.g. EU vs Rest of the world).
- Patient response after induction treatment as per eCRF data: CR/PR vs. SD. For inferential analysis, “SD” will be used as reference, unless otherwise specified.

4.7 SUBGROUP ANALYSIS

The following subgroups will be considered to repeat PFS and OS analysis by subgroup:

- Demographic characteristics:
  - Age (<65 years, >= 65 years)
  - Gender (male vs female)
  - Region as per clinical database (EU versus Rest of the World)
  - Tumor response at end of ITP (SD vs. CR/PR) as per eCRF
  - Baseline ECOG performance status (0 vs. 1/2),
- Baseline disease characteristics:
  - Initial AJCC/UICC stage (stage I/II/III vs. stage IV)
  - Prior systemic adjuvant therapy (yes vs no)
  - Number of metastatic sites at screening (<2 x vs. >= 2)
  - Liver metastatic site at baseline (yes vs no)
  - Cancer type (colon vs rectal)
  - Tumor colon location (right vs left)
  - Initial diagnosis (synchronous vs metachronous)
- Biomarker:
  - RAS status (RASwt vs RASmut)
  - Microsatellite stability status (MSS vs MSI-H)
  - RAS status (RASwt vs RASmut) for MSS patients
  - Tumor colon location (right vs left) for RASwt patients
  - Tumor colon location (right vs left) for RASmut patients
  - Tumor colon location (right vs left) for MSS patients

The subset tumor colon location (left, right) will be derived based on the primary tumor location information collected on the colorectal cancer history eCRF page. Right colon is defined as patients with ceacum, appendix, ascending colon or right hepatic flexture or transverse colon

as primary tumor location. Left colon is defined as patients with left splenic flexture or descending colon or sigmoid or rectum as primary tumor location.

The subset cancer type (colon, rectal) will be derived based on the primary tumor location collected on the colorectal cancer history eCRF page. Colon cancer type is defined as patients with ceacum, appendix, ascending colon or right hepatic flexure or transverse colon or left splenic flexure or descending colon or sigmoid as primary tumor location. Rectal cancer type is defined as patients with rectum as primary tumor location.

The subset initial diagnosis (synchronous, metachronous) will be derived based on the time from initial histological diagnosis to first diagnosis of metastatic disease. If this time is longer than 6 months then the initial diagnosis of the corresponding patient will be considered metachronous, or as synchronous otherwise. In case date of first diagnosis of metastatic disease is missing, this one will be replaced by the date of first diagnosis of locally recurrent disease. In case both are missing, the corresponding patients will be excluded from the corresponding subgroup analysis. In case one of the dates (i.e. date of initial histological diagnosis or date of first diagnosis of metastatic disease or date of first diagnosis of locally recurrent disease) is partially missing, it will be imputed as described in section 4.14.

4.8 ANALYSIS POPULATIONS

The following patient populations will be evaluated and used for presentation and analysis of the data.

4.8.1 All Population

ALL Population: The ALL population consists of all patients without a confirmed BRAF mutation result who signed an Inform consent form until June 3, 2016.

Induction Treatment Phase (ITP) Population: all patients included in the ALL Population and who are treated in the ITP, i.e. who received at least one non-null dose of any study medications during the ITP. ITP population is the main population to be used to summarize ITP data and Post Induction Treatment data. The 2 following groups will be considered when tabulating ITP data: patients randomized into MTP versus patients not randomized into MTP. Post Induction Treatment data will be summarized using one single group, i.e. patients not randomized into MTP. ITP population will be the main population for the data listings, unless otherwise specified; the 3 following groups will be displayed in listings: patients randomized in the experimental group of MTP, patients randomized in the control group of MTP, patients not randomized into MTP.

4.8.2 Randomized Population

Maintenance Treatment Phase (MTP) Population is defined as all patients randomized into the Cohort 2 MTP of the study, irrespective of whether or not they received study medication. Patients will be allocated to the treatment group into which they were randomized (as per interactive voice or web-based response system [IxRS]). The MTP population is the primary population for the analysis of efficacy parameters and baseline characteristics for the MTP. The MTP population will be used as well to report the Post Maintenance Treatment data.

4.8.3 Safety Population

Safety (SAF) Population: all patients randomized in Cohort 2 who have been treated, i.e. who received at least one non-null dose of any study medications during the MTP.

Patients will be allocated to the treatment group they actually received using the following rule:

- Patients receiving at least one dose (non-null) of atezolizumab, while on treatment will be allocated to the experimental group FP+bevacizumab+ atezolizumab. Even if a patient was allocated to the control group and received by mistake a dose of atezolizumab, then this patient will be reallocated to the experimental group.
- Patients who did not receive any dose of atezolizumab will be allocated to the control group FP+bevacizumab.

The SAF population is the primary population for the analysis of MTP safety parameters.

4.8.4 Per Protocol (PP) Population

As stated in the protocol, the PP Population will not be defined for this study but major protocol violations will be listed.

4.8.5 Pharmacokinetic-Evaluable Population

Not applicable.

4.8.6 Biomarker-Evaluable Population

Not applicable.

4.9 ANALYSIS OF STUDY CONDUCT

This SAP focuses only on the description of the analysis required for cohort 2 data. All MTP data will be reported. ITP data for non-BRAF mutant patients randomized and not randomized into the MTP will be tabulated in 2 separate columns. Post-treatment data will be reported separately for induction and maintenance. This Post-treatment data includes adverse events, deaths, subsequent anti-cancer therapies and tumor assessments (until PD if PD not experienced before study treatment discontinuation visit), but this last one applies only for Post Maintenance treatment.

4.9.1 Patient Disposition

The patient disposition table for ITP will be based on the ALL population and will include the following information:

- Number of patients enrolled (ALL)
- Number of patients not treated in induction who discontinued trial without being treated and associated reason

- Number of patients treated with induction treatment (ITP population)
- Number of patients who completed the ITP
- Number of patients treated in induction who discontinued early ITP and reason for early discontinuation
- Number of patients treated in induction and not randomized who went to post-treatment follow-up phase post induction
- Number of patients being treated in induction who discontinued study prior to MTP and associated reason

The patient disposition table for MTP will include the following information:

- Number of randomized patients (MTP population) (percentage based on MTP)
- Number of randomized patients without being treated in MTP still on-trial
- Number of randomized patients who discontinued trial without being treated in MTP and the corresponding reason for trial discontinuation (percentages based on MTP)
- Number of treated patients with maintenance treatment (SAF) (percentages based on MTP)
- Number of patients treated who discontinued all treatments received in MTP and the reason for discontinuation from each maintenance treatment (percentage based on MTP). All reasons for treatment discontinuation will be displayed and will be taken from the individual treatment completion/Early discontinuation eCRF pages.
- Number of patients treated in MTP who discontinued trial during MTP and the corresponding reason for trial discontinuation (percentages based on MTP)
- Number of patients who entered in the follow-up post-MTP
- Number of patients being treated in MTP who discontinued trial during follow-up and the corresponding reason for trial discontinuation (percentages based on MTP)

A consort flow diagram will be provided to show progress of screened patients who signed an informed consent form until June 3, 2016 and especially for non-BRAF mutant patients through the different phases (screening, ITP, MTP, end of treatment, follow-up, end of study).

The following supportive listings will be provided:

- Patient disposition (including the tumor response status at the end of ITP) and study termination information based on ITP
- Patients who discontinue treatment due to AE (based on ITP)

4.9.2 Protocol Deviations

All major protocol deviations from Protocol Deviation Management System (PDMS) will be reported for each phase separately and will be summarized by group. The ITP population will be used for ITP data and the MTP population for the MTP data.

The following will be displayed

- Number of patients having at least one major protocol deviation
- Number of patients by major protocol deviations category

Listings for protocol deviations and analysis population will be provided based on ITP population.

4.10 ANALYSIS OF TREATMENT GROUP COMPARABILITY

4.10.1 Demographics and Baseline Disease Characteristics

Baseline and demographic characteristics will be summarized using descriptive statistics. No formal statistical comparisons will be performed.

Summaries of Patient Demographics will be provided based on the ITP and MTP population and will present the following information:

- Age at informed consent (yrs)
- Age categories (yrs) : < 18, 18-64, 65-84, 85 and over
- Sex
- Ethnicity: Hispanic or Latino, Not Hispanic or Latino, Not reported, Unknown
- Race
- Region: Europe, Americas, Africa, Asia (derived based on country information from the clinical database)
- Smoking status: Never, Current, Previous
- Alcohol use history: Never, Current, Previous
- Drug Use: Never, Current, Previous
- ECOG Performance Status at baseline: 0,1,> 1,
- Baseline Weight (kg)
- BMI (see definition in section 4.3)
- BSA (see definition in section 4.3)
- Baseline Height (cm)
- Female reproductive status (for female participants only. Percentage will be based on the total number of female patients)

The summary of patients characteristics based on MTP will include in addition the serology results (positive, negative, not done) for the following parameters HIV, Hepatitis B surface antigen (HBsAg), Hepatitis B core antibody (HBcAb), HCV Antibody, HCV RNA (only if HCV Antibody positive). For the summary based on MTP only, ECOG and weight collected just prior to or on the first day of MTP will be used as baseline. Please refer to sections 4.2.1 and 4.2.2 for further details related to definition of baseline evaluations.

All the biomarker outcomes of interest as per section 4.7 will be summarized using descriptive statistics by treatment group on MTP population:

Given that the end of the induction phase is the same timepoint as the baseline tumor response for the MTP two summary tables presenting the information as mentioned below will be produced. One for the tumor response status at the end of the induction phase based on ITP and as per data collected on the eCRF and will present the following information.

- Number of patients with CR or PR at end of ITP

- Number of patients with SD at end of ITP
- Number of patients with PD at end of ITP
- Number of patients with NE at end of ITP
- Number of patients with NA at end of ITP (i.e. no tumor response during ITP)

Another table will be generated for baseline tumor response for the MTP based on MTP and as per data collected on the eCRF and will present the following information.

- Number of patients with CR or PR at end of ITP
- Number of patients with SD at end of ITP
- Number of patients with tumor response other than CR, PR or SD at end of ITP

The number of patients in MTP will be summarized by country and study center (as per clinical database and by treatment group based on the MTP population.

In addition, the number of patients will be summarized by the following stratification factors as per IxRS, by treatment group on the MTP:

- Region
    - European Union
    - Americas
    - Africa
    - Asia
- Tumor response at the end of ITP
    - CR/PR
    - SD

A table will show the concordance between the tumor response status at the end of ITP as per IxRS and the tumor response status at the end of ITP as per data collected on the eCRF. This table will be based on the MTP population and will display the following categories:

- CR/PR, SD, Total for the IxRS tumor response
- CR, PR, CR/PR, SD for eCRF tumor response

eCRF Tumor response status (CR, PR, SD, PD, NE) at the end of ITP is defined as the last tumor response observed during the ITP. Patients without tumor assessment after first day of induction treatment will be assigned a tumor response of NA (Not available). Patients with only non-target lesions classified as having an eCRF tumor response status at the end of the ITP of "Non-CR/Non-PD" are classified as SD for the 2 summary tables mentioned above.

Summary of colorectal cancer history will be provided based on the ITP and MTP population and will present the following information:

- Histological grade at diagnosis
- Location of primary tumor

- Colon Location: left, right
- Cancer type: colon, rectal
- Initial AJCC/UICC stage
- Initial diagnosis: synchronous, metachronous
- Locally recurrent disease: yes, no
- Metastatic disease: yes, no
- Sites of metastatic disease at time of study enrolment (adrenal gland, ascites, bone, liver, lung, mediastinum, skin, other)
- Liver as metastatic site: yes, no
- Extent of disease by number of sites at time of study enrolment: 0, 1, > 1
- Time from initial diagnosis to first dose of ITP (in years)
- Time from first diagnosis of locally recurrent disease to first dose of ITP (in years)
- Time from first diagnosis of metastatic disease to first dose of ITP (in years)
- Number of target lesions at baseline

Of note, if start and/or end dates are incomplete or missing the corresponding time between the start and the end date cannot not be derived. In this case, time from initial diagnosis to first dose of ITP or time for first diagnosis of locally recurrent disease to first dose of ITP or time from first diagnosis of metastatic disease to first dose of ITP cannot not be derived and will be missing.

Summary of RECIST tumor-specific characteristics at baseline will be generated on the MTP population and will provide the following information:

- Number of site/organs involved; 1, 2, >2
- Site/organ type involved: colon, rectum, liver, lung, lymph nodes, peritoneum, brain, other
- Type of lesions: target only, non-target only, target and non-target lesions

Of note for the above summary table, tumor-specific characteristics at baseline refer to the tumor assessment prior to randomization in MTP, i.e. last tumor assessment from the induction treatment phase.

The following listings will be provided:

- Patient Demographics based on ITP population
- Biomarker status based on MTP population
- Serology values and tuberculosis test values (for which results are collected prior to randomization only to determine eligibility for randomization in MTP) based on MTP population
- Patients by randomization stratification factors as per IxRS and eCRF (based on MTP)
- Colorectal cancer history based on ITP population

4.10.2 Medical History

Medical history, as collected on the “General Medical History and Baseline Conditions” eCRF page will be summarized using the ITP and MTP population. This summary table will include

the number and percentage of patients with at least one medical history by Primary System Organ Class (SOC) sorted in a descending order of the total frequency count and by preferred term [PT] (sorted in a descending order of the total frequency count within each SOC).

A patient with more than one occurrence of the same medical history in a particular SOC/PT will be counted only once in the total of those experiencing events in that particular system organ class/preferred term.

Medical history data will be listed based on ITP population.

4.10.3 Prior and Concomitant Medications

4.10.3.1 Prior Anti-Cancer Treatment/Procedure

Prior anti-cancer treatments/procedures summary based on the ITP and MTP population will present the following information:

- Number of patients with prior colorectal cancer surgery: Yes, No
- Number of patients by site of prior colorectal cancer surgery: Colon, Rectum, Colon and Rectum, Other.
- Number of patients with prior radiotherapy: yes, no
- Number of patients with prior anti-cancer therapies: yes, no
- Number of patients by setting of prior systemic therapy
- Number of patients with prior systemic adjuvant therapy: yes, no
- Number of regimens for prior systemic therapy: 0, 1, 2, >=3.

The following listings will be provided based on the ITP population:

- Prior anti-cancer therapy
- Prior cancer radiotherapy
- Prior cancer colorectal surgery

4.10.3.2 Non Anti-Cancer Treatment/Procedure

A prior medication/therapy is defined as any medication/therapy with an end date prior to the start of the induction treatment.

Concomitant medication for ITP

Concomitant medication includes both medication concomitant at baseline and concomitant medication initiated post-baseline. It is defined as any medication/therapy with

- start date before or on:
  - the randomization date for patients randomized in the MTP
  - last dosing date of ITP+30 days for patients not randomized in the MTP
- and end-date on or after first dosing date of the ITP or with a missing (ongoing) end-date

Concomitant medication for MTP

It is defined as any medication/therapy with

- start date before or on last dosing date in the MTP+30 days
- and end-date on or after first dosing date of the MTP or with a missing (ongoing) end-date.

Post-treatment Medication

It is defined as any medication/therapy with a start date more than 30 days after the last dosing date.

In case a medication has an incomplete or missing start date/end date, please refer to section 4.14 for the rules to be applied in order to identify prior, concomitant or post-treatment medications.

Prior and Concomitant Medications/therapies will be summarized. Summary tables will present number and percentage of patients with any medication overall and by Drug Thesaurus Class and Generic Name. At each level of summation (overall, Drug Thesaurus Class, Generic Name), patients reporting more than one medication are counted only once. Drug Thesaurus Class will be sorted in a descending order of the total frequency count and the generic names with the highest frequency will be displayed first within each Drug Thesaurus class, unless otherwise indicated. The analysis population will be the ITP and the MTP population for ITP and MTP data, respectively.

The following tables will be provided:

- Prior medications based on ITP population
- Concomitant medications for the ITP based on ITP population
- Concomitant medications for the MTP based on SAF population
- Concomitant radiotherapy performed during the ITP based on ITP population (as collected on the On-Study Cancer Radiotherapy eCRF page): Number of patients with radiotherapy, site (colon, other) and setting (neo-adjuvant, adjuvant, palliative. other) of therapy
- Concomitant radiotherapy performed during the MTP based on SAF population (as collected on the On-Study Cancer Radiotherapy eCRF page): Number of patients with radiotherapy, site (colon, other) and setting (neo-adjuvant, adjuvant, palliative, other) of therapy
- Concomitant colorectal cancer surgery during ITP based on ITP: Number of patients with at least one surgery, site of surgery, surgical procedure and intent
- Concomitant colorectal cancer surgery during MTP based on SAF: Number of patients with at least one surgery, site of surgery, surgical procedure and intent

Corresponding listings will be provided using the ITP population.

4.10.4 Subsequent Anti-Cancer Therapy

Post Induction Treatment and Post Maintenance Treatment subsequent anti-cancer therapies will be listed using the ITP population who has a study treatment discontinuation visit date.

4.11 EFFICACY ANALYSIS

Efficacy analysis will be conducted on the data collected during the MTP/Post maintenance treatment (when applicable) and using the MTP population. Analysis will be performed by randomized treatment group. Tumor assessments collected during the ITP will be listed only but will not be part of the efficacy analysis and will be listed on the ITP population. ITP and MTP tumor assessment will be flagged, as appropriate for patients randomized in the MTP.

All formal statistical tests will be two-sided and performed at an alpha of 5%. Therefore 95% two sided CI will be presented. No adjustment will be made for multiplicity of testing secondary endpoints or subgroups for single efficacy endpoints.

4.11.1 Primary Efficacy Endpoint

The primary efficacy objective of this study is to evaluate PFS.

To answer the primary objective, the following null and alternative hypotheses will be tested

- H0: the distribution of the PFS time is the same in the two treatment groups, i.e. PFS (Experimental group) = PFS (Control group)
- H1: the distribution of the PFS time is different in the two treatment groups, i.e. PFS (Experimental group) ≠ PFS (Control group)

The primary analysis of PFS will be a comparison between the experimental and the control group using an unstratified log-rank test. Please refer to Appendix 4 for the SAS code to be used.

PFS for each treatment group will be estimated using KM product-limit method estimates. PFS will be summarized by treatment group and will display the following information:

- Number of patients in the population (N)
- Number of patients with PFS event
- Number of patients censored
- Median and two-sided 95% CI computed according to Brookmeyer and Crowley method,
- 25th and 75th quantile, and the corresponding two-sided 95% CI computed according to Brookmeyer and Crowley method,
- Minimum and maximum
- The PFS rates (with the two-sided 95% CI) at 3, 6, 9, 12, 15 and 18 months
- Unstratified log-rank test p-value

KM plot of PFS by treatment group will be generated.

PFS time will be listed on MTP population in a dedicated time to event listing.

Model checking

Sensitivity analyses concerning proportional hazards assumption will consist of log-log-Survival plots (log(-log(S(t))) vs log(time) by treatment group (plots=(lls) in PROC LIFETEST).

4.11.2 Secondary Efficacy Endpoints

4.11.2.1 Overall Survival

This study is not powered for OS, so adequately powered statistical testing for this endpoint will not be possible. However, the results of an unstratified log-rank test will be provided in an exploratory manner to assess the difference between treatment groups for OS.

The same analysis as those described for the primary endpoint will be repeated for OS on MTP population The survival rate will be displayed at the following time points: 6, 9, 12 and higher (every 3 months) if appropriate.

OS time will be listed on MTP population in a dedicated time to event listing.

4.11.2.2 Overall Response Rate (based on Primary Definition of BOR)

The Best Overall Response for MTP as per main definition will be tabulated on MTP by treatment group.

ORR for the MTP will be summarized in each treatment group on MTP and will present the number and percentage of patients with objective response (CR or PR) as best response along with the two-sided 95% Clopper-Pearson confidence interval. The difference in ORR among treatment groups will be estimated with associated two-sided 95% CI using the Hauck-Anderson approach. The treatment difference will be tested using a Chi-square test at a two-sided alpha level of 5%.

A logistic regression analysis, using treatment and the stratification factors as covariates will be performed. An estimate of the odds ratio with an associated two-sided 95 % confidence interval and a p-value for the coefficient will be presented for each covariate, including treatment. Please refer to Appendix 4 for the SAS code to be used. The stratification factors: region as per clinical database and tumor response at end of induction as per eCRF data will be included as covariates as mentioned below:

- cov1 (EU vs Americas)
- cov2 (EU vs Africa)
- cov3 (EU vs Asia)
- cov4 (SD vs CR/PR)

Note: EU and SD will be used as reference. If the number of patients in a region is small, regions may be pooled together (e.g. EU vs Rest of the world).

Forest plots displaying ORR odds ratio from the logistic regression by subgroups will be generated, for further details please refer to section 4.11.5.

Waterfall plots (both treatment groups one the same plot) of the best percentage change from baseline in sum of diameter collected during the MTP will be provided.

A listing of tumor assessments per timepoint will be provided based on the ITP. It will include:

- MTP/ITP/Post-treatment flag
- visit
- imaging date
- lesions number

- location, site/organ, assessment method and type of lesion
- diameter (mm) for target lesion, status for non-target lesion
- sum of diameter of target lesions (mm)
- response per timepoint for target lesion and non-target lesion, presence/absence of new lesion(s)
- overall Response per timepoint

Information will be collected from the “RECIST 1.1 Target Lesions”, “RECIST 1.1 Non-Target Lesions”, “RECIST 1.1 New Lesions” and "RECIST 1.1 - Overall Response Assessment" eCRF pages.

Another listing based on the MTP population will provide the best overall response (main and secondary definitions), time to response and the duration of response. Censored patients for the duration of response will be flagged as per section 2.2.2.6.

4.11.2.3 Overall Response Rate (based on Secondary Definition of BOR)

The analyses performed for Overall Response Rate for MTP based on main definition of BOR will be repeated using secondary definition of BOR (refer to section 0).

4.11.2.4 Disease Control Rate

Same analysis as described for ORR for MTP will be provided for the following endpoints:

- DCR for MTP based on main definition of BOR using the MTP population
- DCR for MTP based on secondary definition of BOR using the MTP population

All corresponding information will be listed on the MTP population.

4.11.2.5 Time to Treatment Response

Time to objective response (CR and PR) for each treatment group will be summarized separately based on the main and secondary definition of BOR using descriptive statistics (median, minimum and maximum) which will be calculated using PROC UNIVARIATE and are based on MTP population restricted to responders.

Two separate summary tables will be created: one for the time to response by considering all tumor assessments as in the main definition of BOR and another one by considering on-treatment tumor assessment as in the secondary definition of BOR. No formal statistical comparisons between the treatment groups are planned.

Time to response will be listed on MTP.

4.11.2.6 Duration of Response

The duration of response (DoR) for each treatment group will be estimated using KM product-limit method estimates. Summary table for duration of response based on MTP population restricted to responders will display, by treatment group, the number of patients with best overall response CR or PR (N), number of patients with progression or death, number of patients censored, min, max, 25th quantile, 75th quantile and median with the associated two-sided 95% CIs computed according to Brookmeyer and Crowley method.

Two separate summary tables will be created: one for duration of response by considering all tumor assessments as in the main definition of BOR and another one by considering on-treatment assessments as in the secondary definition of BOR.

The duration of response will be compared between the experimental and the control group using an unstratified log-rank test.

Duration of response will be listed on MTP.

4.11.2.7 Progression-Free Survival 2 (PFS 2)

PFS2 will be estimated using KM product-limit method estimates. Number of patients in the population, number of patients with PFS2 events, number of patients censored, min, max, 25th quantile, 75th quantile and median with the associated two-sided 95% CIs computed according to Brookmeyer and Crowley method as well as PFS2 rates (with the two-sided 95% CI) at 6, 9, 12, 15, 18 months (and higher every 3 months if appropriate) will be reported.

PFS2 hazard ratio, and its 95% two-sided confidence interval, of experimental group versus control group, will be estimated using a Cox proportional hazards model with treatment as the single covariate.

As for OS, despite not being adequately powered for PFS2, an unstratified log-rank test will be performed in an exploratory manner to assess the difference between treatment groups.

KM plot of PFS2 by treatment group will be generated.

PFS2 time will be listed on MTP population.

4.11.2.8 Eastern Cooperative Oncology Group (ECOG) Performance Status

Summary table presenting the number of patients and percentage by ECOG performance status will be displayed by visit occurring during the MTP. In addition, a shift table of MTP baseline ECOG PS versus ECOG PS at the end of MTP will be provided. Supportive listing will be provided for the MTP.

ECOG PS data will be listed based on the ITP population. ITP and MTP evaluations will be flagged.

4.11.3 Exploratory Efficacy Endpoints

4.11.3.1 PFS in Patients Randomized to Atezolizumab (Anti-PD-L1 Antibody) According to mRECIST (Experimental Group Only)

This endpoint will only be assessed in patients from MTP population randomized to the experimental group (i.e. patients treated with atezolizumab). The Overall patient response per Modified RECIST and per timepoint will be retrieved from the “Modified RECIST Response Assessment” eCRF page.

PFS will be estimated using KM product-limit method estimates. Number of patients in the population, number of patients with PFS events, number of patients censored, min, max, 25th quantile, 75th quantile and median with the associated two-sided 95% CIs computed according to Brookmeyer and Crowley method as well as PFS rates (with the two-sided 95% CI) at 3-, 6-, 12- and 18-month will be reported.

KM plot of PFS for this experimental group will be generated. This KM plot will display the 3 following curves on the same graph:

- KM curves of PFS for the experimental and control group as per RECIST 1.1
- KM curve of PFS for the experimental group according to mRECIST

Supportive listing for Overall Response per timepoint and for PFS as per Modified RECIST will be provided.

4.11.4 Sensitivity Analyses

In addition, the following sensitivity analyses will be performed on PFS, the primary efficacy endpoint:

- The PFS hazard ratio, and its 95% two-sided confidence interval, of experimental group versus control group, will be estimated using a Cox proportional hazards model with treatment as the single covariate. Please refer to Appendix 4 for the SAS code to be used.
- The PFS hazard ratio, and its 95% two-sided confidence interval, of experimental group versus control group, will be estimated using different adjusted Cox proportional hazards models, using as covariates the treatment and the stratification factors, i.e. region (as per clinical database) and tumor response at the end of induction treatment as mentioned below
    - cov1 (EU vs Americas), cov2 (EU vs Africa), cov3 (EU vs Asia) cov4 (SD vs CR/PR as per eCRF)
    - cov1 (EU vs Americas), cov2 (EU vs Africa), cov3 (EU vs Asia) cov4 (SD vs CR/PR as per IxRS)
    - cov1 (EU vs Rest of the world), cov2 (SD vs CR/PR as per eCRF)
    - cov1 (EU vs Rest of the world), cov2 (SD vs CR/PR as per IxRS)

  Note: If the number of patients in a region is small, only models with pooled region (i.e. EU vs Rest of the world) will be considered.

- A sensitivity analysis will be performed for PFS by considering all PFS events reported in MTP regardless of the surgery.

  An unstratified log-rank test will be performed to compare PFS between the experimental and the control group. PFS will be estimated for each treatment group using KM product-limit method estimates. PFS will be summarized by treatment group and will display the information as mentioned in section 4.11.1. The PFS hazard ratio, and its 95% two-sided confidence interval, of experimental group versus control group, will be estimated using a Cox proportional hazards model with treatment as the single covariate.

- A sensitivity analysis will be performed for PFS, using an on-treatment PFS analysis as below:

  The derivation of the PFS will be the same as per section 2.2.1, the only change being the time window during which the progression free survival is observed. In other words, the primary endpoint PFS considers all tumor assessments and deaths reported on study (i.e. including Post Maintenance Treatment tumor assessments for patients

withdrawing maintenance treatment for other reason than PD) whereas the on-treatment definition considers only tumor assessments and death reported on maintenance treatment (i.e within 30 days from last day of treatment of MTP, up to the day before the start of further anti-cancer therapy, whichever comes first).

Using the on-treatment PFS, an unstratified log-rank test will be performed to compare on-treatment PFS between the experimental and the control group. On-treatment PFS will be estimated for each treatment group using KM product-limit method estimates. On-treatment PFS will be summarized by treatment group and will display the information as mentioned in section 4.11.1. The on-treatment PFS hazard ratio, and its 95% two-sided confidence interval, of experimental group versus control group, will be estimated using a Cox proportional hazards model with treatment as the single covariate.

- A sensitivity analysis will be performed for PFS considering the first 259 PFS events. For this sensitivity analysis, PFS definition as per section 2.2.1 will be used and a new cut-off date being the date of the 259th PFS event will be applied. For event/censor date from the primary analysis that was after the new cut-off date, then the patient will be censored at the last tumor assessment available prior the new cut-off date.

An unstratified log-rank test will be performed to compare PFS considering the first 259 PFS events between the experimental and the control group. PFS considering the first 259 PFS events will be estimated for each treatment group using KM product-limit method estimates. PFS will be summarized by treatment group and will display the information as mentioned in section 4.11.1. The PFS hazard ratio, and its 95% two-sided confidence interval, of experimental group versus control group, will be estimated using a Cox proportional hazards model with treatment as the single covariate.

- A sensitivity analysis will be performed for PFS considering the planned sample size as per protocol, i.e. the first 405 randomized patients. For this sensitivity analysis, both PFS definition as per section 2.2.1 and a subset of the MTP population considering the first first 405 randomized patients will be used.

An unstratified log-rank test will be performed to compare PFS considering the first 405 randomized patients between the experimental and the control group. PFS considering the first 405 randomized patients will be estimated for each treatment group using KM product-limit method estimates. PFS will be summarized by treatment group and will display the information as mentioned in section 4.11.1. The PFS hazard ratio, and its 95% two-sided confidence interval, of experimental group versus control group, will be estimated using a Cox proportional hazards model with treatment as the single covariate.

- The OS hazard ratio, and its 95% two-sided confidence interval, of experimental group versus control group, will be estimated using a Cox proportional hazards model with treatment as the single covariate. Please refer to Appendix 4 for the SAS code to be used.
- For ORR and DCR, a logistic regression analysis, using treatment as single covariates will be performed. An estimate of the odds ratio with an associated two-sided 95 % confidence interval and a p-value for the coefficient will be presented for treatment. Please refer to Appendix 4 for the SAS code to be used.
- To assess any bias regarding the completeness of the follow up to capture PFS events, KM curve with reverse censoring will be produced by treatment group. In this analysis,

censored patients in the primary analysis will be considered as having an event, for these patients the event date will be the date of last evaluable tumor assessment or date of randomization, whichever comes last. Patients with a PFS event in the primary analysis will be censored in this analysis, for these patients the censor date will be the earliest date between PD date and death date.

4.11.5 Subgroup Analyses

Subgroup analyses of PFS and OS will be conducted on each level of the:

- Stratification factors
- Tumor colon location subset
- Biomarker subset

Please refer to section 4.7 for the definition of these subsets.

The following information will be provided/computed within each subset:

- Number of patients in the subgroup
- Number of patients with PFS event
- Number of patients censored
- Median and two-sided 95% CI computed according to Brookmeyer and Crowley method,
- 25th and 75th quantile, and the corresponding two-sided 95% CI computed according to Brookmeyer and Crowley method,
- PFS HR of experimental versus control group and its two-sided 95% CI computed by means of an un-stratified Cox proportional hazards model with treatment as the single covariate.

Forest plots presenting the PFS HR of experimental group versus control group and corresponding 95% CI obtained from adjusted Cox model for each subset as defined in section 4.7 will be generated.

Forest plots presenting the OS HR of experimental group versus control group and corresponding 95% CI obtained from adjusted Cox model for each subset as defined in section 4.7 will be generated.

Each forest plot will be provided twice one for the baseline characteristics subsets, and another one for the biomarker subsets.

The Best Overall Response for MTP as per main and secondary definition (see section 0) will be tabulated on MTP by treatment group on each level of the baseline and biomarker subsets as defined in section 4.7

For each level of the baseline and biomarker subsets as defined in section 4.7, ORR for the MTP will be summarized in each treatment group on MTP and will present the number and percentage of patients with objective response (CR or PR) as best response along with the two-sided 95% Clopper-Pearson confidence interval. The difference in ORR among treatment groups will be estimated with associated two-sided 95% CI using the Hauck-Anderson approach.

For each level of the baseline and biomarker subsets as defined in section 4.7, a logistic regression analysis, using treatment as single covariate will be performed. An estimate of the

odds ratio (experimental vs control group) with an associated two-sided 95 % confidence interval will be provided.

Forest plots displaying the ORR odds ratio of experimental group compared to control group and corresponding 95% CI from the logistic regression with treatment as unique covariate for each subset as defined in section 4.7 will be provided. One forest plot will be generated for baseline characteristics subsets, and another one for the biomarker subsets.

No formal statistical comparisons will be conducted within subsets.

4.12 PHARMACOKINETIC AND PHARMACODYNAMIC ANALYSES

Not applicable

4.13 SAFETY ANALYSES

Separate safety summaries will be produced for ITP, MTP, Post Induction Treatment and Post Maintenance Treatment.

For ITP data, outputs will be generated on the ITP displaying randomized vs. non randomized patients in MTP. MTP outputs will be based on the SAF population and will be presented by treatment group. For Post Induction Treatment data, outputs will be generated on ITP for patients who completed study treatment discontinuation visit, whereas for Post Maintenance Treatment data, outputs will be generated on MTP for patients who completed study treatment discontinuation visit.

No inferential statistical analyses are planned.

4.13.1 Exposure of Study Medication

4.13.1.1 Treatment Duration and Dose Exposure

A patient will be considered as having initiated a cycle in the ITP if at least one (non-null) dose of any study drugs of the ITP has been administered in the corresponding cycle.

The overall number of cycles initiated during the ITP is defined as the sum of all initiated cycles (as defined above) in the ITP.

For the MTP, the overall number of cycles initiated (i.e. for drug combination) will be computed as the sum of all initiated cycles as defined below:

- Day 1 of a cycle is defined as the first day in the considered cycle when treatment is administered.
- The cycle length is assumed to be 2 weeks
- For experimental group:
    - If capecitabine is administered: a cycle will be assumed to be initiated if capecitabine and atezolizumab and bevacizumab are administered at any time during the same cycle with cycle defined according to atezolizumab and bevacizumab cycles

- If 5-FU/LV or LV substitute is administered: a cycle will be assumed to be initiated if atezolizumab, bevacizumab and 5-FU and LV or any LV substitute are administered at any time during the same cycle

- For control group:
  - If capecitabine is administered: a cycle will be assumed to be initiated if capecitabine and bevacizumab are administered at any time during the same cycle
  - If 5-FU/LV or LV substitute is administered: a cycle will be assumed to be initiated if bevacizumab and 5-FU and LV or any LV substitute are administered at any time during the same cycle

The overall duration (in weeks) for all components of maintenance treatment is defined as follows:

- Experimental group:
  - If capecitabine is administered in the last cycle:

[MAX(min(last dosing date of capecitabine+6, death date), min(last dosing date of bevacizumab+13, death date), min(last dosing date of atezolizumab+13, death date)) – min (first dosing date of FP, first dosing date of bevacizumab, first dosing date of atezolizumab) + 1]/7

  - If 5-FU/LV is administered in the last cycle:

[MAX(min(last dosing date of 5-FU/LV+13, death), min(last dosing date of bevacizumab+13, death date), min(last dosing date of atezolizumab+13, death date)) – MIN (first dosing date of FP, first dosing date of bevacizumab, first dosing date of atezolizumab) + 1]/7

with last dosing date of 5-FU/LV = max(last dosing date of 5-FU, last dosing date of LV) and first dosing date of 5-FU/LV = min(first dosing date of 5-FU, first dosing date of LV)

- Control group:
  - If capecitabine is administered in the last cycle:

[MAX(min(last dosing date of capecitabine+6, min(last doing date of bevacizumab+13, death date)) – MIN (first dosing date FP, first dosing date of bevacizumab) + 1]/7.

  - If 5-FU/LV is administered in the last cycle:

[MAX(min(last dosing date of 5-FU/LV+13, death), min(last dosing date of bevacizumab+13, death date)) – MIN (first dosing date of FP, first dosing date of bevacizumab) + 1]/7

with first dosing date of FP = min(fist dosing date of 5-FU, first dosing date of LV or any LV substitute, first dosing date of capecitabine) and last dosing date of 5-FU/LV = max(first dosing date of last administration of 5-FU, first dosing date of last administration of LV or any LV substitute)

The number of cycles administered, duration of dosing, cumulative dose, dose intensity and relative dose intensity (RDI) definitions are provided for each drug individually in Table 3 and Table 4 for induction and maintenance, respectively.

According to protocol, the cycle length is 2 weeks, excepted for capecitabine for which each cycle lasts 3 weeks in the experimental arm and is as per local practise in the control arm. A 2-week cycle schedule will be considered for other drugs than capecitabine and for drug combination. For capecitabine, a cycle is defined as any continuous administration separated by a rest period, regardless of the duration of the continuous administration and the duration of the rest period A patient will be considered as having initiated a cycle in the MTP for a specific drug if at least one (non-null) dose of this study drug has been administered in the corresponding cycle.

Table 2: Exposure Definitions for Induction Treatments

	FOLFOX	5-FU/LV	bevacizumab
Number of cycle	sum of all cycles in which at least one non-null dose of FOLFOX has been administered	sum of all cycles in which at least one non-null dose of 5-FU and LV has been administered. Of note, consider only cycles where oxaliplatin is not administered concomitantly with 5-FU/LV.	sum of all cycles in which at least one non-null dose of bevacizumab has been administered
Duration of dosing (weeks) (1)	[min (last date of FOLFOX+13, death date) – first FOLFOX dosing date+1] / 7 or If FOLFOX-4 or FOLFOX-7 or modified FOLFOX-7 is administered in the last cycle initiated [min (last date of FOLFOX +12, death date) – first FOLFOX dosing date+1] / 7	max (min(last date of 5-FU+13, death date), min(last date of LV+13, death date)) – min (first date of 5-FU, first date of LV) +1] / 7 Of note, consider only records/cycles where oxaliplatin is not administered concomitantly with 5-FU/LV.	[min (last date of bevacizumab +13, death date)) – (first bevacizumab dosing date in the induction) +1] / 7

(1) According to the proposed formula, the duration of dosing may be overestimated in case patients discontinued treatment prior to the end of the last cycle.

(2) The baseline weight will be used as reference. If the last available weight of the patient prior to or on the cycle start has changed by 10% or greater (i.e. patient has gained or lost more than 10% of their body weight since baseline) the patient new weight will be set as the baseline weight and will be used at the patient current and subsequent cycles. If a patient weight has changed by 10% or greater at a later cycle then this new weight will be set as the base weight as aforementioned

Table 3: Exposure Definitions for Maintenance

	capecitabine	5-FU	LV	bevacizumab	atezolizumab
Number of cycle	The sum of all cycles in which at least one non-null dose of <*treatment*> has been administered				
Duration of dosing (weeks) [(1)]	[min (last dosing date of <treatment> + x, death date)) – (first <treatment> dosing date in the maintenance) +1] / 7 Where x=13, excepted for capecitabine where x=6 For 5-FU and LV, last dosing date of treatment will be replaced by the first dosing date of the last administration				
Actual dose	<treatment> dose administered (in mg) as collected on the dosing eCRF page [(5)] Unit: mg				
Planned dose	<treatment> planned dose (in mg) as collected on the dosing eCRF page [(5)] Unit: mg				
Normalized dose	dose / recalculated BSA[(2)] Unit: mg/m^2			dose / weight[(4)] Unit: mg/kg	NA
Cumulative dose	The cumulative dose will be derived for each records as below: (end date of administration - start date of administration +1) * normalized actual dose for the record * 2 Cumulative dose= sum of cumulative dose across all records Unit: mg/m^2	sum of the all <treatment > normalized actual doses (in mg/m^2) administered in all cycles Unit: mg/m^2		sum of the all bevacizumab normalized actual doses (in mg/kg) administered in all cycles Unit: mg/kg	sum of the all of atezolizumab actual doses (in mg) administered in all cycles Unit: mg
Dose intensity	Cumulative dose / (duration of	Cumulative dose / duration of dosing		Cumulative dose /	Cumulative dose /

	capecitabine	5-FU	LV	bevacizumab	atezolizumab
	dosing *7) Unit: mg/m^2/day	Unit: mg/m^2/week		duration of dosing Unit: mg/kg/week	duration of dosing Unit: mg/week
Cumulative planned dose (CPD)	sum of the all normalized planned doses (in mg/m^2) reported in all records	sum of the all <treatment > normalized planned doses (in mg/m^2) reported in all cycles		sum of the all normalized planned doses (in mg/kg) reported in all cycles	sum of the all planned doses (in mg) reported in all cycles
Planned dose intensity	CPD/ (duration of dosing *7) Unit: mg/m^2/day	CPD/ duration of dosing Unit: mg/m2/week		CPD/duration of dosing Unit: mg/kg	CPD/duration of dosing Unit: mg/ week
Relative dose intensity (RDI) (%)	RDI (%) = 100 * (dose intensity) / (planned dose intensity)				

(1) According to the proposed formula, the duration of dosing may be overestimated in case patients discontinued treatment prior to the end of the last cycle.
(2) The BSA will be recalculated based on the height and weight (see point 3 for identification of weight) of the patient using the formula as mentioned in section 4.3.
(3) The baseline weight will be used as reference. If the last available weight of the patient prior to or on the cycle start has changed by 10% or greater (i.e. patient has gained or lost more than 10% of their body weight since baseline) the patient new weight will be set as the baseline weight and will be used at the patient current and subsequent cycles. If a patient weight has changed by 10% or greater at a later cycle then this new weight will be set as the baseline weight as aforementioned
(4) If treatment= 5-FU and in case 5-FU administration was interrupted and then 5-FU administration resumed within a cycle, the actual dose within this specific cycle will be equal to the sum of the 5-FU doses administered (in mg)) as collected on the dosing eCRF page /recalculated BSA[(2)]

The following information will be tabulated for the ITP using the ITP population:

- Summary of total number of cycles initiated per patient
  - Total number of cycles initiated (1,2,3,4,5,6,7,8)
  - Summary statistics of total number of cycles initiated
- Summary of drug exposure
  - The number of cycles administered and treatment duration (in weeks) for bevacizumab, FOLFOX and 5-FU/LV alone

The following information will be tabulated for the MTP using the SAF population:

- Summary of overall duration of treatment and overall number of cycles initiated
  - Overall duration of maintenance treatment (in weeks)
  - Overall number of cycles initiated: 1,2,3,4,5,6,7,8,9,10, 10-15, >=15
  - Summary statistics of overall number of cycles initiated per patient
- Summary of drug exposure
  - Total number of cycles administered (tabulated separately for each drug)
  - Duration of dosing (in weeks) (tabulated separately for each drug)
  - Cumulative dose (tabulated separately for each drug according to definition provided in table 3)
  - Dose intensity (tabulated separately for each drug according to definition provided in table 3)
  - Relative dose intensity: ≤90%, >90%-≤100%, >100% (tabulated separately for each drug according to definition provided in table 3) Note: Number and percentage will be based on the patients who received the corresponding drug.

Supportive listings presenting the study drug administration as well as the exposure information will be provided separately based on ITP and SAF population for the induction and for the maintenance, respectively.

4.13.1.2 Cycle Delay

Cycle delay is applicable to the following treatments: FP (5-FU, LV or capecitabine), bevacizumab and atezolizumab.

For 5-FU, LV, bevacizumab and atezolizumab, a cycle delay will be defined as the number of days in excess of the expected days between two consecutive doses of <treatment> (14 days) and will be calculated as D1Cn+1 - D1Cn where D1Cn+1 and D1Cn correspond to date of administration of <treatment> in cycle n+1 and cycle n, respectively. An excess of more than 3 days will qualified cycle Cn+1 as delayed for <treatment>. Of note, the first cycle (C1) cannot be identified as cycle delay.

For capecitabine, a cycle delay will be defined as the number of days in excess of the expected days between two non-zero administrations (21 days, i.e. 14 days of administration and a rest period of 7 days) and will be calculated as D_1C_{n+1} - D_1C_n where D_1C_{n+1} and D_1C_n correspond to the start date of the first administration of capecitabine in cycle n+1 and cycle n, respectively. An excess of more than 3 days will qualify cycle C_{n+1} as delayed for capecitabine. Of note, the first cycle (C_1) cannot be identified as cycle delay.

The following information will be tabulated for the MTP on the SAF population:

- Summary of <*treatment*> cycle delay (for 5-FU, LV, capecitabine, bevazicumab and atezolizumab) at the patient level
  - Number of patients with at least one cycle delayed for <*treatment*>,
  - Number of patients with 1, 2, 3, ≥3 cycles delayed for <*treatment*>
- Summary of <*treatment*> cycle delay (for 5-FU, LV, capecitabine, bevazicumab and atezolizumab) at the cycle level
  - Number of cycles delayed
  - Length of cycle delayed (>3 -7 days, >7-14, >14-21, >21)

4.13.2 Adverse Events

Adverse events variables are defined in Table 4.

Table 4: Adverse Events Definitions

Variable	Definition
Treatment Emergent Adverse Events (TEAEs) for the induction treatment phase [(1)]	Any adverse events (serious and non-serious) with an onset date on (only if the "Event occurred prior to first study drug administration" from the AE eCRF page is not checked) or after the first day of treatment of the ITP and up to the: • first day of treatment of the MTP (excluding) if it occurs within the 30 days from last day of treatment of induction treatment for patients treated with maintenance treatment • within 30 days from last day of treatment of induction treatment (as defined in section 4.2.1), for patients not treated with maintenance treatment or for patients treated with maintenance treatment but with first day of treatment of MTP being more than 30 days after last day of treatment of ITP.
TEAEs for the maintenance treatment phase[(1)]	Any adverse events (serious and non-serious) with an onset date on (only if the "Event occurred prior to first study drug administration" from the AE eCRF page is not checked) or after the first day of treatment of the MTP and up to 30 days (for patients in control group, i.e. not treated with atezolizumab) and 90 days (for patients in experimental group, i.e. treated with atezolizumab) from the last day of treatment of MTP (as defined in section 4.2.2)
Post induction treatment Adverse Events	Any adverse events (serious and non-serious): • with an onset date more than 30 days after the last day of treatment of the ITP (as defined in section 4.2.1) for patients not treated with maintenance treatment. • with an onset date more than 30 days after the last day of treatment of the ITP and prior the first day of treatment of the MTP, for patients treated with maintenance treatment with first day of treatment of MTP being more than 30 days after last day of treatment of ITP..
Post maintenance treatment Adverse events	Any adverse events (serious and non-serious) with an onset date more than 30 days (for patients in control group, i.e. not treated with atezolizumab) and more than 90 days (for patients in experimental group, i.e. treated with atezolizumab) after the last day of treatment of the MTP (as defined in section 4.2.2) (as defined in section

	4.2.2).
Adverse Events NCI CTCAE grade	The adverse events grade will be the one with tick box checked for "AE most extreme NCI CTCAE grade"
Serious Adverse Events (SAEs)	Any adverse events qualified as “serious” by the investigator.
Adverse Events with fatal outcome	Any adverse events with outcome of “Fatal”.
Adverse events related to <FOLFOX, bevacizumab, FP, atezolizumab>	Any adverse events with an “AE suspected to be caused by study drug <FOLFOX, bevacizumab, FP, atezolizumab> as ‘Yes’. For AE suspected to be caused by FOLFOX while starting in the maintenance phase, the unique text ‘“AE considered related to Folfox”‘ has been reported in the comment field ‘
Adverse events leading to <FOLFOX, bevacizumab, FP, atezolizumab> discontinuation	Any adverse events with an “Action taken with <FOLFOX, bevacizumab, FP, atezolizumab> due to SAE/AE” of “drug withdrawn”
Adverse events of Special Interest (AESI) as reported on eCRF	AESIs will be selected based on the tick box from the eCRF.

(1) Of note, in case an event has an incomplete or missing start date, which consequently prevents its allocation to only one treatment phase of the study, the event will be allocated to both the induction and maintenance phase. Refer to section 4.14 for further details.

Safety summaries will be produced for the ITP on the ITP population and for the MTP on the SAF population, unless otherwise specified. ITP summaries will display patients randomized vs. patients not randomized in MTP. MTP summaries will be done by actual maintenance treatment group as defined for the SAF. Descriptive statistics will be generated as appropriate. No inferential statistical analyses are planned.

Summaries of adverse events for ITP and MTP will be generated for those events that are considered treatment emergent. The AE tables will include the number and percentage of patients with at least one AE, by MedDRA primary System Organ Classes (SOC) (sorted in a descending order of the total frequency count) and MedDRA Preferred Terms (PT) (sorted by descending order of the overall frequency count within each SOC) unless otherwise indicated. A patient with more than one occurrence of the same adverse event in a particular system

organ class/preferred term will be counted only once in the total of those experiencing adverse events in that particular system organ class/preferred term. For the overall summary tables, information presented by grade will not be restricted to the worst grade per patient i.e. all events will be presented. Any AEs with a missing CTC grade will be reported in the "missing" category grade.

An overview table will be produced for the ITP based on the ITP population and will present:

- Number of TEAEs
- Number of patients with at least one TEAE
- Number of patients with at least one TEAE by CTC grade: 1, 2, 3, 4, 5, ≥3, missing
- Number of patients with at least one related TEAE
    - Any study drug
    - FOLFOX
    - 5-FU/LV
    - bevacizumab
- Number of patients with at least one serious TEAE
- Number of patients with at least one related serious TEAE
    - Any study drug
    - FOLFOX
    - 5-FU/LV
    - bevacizumab
- Number of patients with at least one TEAE with fatal outcome
- Number of patients with at least one TEAEs leading to treatment discontinuation of:
    - Any study drug
    - FOLFOX
    - 5-FU/LV
    - bevacizumab

An overview table will be produced for the Post Induction Treatment AEs, i.e. occurring more than 30 days after last day of treatment during the Induction Phase (as defined in section 4.2.1), based on patients from the ITP population who has a study treatment discontinuation visit date. This table will present the following information for the non-randomized patients to MTP only:

- Number of AEs
- Number of patients with at least one AE
- Number of patients with at least one AE by CTC grade: 1, 2, 3, 4, 5, ≥3, missing
- Number of patients with at least one related AE
- Number of patients with at least one serious AE
- Number of patients with at least one related serious AE
- Number of patients with at least one AE with fatal outcome

An overview table will be produced for the maintenance phase based on the SAF and will present:

- Number of TEAEs
- Number of patients with at least one TEAE
- Number of patients with at least one TEAE by CTC grade: 1, 2, 3, 4, 5, ≥3, missing
- Number of patients with at least one related TEAE

    - Any study drug
    - Fluoropyrimidines
    - bevacizumab
    - atezolizumab
    - FOLFOX
- Number of patients with at least one serious TEAE
- Number of patients with at least one related serious TEAE
    - Any study drug
    - Fluoropyrimidines
    - bevacizumab
    - atezolizumab
    - FOLFOX
- Number of patients with at least one TEAE with fatal outcome
- Number of patients with at least one TEAEs leading to treatment discontinuation of:
    - Any study drug
    - Fluoropyrimidines
    - bevacizumab
    - atezolizumab
- Number of patients with at least one treatment emegent AESI (as reported on eCRF)
- Number of patients with at least one serious treatment emergent AESI (as reported on eCRF)

An overview table will be produced for the Post Maintenance Treatment AEs, i.e. AEs occurring more than 30 days (for patients in control group, i.e. not treated with atezolizumab) and more than 90 days (for patients in experimental group, i.e. treated with atezolizumab) after the last day of treatment during the Maintenance Phase (as defined in section 4.2.2), based on patients from the MTP population who has a study treatment discontinuation visit date. This table will present the following information:

- Number of AEs
- Number of patients with at least one AE
- Number of patients with at least one AE by CTC grade: 1, 2, 3, 4, 5, ≥3, missing
- Number of patients with at least one related AE
- Number of patients with at least one serious AE
- Number of patients with at least one related serious AE
- Number of patients with at least one AE with fatal outcome

In addition, the following tables (number and percentage of patients) will be presented for the ITP based on the ITP population and will display the number of patients (and corresponding number of TEAEs) and percentage with any:

- TEAEs by SOC and PT and by Worst Intensity
- Grade 3-5 TEAEs by SOC and PT
- Related TEAEs by SOC and PT: to any study drugs, FOLFOX, 5 FU/LV, bevacizumab
- Serious TEAEs by SOC and PT
- Related serious TEAEs by SOC and PT: to any study drugs, FOLFOX, 5 FU/LV, bevacizumab
- TEAEs leading to treatment discontinuation by SOC and PT: FOLFOX, 5 FU/LV, bevacizumab

- TEAEs leading to dose reduction or interruption by SOC: any study drugs, FOLFOX, 5 FU/LV, bevacizumab
- Grade 5 TEAEs or TEAEs with fatal outcome by SOC and PT

The following tables will be presented for the MTP only and will display the number and percentage of patients (and corresponding number of TEAEs) with any:

- TEAEs by SOC and PT and by Worst Intensity
- Grade 3-5 TEAEs by SOC and PT
- Related TEAEs by SOC and PT: any study drugs, capecitabine, 5-FU/LV, atezolizumab, bevacizumab, FOLFOX
- Serious TEAEs by SOC and PT
- Related Serious TEAEs by SOC and PT: any study drugs, capecitabine, 5-FU/LV, atezolizumab, bevacizumab, FOLFOX
- Grade 5 TEAEs or TEAEs with fatal outcome by SOC and PT
- TEAEs leading to treatment discontinuation by SOC and PT: any study drugs, capecitabine, 5-FU/LV, atezolizumab, bevacizumab
- TEAEs leading to dose reduction or interruption by SOC and PT: any study drugs, capecitabine, 5-FU/LV, atezolizumab, bevacizumab
- Treatment emergent AESI by AESI categories, SOC and PT and by Worst Intensity
- Serious Treatment emergent AESI by AESI categories, SOC and PT and by Worst Intensity
- Treatment emergent AESI by AESI categories, SOC and PT
- Serious Treatment emergent by AESI categories, SOC and PT

By-patients listings will be provided for AEs; they will include Post-treatment adverse events. Appropriate flagging of study phase (ITP/MTP) as well as TEAEs/Post-treatment AEs will be done. The following listings will be provided based on ITP population

- All adverse events
- All Grade 5 adverse events or any adverse events with fatal outcome
- All adverse events leading to treatment discontinuation
- All AESI (as reported on eCRF)

4.13.3 Death

The following summary tables will be provided and will present:

- The number of patients who died within 30 days from last day of treatment of the ITP (as defined in section 4.2.1) and the corresponding reason of death based on ITP population
- The number of patients who died more than 30 days from last day of treatment of ITP (as defined in section 4.2.1) and the corresponding reason of death based on ITP population who has a study treatment discontinuation visit date
- The number of patients who died within 30 days from last day of treatment of MTP for treated patients or within 30 days from randomization with the corresponding cause of death based on MTP population

- The number of patients who died within 30 days from last day of treatment of MTP (as defined in section 4.2.1) with the corresponding death reason using the SAF population
- The number of patients who died more than 30 days from last day of treatment of maintenance treatment and the corresponding reason of death based on patients from the MTP population who has a study treatment discontinuation visit date

One listing will be generated for deaths based on the ITP population and including appropriate flagging of study phase (ITP and MTP) and on-treatment/post-treatment deaths (i.e. within 30 days from last day of treatment/more than 30 days from last day of treatment).

All deaths information (including reason and date) will be retrieved from the Study Completion/Early Discontinuation eCRF page.

4.13.4 Laboratory Data

The following laboratory parameters will be considered as CTC gradable parameters.

Haematology
- Absolute Neutrophils Count (ANC)
- Hemoglobin (Hb)
- Leukocytes/White Blood Cells counts (WBC)
- Platelet Count

Blood chemistry
- Albumin
- Alkaline Phosphatase (ALP)
- Calcium
- Creatinine
- Glucose
- Potassium
- SGPT or alanine aminotransferase (ALT)
- SGOT or aspartate aminotransferase (AST)
- Sodium
- Total Bilirubin

Coagulation
- international normalized ratio (INR)
- activated partial thromboplastin time (aPTT)

The following parameters will be considered as non CTC gradable parameters.

Hematology
- Red blood Cell (RBC)
- Hematocrit
- Lymphocytes
- Neutrophils
- Eosinophils

- Basophils
- Monocytes

Blood Chemistry
- Blood Urea Nitrogen
- Bicarbonate
- Chloride Lactate dehydrogenase (LDH)
- Phosphorus
- Total Protein

Urinalysis
- Urine Protein Dipstick
- 24 hour urine protein

Thyroid
- Thyroid-Stimulating Hormone (TSH)
- Free T3
- Free T4

All laboratory parameter information will be summarized for each phase separately. Laboratory information reported in tables will be restricted to the baseline and on-treatment measurements. The analysis population will be the ITP and the SAF population for the ITP and MTP, respectively.

Clinical laboratory values will be expressed using Système International (SI) units.

When applicable, laboratory tables will display their High (hyper)/Low (hypo) values of a specific parameter (e.g. calcium (high) and calcium (low) in separate tables.

In case of missing normal ranges for parameters that are not differential and have only grade 1 defined from normal ranges (e.g. Neutrophils, WBC, Albumin…) the worst case scenario will be applied, i.e. grade 1.

A “Missing” category will be reported for patients with missing grades or missing reference range indicators at baseline and/or on-treatment and patients with no laboratory assessments.

For hematology, blood chemistry and coagulation parameters which can be graded per CTCAE, the information will be summarized by means of a shift table summarizing the baseline grade versus the worst CTC grade per patient defined as the highest CTC grade among the on-treatment evaluations. If there is no on-treatment evaluation then the worst grade will be set to ‘Missing’.

Hematology and blood chemistry parameters which cannot be graded per CTCAE, the information will be summarized by means of a shift table from baseline category to worst on-treatment category. The following categories will be used:

- Baseline: Low/Normal/High/Missing/Overall
- Worst on-treatment: Low/Normal/High/Missing/Overall

Patient with “High” and “Low” for the same laboratory test (at different visits) is counted for each direction in summary tables.

For urinalysis protein dipstick, all non-missing assessments excepted “0-absent” assessment will be considered “Present”. A shift table presenting baseline category versus worst on-treatment category will be produced with the following categories:

- Baseline: Absent/Present/Missing/Overall
- Worst on-treatment: Absent/Present/Missing/Overall

For urinalysis, 24 hour urine protein values will not be tabulated but listed only.

All laboratory values will be listed along with CTC grade/category. Separate listings will be generated to include all abnormal laboratory values.

4.13.5 Vital Signs

Vital signs parameters include:

- Temperature (°C)
- Systolic blood pressure (SBP seated position) (mmHg)
- Diastolic blood pressure (DBP seated position) (mmHg)
- Weight (kg)
- BSA (m^2)
- Heart rate (beats/min)
- Respiratory rate (breaths/min)

Vital signs information will be summarized for each phase separately and by treatment group when applicable. Vital signs information reported in tables will be restricted to non-missing baseline and non-missing on-treatment measurements. The analysis population will be the ITP population for the ITP and the SAF population for the MTP.

Actual value and change from baseline for heart rate and systolic and diastolic blood pressure will be summarized by treatment group for each visit using descriptive statistics.

For the experimental arm, vital signs are collected within 60 minutes before the infusion and at other timepoints when clinically indicated and at the first infusion. Only the timepoint ‘Within 60 minutes before the infusion’ will be included in the summary table.

All vital signs data including change from baseline (and data reported at timepoints not included in the summary table) will be listed.

4.13.6 Other Safety Assessment - Applicable only for the experimental group

Blood oxygen saturation is measured only in patients randomized to the experimental treatment group. Blood oxygen saturation will be measured by pulse oximetry.

Non-missing pulse oximetry values will be summarized by visit through descriptive statistics.

Blood oxygen saturation will be listed with the vital signs parameters.

4.13.7 Other Safety Assessment

Pregnancy test data will be listed on the ITP population, ITP and MTP data will be flagged.

4.14 MISSING DATA

Imputation of partial/missing death date will be done as follows:

- If the date is completely missing, then the day of "Last known to be alive" +1 will be used
- If only day is missing and year and month are same as "Last known to be alive", then the day of "Last known to be alive"+1 will be used otherwise the 1st day of the month will be used
- If day and month are missing and year is same as "Last known to be alive", then the "Last known to be alive"+1 will be used, otherwise 1st of January will be used

Partially missing dates for adverse events (AEs) will be imputed as follows. Of note, imputation of missing/partial AE date will be done only to identify treatment emergent AEs.

AE onset dates

- Partially missing onset dates will be imputed as follows
  - When only Day is missing :
    - If Month & Year of the onset date are the same as Month & Year of the first day of treatment of the induction/maintenance treatment phase, the imputed onset date will be imputed as the minimum of the first day of treatment of the induction/maintenance treatment phase and the AE resolution date (imputed if needed).
    - Otherwise, the missing day will be replaced by "1".
  - When Day & Month are missing:
    - If Year of the onset date is the same as Year of the induction/maintenance treatment phase, the imputed onset date will be imputed as the minimum of the first day of treatment of the induction/maintenance treatment phase and the AE resolution date (imputed if needed).
    - Otherwise, the missing Day & Month will be replaced by "01JAN".

- Complete missing onset dates for AEs will be imputed by first day of treatment of the induction/maintenance treatment phase and the AE will be considered as treatment emergent, unless the end date of the AE (imputed if needed) or the end year of the AE (if day and month are missing) is entered and is before the year of the first treatment administration of the induction/maintenance treatment phase.

AE resolution dates

- Incomplete resolution dates will be replaced by the last day of the month (if day is missing only), if not resulting in a date later than the date of patient's death. In the latter case the date of death will be used to impute the incomplete resolution date
- In all other cases the incomplete resolution date will not be imputed

Of note, the above rules may allow allocation of an event to both the ITP and MTP treatment phase.

Partially missing dates for medications/therapies will be imputed as follows. Of note, imputation of missing/partial medicationstherapies date will be done only to identify concomitant medications/therapies.

Partial dates will be imputed as follow:

- Start dates
  - When only Day is missing : the missing day will be replaced by “1”
  - When Day & Month are missing: the missing Day & Month will be replaced by “01JAN”.
- End dates
  - When only Day is missing : the missing day will be replaced by the last day of the month
  - When Day & Month are missing: the missing Day & Month will be replaced by “31DEC”.

And rules described in section 4.10.3.2 and below will be applied using imputed dates.

In case of complete missing dates, the following will be applied:

- If the start date of the medication/therapy is unknown (i.e. complete missing date) and there is no end date, medication/therapy is flagged as taken prior to study but not as ongoing then the medication/therapy will be considered as a prior medication .
- If both the start date and end date of the medication/therapy is unknown (i.e. complete missing date), then the medication/therapy will be considered as a concomitant medication/therapy for both the induction and maintenance phase if the patient is treated in the phase of interest.
- If the start date of the medicationtherapy is unknown (i.e. complete missing date), but the end date is known and is prior to the first dosing date of the considered phase, then the medicationtherapy will not be considered as concomitant for the corresponding phase.
- If the start date of the medication/therapy is available and the end date is unknown, then the medication/therapy will not be considered as prior. Concomitance to ITP/MTP will be assessed using the available start date.

Partially missing dates for surgery will be imputed as follows. Of note, imputation of missing/partial surgeries date will be done only to identify concomitant surgeries.

Partial dates will be compared as follow:

- When only Day is missing : Month & Year of the surgery will be compared to Month & Year of the first dosing date of interest (either ITP or MTP). If on or after, the surgery will be considered as concomitant to the period of interest. If on or before the first doing date of ITP, the surgery will be considered as prior.
- When Day & Month are missing: Year of the surgery will be compared to Year of the dosing date of interest (either ITP or MTP). If on or after, the surgery will be considered as concomitant to the period of interest. If on or before the first doing date of ITP, the surgery will be considered as prior.

Of note, the above rules may allow a medication/procedure to be concomitant to both the ITP and MTP treatment phase.

For patients who discontinued study treatment but without any study treatment discontinuation visit date, this visit will be imputed as follows:

- If patient was treated in the MTP, the last dose will be retrieved from the treatment drug completion/early discontinuation page from the eCRF in the maintenance phase. The maximum date among the date mentioned for each treatment during MTP + 30 days will be considered.
- If patient was treated in the ITP, the last dose will be retrieved from the treatment drug completion/early discontinuation page from the eCRF in the induction phase. The maximum date among the date mentioned for each treatment during ITP + 30 days will be considered

with the following exception:

  - If a patient died within 30 days from last dose, the follow up phase does not exist for this patient

Partially missing dates for date of initial histological diagnosis or date of first diagnosis of metastatic disease or date of first diagnosis of locally recurrent disease will be imputed as follows:

Imputation of these partial dates will be done only to determine if the initial diagnosis is synchronous or metachronous and only in case the date day is missing. The imputation will consist in replacing the missing day by “1”. In case month and/or year are missing, no imputation will be done.

No other dates will be imputed, unless otherwise specified. The original incomplete, missing or partial dates will be presented in the listings, not the imputed dates

4.15 INTERIM ANALYSES

A preliminary evaluation of tumor response will be made by the iDMC once a total of 27 patients in the experimental treatment arm of the cohort have completed a tumour assessment at Month 2 of the Maintenance Treatment Phase to assure these data continue to support an early positive benefit-risk ratio and to confirm that continued enrolment into the cohort is appropriate.

No other formal interim analyses on PFS or OS are planned.

5. REFERENCES

Di Nicolantonio F, Martini M, Molinari F, et al. Wild-type BRAF is required for response to panitumumab or cetuximab in metastatic colorectal cancer. J Clin Oncol. 2008 Dec 10;26(35):5705-12. doi: 10.1200/JCO.2008.18.0786. Epub 2008 Nov 10.

Ron Brookmeyer and John Crowley, A Confidence Interval for the Median Survival Time. Biometrics Vol. 38, No. 1 (Mar., 1982), 29-41

Appendix 1: Protocol Synopsis

Objectives

Efficacy Objectives

Within each cohort, the study has the following co-primary efficacy objectives as follows:

- Assessing early efficacy during the Maintenance Treatment Phase based on a 20% reduction in tumour size after 2 months of treatment
- Evaluating progression-free survival (PFS)

Secondary efficacy objectives include the evaluation of efficacy through other endpoints:

- Overall survival (OS)
- Overall response rate (ORR)
- Disease control rate (DCR)
- Time to treatment response (TTR)
- Duration of response (DoR)
- Eastern Cooperative Oncology Group (ECOG) performance status

Safety and Tolerability of the Treatment Regimen

Additional objectives for this study are to assess the safety of each treatment including:

- the 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

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Adverse events (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 modified RECIST (mRECIST) in patients treated with atezolizumab

The exploratory biomarker objectives for 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

Description of Study

All Cohorts

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). The study has two co-primary endpoints of reduced tumour size after 2 months in the Maintenance Treatment Phase and PFS. Secondary outcomes include other efficacy measurements and safety. In addition, exploratory outcomes will focus on the correlations between biomarkers and study outcomes.

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. Results from routine assessments conducted prior to informed consent signature may be used as screening assessments as long as they were done within 7 days prior to informed consent signature. The primary tumour tissue block prepared at the time of the initial diagnosis will be used for biomarker assessment for maintenance treatment cohort assignment (see Appendix 12). Prior to performing any screening procedures, the Investigator must ensure that adequate archival tissue from a potential participant's primary tumour is available for shipping to the Sponsor's designated laboratory during the Screening Phase. If the tumour block is not available, ≥ 20 slides cut within 2 weeks of shipping to the Sponsor's designated laboratory will be accepted as an alternative.

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. All patients enrolled in the study will be asked to give written informed consent to allow all available residual samples of tumour, blood and plasma samples to be used for additional exploratory biomarker research using the Roche Clinical Sample Repository. No additional sampling

is required. Patients at selected centres may participate in the optional Supplemental Biomarker Program (described in Appendix 13).

Eligible patients will enter a 4-month Induction Treatment Phase. Treatment during this phase, based on Investigator's choice (see Appendix 4), 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 prematurely discontinue study treatment for any reason during the Induction Treatment Phase, or who experience PD at any time during or at the end of the Induction Treatment Phase, or who refuse to proceed to the Maintenance Treatment Phase or who are not eligible for any study cohort will undergo a Study Treatment Discontinuation Visit within 30 days after the last dose of study treatment and will then enter the Post-treatment Follow-up Phase. All patients need to be evaluated for potential resection of metastasis at completion of the induction period. This is of particular importance for patients with liver metastases. If the patient is found to be resectable they will undergo a Study Treatment Discontinuation Visit within 30 days after the last dose of study treatment and will then enter the Post-treatment Follow-up Phase. Patients participating in the Supplemental Biomarker Plan will undergo a tumour core biopsy of metastasis at the time of progressive disease (see Appendix 13).

Patients who do not have progressive disease and who have completed the Induction Treatment Phase can then proceed to the Maintenance Treatment Phase.

Patients participating in the Supplemental Biomarker Plan will have an additional tumour core biopsy of metastasis upon completion of induction treatment prior to initiation of maintenance treatment (see Appendix 13).

Each cohort will consist of a cohort-specific experimental treatment arm and a standard control arm of fluoropyrimidine (5-FU/LV or capecitabine) and bevacizumab. Within 3 weeks of completion of the Induction Treatment Phase of the study, patients who have not progressed and continue to the biomarker-driven Maintenance Treatment Phase of the study will be randomised on a 2:1 (experimental:control) basis to either the experimental treatment arm or the control arm of that cohort. Randomisation will be stratified according to specific biomarkers identified for each cohort (if applicable, see Appendix 12), by geographical region (EU, Americas, Africa or Asia) and by patient response after the Induction Treatment Phase (CR/PR vs. SD).

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 (see Figure 1).

Cohort 1 – $BRAF^{mut}$

(5-FU/LV) with cetuximab and vemurafenib

vs.

fluoropyrimidine (5-FU/LV or capecitabine) and bevacizumab

Cohort 2 – No Biomarker

fluoropyrimidine (5-FU/LV or capecitabine) with bevacizumab and atezolizumab

vs.

fluoropyrimidine (5-FU/LV or capecitabine) and bevacizumab

No other anti-cancer therapy is permitted during the Induction or Maintenance Treatment Phases except for radiotherapy for pain control.

All Cohorts

A preliminary evaluation of response will be made for each cohort independently once a total of 27 patients in the experimental treatment arm of that cohort have completed a tumour assessment at Month 2 of the Maintenance Treatment Phase (see Figure 2). Cohort randomisation will continue until a decision regarding response criteria has been made. If the evaluation of response for these first 27 patients does not show sufficiently promising results then, after this evaluation, no further patients will be entered into that cohort. Otherwise, recruitment will continue until the required target number of patients has been enrolled for the assessment of PFS as specified in the sample size section.

For all patients who are not receiving atezolizumab, study treatment during the Maintenance Treatment Phase will continue until disease progression (based on Investigator's assessment), unacceptable toxicity, initiation of another anti-cancer therapy, patient or physician decision to discontinue, or patient death, whichever occurs first.

For all patients who are receiving atezolizumab, study treatment during the Maintenance Treatment Phase will continue as long as patients are experiencing clinical benefit as assessed by the Investigator and meet the following criteria:

- Evidence of clinical benefit as assessed by the Investigator
- Absence of symptoms and signs (including worsening of laboratory values, e.g. new or worsening hypercalcaemia) indicating unequivocal progression of disease
- No decline in ECOG performance status that can be attributed to disease progression
- Absence of tumour progression at critical anatomical sites (e.g. leptomeningeal disease) that cannot be managed by protocol-allowed medical interventions

Atezolizumab treated patients may be discontinued from study treatment for the following reasons other than loss of clinical benefit: unacceptable toxicity, initiation of another anti-cancer therapy, patient or physician decision to discontinue, or patient death, whichever occurs first.

Patients participating in the Supplemental Biomarker Plan will undergo a tumour core biopsy of metastasis at the time of progressive disease (see Appendix 13).

Efficacy, safety and tolerability will be assessed during the entire Maintenance Treatment Phase. While receiving study treatment during the Maintenance Treatment Phase, 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). An additional safety review (safety run-in) will be conducted for the first six patients treated with the experimental combination of '5-FU/LV + cetuximab + vemurafenib'. Disease status will be evaluated during the Maintenance Treatment Phase in accordance with RECIST 1.1 (see Appendix 7) for all patients, and additionally according to mRECIST (see Appendix 8) for patients in the experimental arm of Cohort 2 – No Biomarker (all patients treated with atezolizumab). The frequency of tumour assessments during the Maintenance Treatment Phase will be based on local standard of care with the exception of the first 27 patients in the experimental arm of each cohort who must have a tumour assessment at Month 2 of the Maintenance Treatment Phase so that the initial response of each cohort can be evaluated. Schedules of Assessments for each cohort are provided in Appendix 2 and Appendix 3.

Patients who discontinue study treatment for any reason during the Maintenance Treatment Phase will undergo a Study Treatment Discontinuation Visit within 30 days after the last dose of study treatment and will then enter the Post-treatment Follow-up Phase.

Patients who prematurely discontinue treatment during the Induction Treatment Phase, who did not proceed to the Maintenance Treatment Phase or who discontinue treatment during the Maintenance Treatment Phase, will be followed for new AEs for 28 days following the discontinuation of study treatment. At the time of treatment discontinuation, any ongoing AE/SAE will be followed until the event resolves, the Investigator assesses the event as stable, or the patient is lost to follow-up, dies or withdraws consent. The Sponsor should be notified if the Investigator becomes aware of any SAE or AEs of special interest occurring after the end of the adverse event reporting period, regardless of causality.

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 (e.g. investigations for squamous cell carcinoma in patients who received vemurafenib) (see Appendices 1, 2 and 3). 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.

Second-line treatment during the Post-Treatment Follow-up Phase is at the Investigator's discretion. However, patients who received atezolizumab should not receive other immunomodulatory agents for 10 weeks after maintenance treatment discontinuation.

$BRAF^{mut}$ Patients and Early Disease Progression

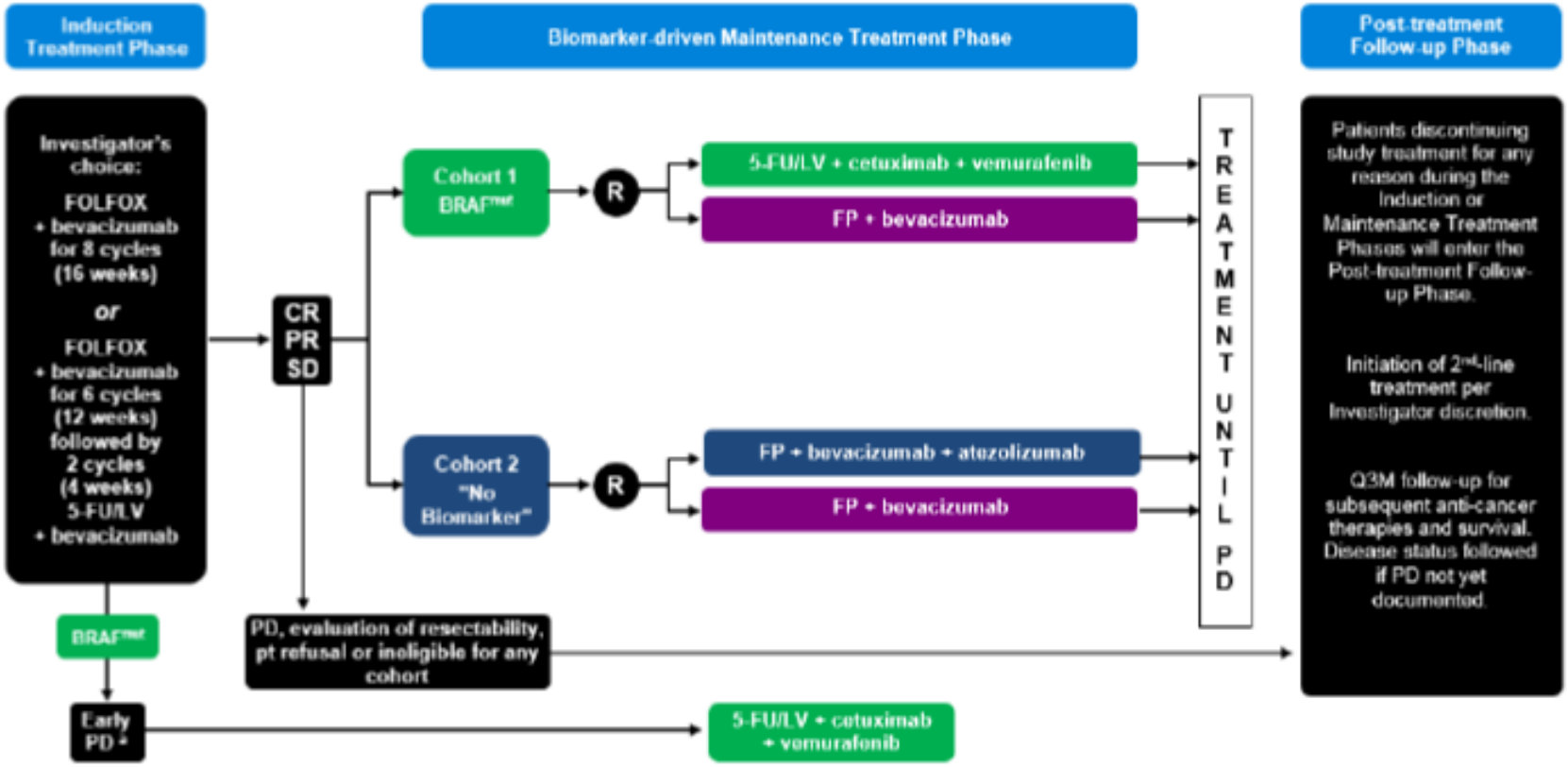
$BRAF^{mut}$ patients experiencing early disease progression during the Induction Treatment Phase will have the option of proceeding immediately to receive second-line treatment with 5-FU/LV, cetuximab and vemurafenib. These patients will be followed for safety and efficacy in accordance with the Maintenance Treatment Phase Schedule of Assessments for Cohort 1 – $BRAF^{mut}$ (see Appendix 2).

All Cohorts

An estimated 1680 patients will be screened and approximately 700 patients will be enrolled into the Induction Treatment Phase in countries in Europe, Asia, Africa and North and South America. Recruitment into specific cohorts will be stopped when the required number of patients has been recruited into that cohort (see Section 6.2). It is anticipated that recruitment will occur over a 3-year period, with study follow-up being completed approximately 3 years after the last patient has completed a Baseline visit.

For an individual patient, the study will consist of a Screening Phase (≤ 28 days), a 4-month Induction Treatment Phase, a Maintenance Treatment Phase, and finally follow-up during the Post-Treatment Follow-up Phase.

Figure 1: Study Design



FP = fluoropyrimidine (5-FU/LV or capecitabine)

a. Patients who progress early and who are not BRAFmut will enter the Post-treatment Follow-up Phase with initiation of 2nd-line treatment per Investigator discretion

Study Conduct

All Cohorts

A Steering Committee (SC) will be responsible for overseeing the general conduct of the study. An independent Data Monitoring Committee (iDMC) will be responsible for evaluating the safety of the patients participating in the trial at regular intervals throughout the study. The iDMC will make recommendations as to whether cohort recruitment should continue based on the initial evaluation of response of each cohort, and will review OS and PFS data on a regular basis as available. In addition, the iDMC will evaluate the safety data from the first six patients treated with the experimental combination of '5-FU/LV + cetuximab + vemurafenib' to determine the initial safety of this experimental regimen and the target dose to be used forsubsequent patients. Otherwise, efficacy data will only be provided if required by the iDMC to estimate risk-benefit for patients. The schedule of iDMC review will be determined by the iDMC and described in the iDMC Charter, although it is anticipated that the iDMC will review the data at a minimum of every six months. Additional data are provided in the respective SC and iDMC Charters.

Number of Patients

Approximately 1680 patients will be screened. Approximately 700 patients will be enrolled in the Induction Treatment Phase of the study in order to randomise 126 patients in Cohort 1 – $BRAF^{mut}$ and 405 patients in Cohort 2 – No Biomarker.

Screening procedures

For comparability reasons, only the archival primary tumour sample from the original diagnosis will be used for the biomarker assessment which determines treatment assignment during the Maintenance Treatment Phase, as this material will be available for all patients. To be eligible for the study, patients must have an adequate archival primary tumour sample for biomarker assessment for cohort assignment. The adequacy of the sample must be determined by the Investigator prior to the conduct of any screening procedures. The sample must be shipped to the designated lab during the Screening Phase. Biomarker analyses for cohort assignment will be conducted during the Induction Treatment Phase and these results will only be available during the Induction Treatment Phase and not during Screening. Patients with an unknown biomarker status due to lack of determinant result (e.g. due to technical issues) can still be included in the study and will be assigned to Cohort 2 – No Biomarker.

If Cohort 2 – No Biomarker reaches the required number of randomized patients, and if no additional cohorts are to be included in the study at that point in time, screening procedures will be modified such that all patients will undergo BRAF mutation testing prior to any other screening procedures and before study enrolment to select for $BRAF^{mut}$ patients. Informed consent must be obtained prior to BRAF mutation testing. This will allow the recruitment of the required number of patients into Cohort 1 – $BRAF^{mut}$. The Sponsor will monitor enrolment rates and initiate this modification when applicable.

Target Population

The target study population consists of patients with mCRC who have not received any prior chemotherapy in the metastatic setting.

The "All Cohort" eligibility criteria are evaluated prior to initiating the first cycle of study treatment during the Induction Treatment Phase. Prior to performing any screening procedures, the Investigator must ensure that adequate archival tissue from a patient's primary tumour is available for shipping to the Sponsor's designated laboratory during the Screening Phase. If the tumour block is not available, ≥ 20 slides cut within 2 weeks of shipping to the Sponsor's designated laboratory will be accepted as an alternative. Cohort-specific exclusion criteria must be assessed within 3 weeks of completing Induction Treatment Phase. Biomarker assessments will be completed prior to randomisation, as the results of the biomarker assessments are required to identify the intended cohort in order to complete the appropriate cohort-specific eligibility assessments.

Inclusion Criteria

Patients must meet the following criteria for study entry:

All Cohorts

Patient Status

1. Have provided written informed consent prior to any study specific procedures
2. Willing and able to comply with the protocol
3. ≥ 18 years of age
4. ECOG status of ≤ 2 (see Appendix 5)
5. At least 16 weeks of life expectancy at time of entry into the study

Disease-related

6. Histologically confirmed mCRC
7. Measureable, unresectable disease according to RECIST 1.1
8. No prior chemotherapy for CRC in the metastatic setting
9. Archival tumour formalin-fixed paraffin-embedded tissue (FFPET) block from the primary tumour obtained at the time of the initial diagnosis is available for submission to the Sponsor's designated laboratory. If the tumour block is not available, ≥ 20 slides cut within two weeks of shipping to the designated laboratory will be accepted as an alternative (see Appendix 12).

Exclusion Criteria

Patients who meet any of the following criteria will be excluded from study entry:

All Cohorts

Other Prior or Current Treatments

1. Less than 6 months from completion of any prior adjuvant chemotherapy or radiotherapy.
2. Prior or current treatment with bevacizumab or any other anti-angiogenic drug (i.e. anti-VEGF or vascular endothelial growth factor receptor [VEGFR] therapies or tyrosine kinase inhibitors)
3. Current or recent (within 10 days of start of study induction treatment) use of aspirin (> 325 mg/day), clopidogrel (> 75 mg/day), therapeutic oral or parenteral anticoagulants, or thrombolytic agents for therapeutic purposes.

   Note: The use of full-dose oral or parenteral anticoagulants is permitted as long as the international normalised ratio (INR) or activated partial thromboplastin time (aPTT) is within therapeutic limits (according to the medical standard of the institution) and the patient has been on a stable dose of anticoagulants for at least two weeks prior to the start of study induction treatment. Prophylactic use of anticoagulants is allowed.
4. Requirement for treatment with any medicinal product that contraindicates the use of any of the study medications, may interfere with the planned treatment, affects patient compliance or puts the patient at high risk for treatment-related complications
5. Treatment with any other investigational agent within 28 days or 5 investigational agent half-lives (whichever is longer) prior to the start of study induction treatment

Haematological, Biochemical and Organ Function

6. Inadequate haematological function indicated by all of the following:
   - Absolute neutrophil count (ANC) < 1.5 x 10^9/L
   - Platelet count < 100 x 10^9/L

- Haemoglobin < 9 g/dL (patients may have transfusions and/or growth factors to attain adequate haemoglobin)

7. Inadequate liver function indicated by all of the following:
   - Total bilirubin ≥ 1.5 x upper limit of normal (ULN)
   - Aspartate transaminase (AST) and alanine aminotransferase (ALT) ≥ 2.5 x ULN (≥ 5 x ULN in patients with known liver metastases)
   - Alkaline phosphatase (ALP) ≥ 2 x ULN (≥ 5 x ULN in patients with known liver metastases)
8. Inadequate renal function indicated by all of the following:
   - Serum creatinine > 1.25 x ULN or calculated creatinine clearance < 50 ml/min
   - Urine dipstick for proteinuria ≥ 2+ unless a 24-hour urine protein < 1 g of protein is demonstrated
9. INR > 1.5 and aPTT > 1.5 x ULN within 7 days prior to the start of study induction treatment for patients not receiving anti-coagulation

   The use of full-dose oral or parenteral anticoagulants is permitted as long as the INR or aPTT is within therapeutic limits (according to the medical standard of the enrolling institution) and the patient has been on a stable dose of anticoagulants for at least two weeks prior to the start of study induction treatment

General Criteria

10. Active infection requiring intravenous antibiotics at the start of study induction treatment
11. Previous or concurrent malignancy, except for adequately treated basal or squamous cell skin cancer, *in situ* cervical cancer, or other cancer for which the patient has been disease-free for five years prior to study entry
12. Evidence of any other disease, neurologic or metabolic dysfunction, physical examination finding or laboratory finding giving reasonable suspicion of a disease or condition that contraindicates the use of any of the study medications, puts the patient at higher risk for treatment-related complications or may affect the interpretation of study results
13. Inadequately controlled hypertension (defined as systolic blood pressure > 150 mmHg and/or diastolic blood pressure > 100 mmHg)
14. Prior history of hypertensive crisis or hypertensive encephalopathy
15. Clinically significant (i.e. active) cardiovascular disease, for example cerebrovascular accidents ≤ 6 months prior to start of study induction treatment, myocardial infarction ≤ 6 months prior to study enrolment, unstable angina, New York Heart Association (NYHA) Functional Classification Grade 2 or greater congestive heart failure, or serious cardiac arrhythmia uncontrolled by medication or potentially interfering with protocol treatment
16. History or evidence upon physical or neurological examination of central nervous system (CNS) disease (e.g. seizures) unrelated to cancer unless adequately treated with standard medical therapy
17. Significant vascular disease (e.g. aortic aneurysm requiring surgical repair or recent arterial thrombosis) within 6 months of start of study induction treatment
18. Any previous venous thromboembolism > National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) Grade 3 within 12 months prior to start of study induction treatment
19. Active or untreated CNS metastases. Treatment of brain metastases, either by surgical or radiation techniques, must have been completed > 4 weeks prior to start of study induction treatment. Patients with evidence of interim progression between the completion of CNS-directed therapy and study baseline disease assessments are excluded from the study.
20. History of haemoptysis ≥ Grade 2 (defined as ≥ 2.5 mL bright red blood per episode) within 1 month of start of study induction treatment

21. History or evidence of inherited bleeding diathesis or significant coagulopathy at risk of bleeding (i.e. in the absence of therapeutic anticoagulation)
22. Surgical procedure (including open biopsy, surgical resection, wound revision, or any other major surgery involving entry into a body cavity) or significant traumatic injury within 28 days prior to start of study induction treatment, or anticipation of need for major surgical procedure during the course of the study.
23. Minor surgical procedure including placement of a vascular access device, within 2 days of start of study induction treatment
24. History of abdominal fistula, gastrointestinal (GI) perforation, intra-abdominal abscess or active GI bleeding within 6 months prior to start of study induction treatment
25. Serious, non-healing wound, active ulcer, or untreated bone fracture
26. Known hypersensitivity to any component of bevacizumab or any of the study medications
27. History of severe allergic, anaphylactic, or other hypersensitivity reactions to chimeric or humanized antibodies or fusion proteins
28. Known dihydropyrimidine dehydrogenase (DPD) deficiency
29. Pregnancy or lactation. A serum pregnancy test is required within 7 days prior to start of study induction treatment, or within 14 days with a confirmatory urine pregnancy test within 7 days prior start of study induction treatment
30. For women who are not post-menopausal (< 12 months of non-therapy-induced amenorrhea) or surgically sterile (absence of ovaries and/or uterus): refusal to use a highly effective contraceptive method (i.e. with a failure rate of < 1% per year such assexual abstinence, hormonal implants, combined oral contraceptives, vasectomised partner), during both the Induction and Maintenance Treatment Phases and for at least 6 months after the last dose of study medication. Periodic abstinence [e.g., calendar, ovulation, symptothermal, postovulation methods] and withdrawal are not acceptable methods of contraception.A combination of male condom with cap, diaphragm or sponge with spermicide (double barrier methods) is not considered highly effective, birth control methods. Acceptable methods of contraception may include total abstinence in cases where the lifestyle of the patient ensures compliance. A Vasectomised partner is a highly effective birth control method provided that partner is the sole sexual partner of the MODUL trial participant and that the vasectomised partner has received medical assessment of the surgical success. Some of the study-related medication, such as vemurafenib may decrease the plasma exposure of those hormonal contraceptives predominantly metabolized by CYP3A4.In these cases, the use of an alternate highly effective method of contraception must be considered.
31. For men: refusal to use a highly effective contraceptive method (i.e. with a failure rate of < 1 % per year such as vasectomy, sexual abstinence or female partner use of hormonal implants or combined oral contraceptives) during both the Induction and Maintenance Treatment Phases and for a period of at least 6 months after the last dose of study medication. Periodic abstinence [e.g., calendar, ovulation, symptothermal, postovulation methods] and withdrawal are not acceptable methods of contraception. A combination of male condom with either cap, diaphragm or sponge with spermicide (double barrier methods) is not considered highly effective, birth control methods. Acceptable methods of contraception may include total abstinence in cases where the lifestyle of the patient ensures compliance. A vasectomised MODUL trial participant is a highly effective birth control method provided that the MODUL trial participant has received medical assessment of the surgical success.

Cohort-Specific Exclusion Criteria

The following criteria will be assessed once the patient's centrally-assessed BRAF biomarker status is known:

Additional criteria for Cohort 1 – BRAF^{mut}

1. Inability to swallow pills

2. Refractory nausea and vomiting, malabsorption, external biliary shunt or significant bowel resection that would preclude adequate absorption
3. History or presence of clinically significant ventricular or atrial dysrhythmias ≥ NCI CTCAE Grade 2
4. Corrected QT (QTc) interval > 480 msec at Baseline or history of congenital long QT syndrome or uncorrectable electrolyte abnormalities
5. For women who are not post-menopausal (< 12 months of non-therapy-induced amenorrhea) or surgically sterile (absence of ovaries and/or uterus): refusal to use an alternate highly effective contraceptive method (i.e. with a failure rate of < 1% per year such as sexual abstinence, vasectomised partner) other than hormonal contraceptives, during both the Induction and Maintenance Treatment Phases and for at least 6 months after the last dose of study medication. Vemurafenib may decrease the plasma exposure of those hormonal contraceptives predominantly metabolized by CYP3A4.

Additional criteria for Cohort 2 – No Biomarker

1. Active or untreated CNS metastases. Patients with a history of treated asymptomatic CNS metastases are eligible provided they meet all the following criteria:
   - Measurable disease outside the CNS
   - Only supratentorial or cerebellar metastases allowed (i.e. no metastases to midbrain, pons, medulla or spinal cord)
   - No ongoing requirement for corticosteroid therapy for CNS disease
2. Known hypersensitivity or allergy to Chinese hamster ovary cell products or any component of the atezolizumab formulation
3. History of autoimmune disease including but not limited to myasthenia gravis, myositis, autoimmune hepatitis, systemic lupus erythematosus, rheumatoid arthritis, inflammatory bowel disease, vascular thrombosis associated with antiphospholipid syndrome, Wegener's granulomatosis, Sjögren's syndrome, Guillain-Barré syndrome, multiple sclerosis, vasculitis, or glomerulonephritis (see Appendix 6 for a more comprehensive list of autoimmune diseases)

   Note: History of autoimmune-related hypothyroidism on a stable dose of thyroid replacement hormone may be eligible for this study.

   Note: Controlled Type 1 diabetes mellitus on a stable insulin regimen may be eligible for this study.
4. Prior allogeneic bone marrow transplantation or prior solid organ transplantation
5. History of idiopathic pulmonary fibrosis (including pneumonitis), drug-induced pneumonitis, organizing pneumonia (i.e., bronchiolitis obliterans, cryptogenic organizing pneumonia), or evidence of active pneumonitis on screening chest CT scan

   Note: History of radiation pneumonitis in the radiation field (fibrosis) is permitted.
6. Positive test for human immunodeficiency virus (HIV)
7. Active hepatitis B (defined as having a positive hepatitis B surface antigen [HBsAg] test prior to randomization) or hepatitis C

   Note: Patients with past hepatitis B virus (HBV) infection or resolved HBV infection (defined as having a negative HBsAg test and a positive antibody to hepatitis B core antigen [anti-HBc] antibody test) are eligible.

   Patients positive for hepatitis C virus (HCV) antibody are eligible only if polymerase chain reaction (PCR) is negative for HCV RNA.
8. Active tuberculosis

9. Administration of a live, attenuated vaccine within 4 weeks prior to start of study maintenance treatment or anticipation that such a live attenuated vaccine will be required during the study
10. Prior treatment with CD137 agonists, anti-CTLA4, anti-PD-1, or anti-PD-L1 therapeutic antibody or pathway-targeting agents
11. Treatment with systemic immunostimulatory agents (including but not limited to interferons or interleukin-2) within 4 weeks or five half-lives of the drug, whichever is longer, prior to start of study maintenance treatment
12. Treatment with systemic corticosteroids or other systemic immunosuppressive medications (including but not limited to prednisone, dexamethasone, cyclophosphamide, azathioprine, methotrexate, thalidomide, and anti-tumour necrosis factor [TNF] agents) within 2 weeks prior to start of study maintenance treatment, or requirement for systemic immunosuppressive medications during the trial. The use of inhaled corticosteroids and mineralocorticoids (e.g., fludrocortisone) is allowed.

    Note: Patients who have received acute, low-dose, systemic immunosuppressant medications (e.g., a one-time dose of dexamethasone for nausea) may be enrolled in the study after discussion with and approval by the Medical Monitor.
13. If receiving a RANKL inhibitor (e.g. denosumab), unwilling to adopt alternative treatment such as (but not limited to) bisphosphonates, while receiving atezolizumab.

Length of Study

All Cohorts

Study recruitment is expected to take approximately 3 years. The entire study duration will be approximately 6 years.

End of Study

All Cohorts

After the clinical cut-off date for the primary analysis of PFS has been reached, patients will continue to be followed every 3 months for survival status over a period of 24 months. The end of the study is defined as the date when the last patient, last visit (LPLV) occurs at the end of the Post-treatment Follow-up. After this, the trial will end and no further data will be collected in the clinical database for this study. Post-trial access to the study drugs used in the experimental treatment arm of any cohort will be in accordance with the Roche Global Policy on Continued Access to Investigational Medicinal Product.

Efficacy Outcome Measures

All Cohorts

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 per Investigator assessment using RECIST 1.1 or death from any cause, whichever occurs first.

Secondary

- 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. 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. 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

Safety Outcome Measures

All Cohorts

The safety outcome measures for this study are as follows:

- Incidence, nature and severity of all adverse events (graded according to NCI CTCAE v4.0)
- Incidence and nature of all Grade 3 – 5 AEs
- Grade 5 AEs or AEs leading to death on study treatment
- All SAEs
- Incidence and reasons for any premature discontinuation of any component of study treatment
- Incidence and reasons for any dose reductions or interruptions of any component of study treatment
- AEs of special interest
- Clinically significant changes in laboratory values

Adverse events 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 Outcome Measures

Cohort 2 – No Biomarker- Experimental Arm Only

PFS in patients treated with atezolizumab defined as the time from randomisation into the Maintenance Treatment Phase until disease progression per Investigator assessment using mRECIST or death from any cause, whichever occurs first.

All Cohorts

The exploratory biomarker outcome measures for this study include molecular markers/marker profiles and efficacy and/or safety outcomes. Efficacy outcomes considered for this analysis may include, but are not limited to, ORR, PFS and OS, as appropriate. Biomarkers and biomarker profiles may be assessed using various methodologies including, but not limited to, immunohistochemistry (single and multiplex), RNA and DNA analysis (e.g mutation, expression and microsatellite instability analyses) of tumour and/or blood samples collected from all study patients.

Study Treatment

Induction Treatment Phase

All Cohorts

All patients will receive 4 months of study treatment in the Induction Treatment Phase. Treatment during this phase, based on Investigator's choice, will be either:

- eight 2-week cycles of 5-FU/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

should be in accordance with locally approved prescribing information including any recommendations for pre-treatment (i.e. antiemetic therapies). The Investigator will select the FOLFOX regimen (e.g. FOLFOX-4, FOLFOX-6, modified FOLFOX-6, FOLFOX-7 or modified FOLFOX-7; see Appendix 4) also in accordance with local standards.

Investigational Medicinal Products

The investigational medicinal products (IMPs) used in this study include:

- all non-fluoropyrimidine agents comprising the experimental arms of each maintenance treatment cohort (i.e. cetuximab, and vemurafenib in Cohort 1 – $BRAF^{mut}$; bevacizumab and atezolizumab in Cohort 2 – No Biomarker)
- bevacizumab in the Induction Treatment Phase
- bevacizumab in the control arms of each maintenance treatment cohort
- cetuximab and vemurafenib administered as optional second-line treatment to early progressing $BRAF^{mut}$ patients

Non-Investigational Medicinal Products

Non-IMPs used in this study include all fluoropyrimidine agents (i.e. 5-FU and capecitabine) and leucovorin administered during the Induction and Maintenance Treatment Phases. Oxaliplatin administered as part of induction treatment is also considered a non-IMP.

Maintenance Treatment Phase

All Cohorts

Each cohort will contain an experimental treatment arm based specifically on the patient's biomarker status based on the patient's archival tumour sample from the initial diagnosis (see Appendix 12 for additional details on cohort assignment). Patients with an unknown biomarker status due to lack of determinant result (e.g. due to technical issues) will be assigned to Cohort 2 – No Biomarker. Each cohort will also include a control treatment arm containing a fluoropyrimidine and bevacizumab.

For patients in Cohort 1 – $BRAF^{mut}$ and patients in the control arm of Cohort 2 – No Biomarker, study treatment during the Maintenance Treatment Phase will continue until disease progression (based on Investigator's assessment according to RECIST 1.1), unacceptable toxicity, initiation of another anti-cancer therapy, patient or physician decision to discontinue, or patient death, whichever occurs first.

For patients randomized to the experimental arm of Cohort 2 – No Biomarker (i.e. patients who are receiving atezolizumab), study treatment during the Maintenance Treatment Phase will continue as long as they are experiencing clinical benefit as assessed by the Investigator and meet the following criteria:

- Evidence of clinical benefit as assessed by the Investigator

- Absence of symptoms and signs (including worsening of laboratory values, e.g. new or worsening hypercalcaemia) indicating unequivocal progression of disease
- No decline in ECOG performance status that can be attributed to disease progression
- Absence of tumour progression at critical anatomical sites (e.g. leptomeningeal disease) that cannot be managed by protocol-allowed medical interventions

Atezolizumab treated patients may be discontinued from study treatment during the Maintenance Phase for the following reasons other than loss of clinical benefit: unacceptable toxicity, initiation of another anti-cancer therapy, patient or physician decision to discontinue, or patient death, whichever occurs first.

Dose reductions are only allowed for specified toxicities (see Section 5.1.3). If any drug of any study treatment regimen is discontinued or held for > 14 days, the patient will come off all study treatment and will enter the Post-Treatment Follow-up Phase.

Cohort 1 – $BRAF^{mut}$

Experimental Arm

5-FU: The first six patients in this cohort will receive 1,600 mg/m^2 5-FU administered via 46-hour IV infusion, in combination with LV 400 mg/m^2 administered via 2-hour infusion, on Day 1 of every 2-week cycle. If the iDMC determines that there are no safety concerns or dose-limiting toxicities in these first six patients, subsequent patients in this cohort will receive 1,600 - 2,400 mg/m^2 5-FU administered via 46-hour IV infusion, in combination with LV 400 mg/m^2 administered via 2-hour infusion, on Day 1 of every 2-week cycle.

Cetuximab: The dose and scheduling of cetuximab is 500 mg/m^2 via IV infusion on Day 1 of every 2-week cycle. Cetuximab must be administered in hospital under the supervision of a physician experienced in the use of antineoplastic medicinal products. Cetuximab must be administered via infusion pump or syringe pump at a rate not exceeding 5 mg/min for the first administration and 10 mg/min for subsequent administrations. Close monitoring is required during the infusion and for at least 1 hour after the end of the infusion. Availability of resuscitation equipment must be ensured. Prior to the first infusion of cetuximab, patients must receive premedication with an antihistamine and a corticosteroid. This premedication is recommended prior to all subsequent infusions. Refer to cetuximab Package Insert (Appendix 11).

Vemurafenib: The dose and scheduling of vemurafenib is 960 mg b.i.d by mouth. Vemurafenib should be taken at approximately the same times each day, the first dose is to be taken in the morning and the second dose is to be taken approximately 12 hours later in the evening. Each dose should always be taken in the same manner i.e. either with or without a meal. Missed doses will not be made up.

Note: A safety run-in will be conducted for the first six patients treated with the experimental combination of '5-FU/LV + cetuximab + vemurafenib'. Safety data from these patients will be reviewed by the iDMC to determine the initial safety of this experimental regimen and the target dose to be used for subsequent patients.

Control Arm

Fluoropyrimidine (5-FU/LV or capecitabine): dose and schedule will be according to local label, where applicable, or otherwise will be determined per the Investigator's discretion. Administration should be according to local prescribing information.

Bevacizumab: 5 mg/kg via 15-30 minute IV infusion on Day 1 of every 2-week cycle. Bevacizumab should be prepared and administered in accordance with local prescribing information.

Cohort 2 – No Biomarker

Experimental Arm

Fluoropyrimidine (5-FU/LV or capecitabine): 1,600 – 2,400 mg/m^2 5-FU administered via 46-hour IV infusion on Day 1 of every 2-week cycle, and LV 400 mg/m^2 administered via a 2-hour infusion on day 1 every 2 weeks; or 1000 mg/m^2 twice-daily capecitabine b.i.d. by mouth given days 1-14 every 2 weeks followed by a one-week treatment break. The chosen fluoropyrimidine should be administered in accordance with local prescribing information.

Bevacizumab: The dose and schedule of bevacizumab is 5 mg/kg via 15-30 minute IV infusion on Day 1 of every 2-week cycle. Bevacizumab should be prepared and administered in accordance with local prescribing information. Patients may be at risk of developing infusion / hypersensitivity reactions with bevacizumab. Close observation of the patient during and following the administration of bevacizumab is recommended as expected for any infusion of a therapeutic humanized monoclonal antibody. If a reaction occurs, the infusion should be discontinued and appropriate medical therapies should be administered. A systematic premedication is not warranted.

Atezolizumab: Atezolizumab is administered in this study at a fixed dose of 800 mg via 60-minute IV infusion on Day 1 of every 2-week cycle. Atezolizumab must be administered in hospital under the supervision of a physician experienced in the use of antineoplastic medicinal products. For the first infusion, the patient's vital signs (heart rate, respiratory rate, blood pressures, and temperature) should be determined within 60 minutes before the infusion, every 15 ± 5 minutes during the infusion, and 30 ± 10 minutes after the infusion. For subsequent infusions, vital signs will be collected within 60 minutes before the infusion and should be collected during or after the infusion if clinically indicated or if symptoms occurred in the prior infusion. If the initial infusion is well tolerated, subsequent infusions will be done over a 30-minute time period. No premedication will be allowed for the first dose of atezolizumab. Premedication may be administered for Cycles ≥ 2 at the discretion of the treating physician. The rate of atezolizumab infusion should be modified in the event of an infusion-related reaction.

Control Arm

Fluoropyrimidine (5-FU/LV or capecitabine): dose and schedule will be according to local label, where applicable, or otherwise will be determined per the Investigator's discretion. Administration should be according to local prescribing information.

Bevacizumab: 5 mg/kg via 15-30 minute IV infusion on Day 1 of every 2-week cycle. Bevacizumab should be prepared and administered in accordance with local prescribing information.

Post-Treatment Follow-up Phase

All Cohorts

Second-line treatment during the Post-Treatment Follow-up Phase is at the Investigator's discretion. However, patients who received atezolizumab should not receive other immunomodulatory agents for 10 weeks after maintenance treatment discontinuation.

BRAF^{mut} Patients and Early Disease Progression

Exceptionally, BRAF^{mut} patients experiencing early disease progression during the Induction Treatment Phase will have the option of proceeding immediately to receive second-line treatment with (5-FU/LV), cetuximab and vemurafenib. These patients will be followed for safety and efficacy in accordance with the Maintenance Treatment Phase Schedule of Assessments for Cohort 1 – BRAF^{mut} (see Appendix 2).

Statistical Methods

All Cohorts

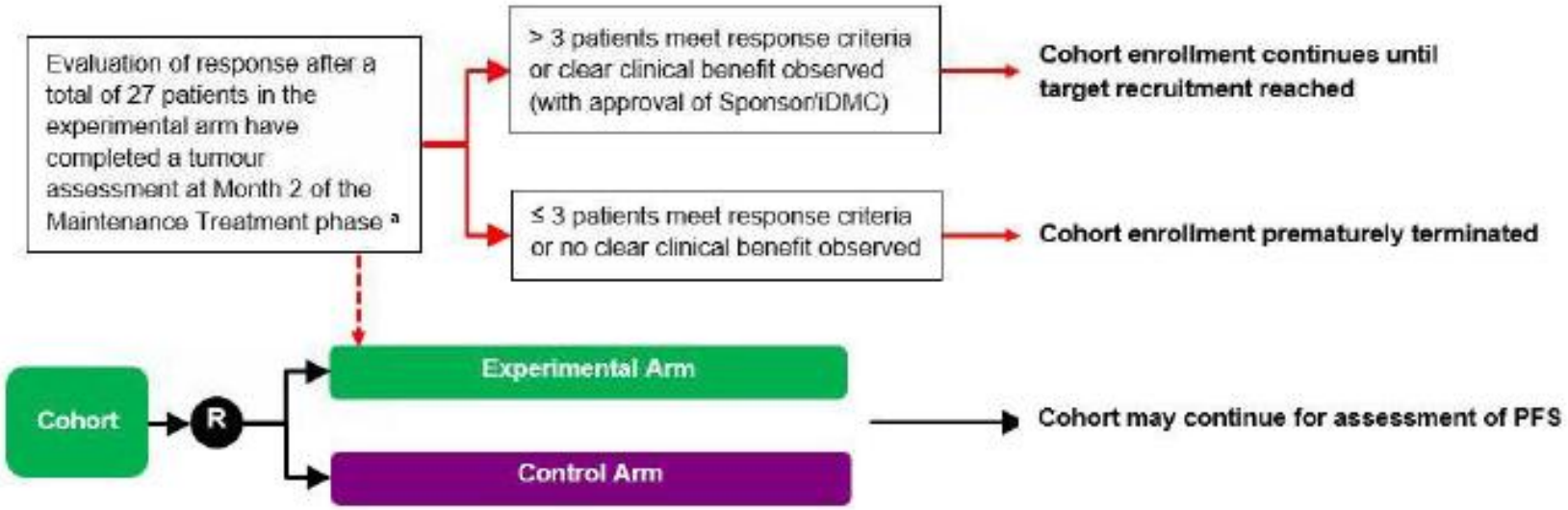
The cohorts will be based on different biomarkers (see Appendix 12), with each cohort consisting of an experimental treatment arm and a control arm. The inclusion of a control group allows discrimination of patient outcomes caused by the experimental treatment from outcomes caused by other factors. Randomisation avoids systematic differences (bias) between the groups with respect to known or unknown baseline variables that could affect outcome. The treatment for patients in the control arms represents standard of care.

Within each cohort, the study has the following co-primary objectives:

- the proportion of patients with a 20% reduction in tumour size after 2 months of treatment in the Maintenance Treatment Phase
- PFS per RECIST 1.1

A preliminary evaluation of response will be made for each cohort independently once a total of 27 patients in the experimental treatment arm of the cohort have completed a tumour assessment at Month 2 of the Maintenance Treatment Phase (see Figure 2). In the opinion of the iDMC, if the evaluation of response for these first 27 patients shows sufficiently promising results then, recruitment will continue until the required target number of patients has been enrolled for the assessment of PFS as specified in the sample size section.

Figure 2: Cohort Evaluation of Response



a. Cohort randomisation continues until decision regarding response criteria has been made

The co-primary endpoints form a hierarchy, and PFS will only be tested between treatments within cohorts that have shown a response in the experimental treatment at the earlier assessment. No adjustment will be made for multiplicity of endpoints or subgroup analyses. The calculated final sample size is based on PFS.

For each cohort, the primary analysis will occur when the target number of PFS events has been reached. Secondary endpoints will also be summarised at this time. The final analysis of the whole study (updated time-to-event endpoints and updated safety) will be provided when the last patient completes follow up.

Data will be summarized using appropriate summary statistics: mean, standard deviation, median, quartiles and range (minimum and maximum) for continuous variables, and number and percentage for categorical variables.

Analysis Populations

For each cohort, the Intent-To-Treat (ITT) Population will include patients entered into the Maintenance Treatment Phase of the study, irrespective of whether or not they received study medication. In this population, patients will be allocated to the study maintenance treatment into which they were randomised. The ITT Population will be used for all efficacy analyses.

The Per Protocol Population will not be defined for this study but major protocol violations will be listed.

The Safety Population will include all patients who received at least one dose of study medication during the Induction or Maintenance Treatment Phases. Patients will be allocated to the treatment regimen that they actually received. The Safety Population will be used for all safety analyses.

Statistical Hypotheses

The hypotheses for all cohorts for the preliminary evaluation of response are written in terms of π, where π is the proportion of responders ($0 \leq \pi \leq 1$):

H_0: $\pi \leq 0.05$

H_1: $\pi \geq 0.20$

where the power is controlled to be at least 80% under the alternative hypothesis H_1 and with an alpha level of 5%. If more than 3 of the initial 27 patients in the experimental arm of a cohort meet the response criteria at the tumour assessment at Month 2 of the Maintenance Treatment Phase, then H_0 is rejected in favour of H_1, and that cohort will continue enrolling patients until the required target number of patients has been enrolled for the assessment of PFS. If ≤ 3 of these patients meet the response criteria then that cohort will be stopped. However, if a clear clinical benefit has been observed for patients in a cohort even though the response criteria were not met, then that cohort may be allowed to continue after discussion with the iDMC and Sponsor.

Cohort 1 – $BRAF^{mut}$

The null and alternative hypotheses when comparing PFS between the two randomised treatments in Cohort 1 – $BRAF^{mut}$ (Arm A: 5-FU/LV with cetuximab and vemurafenib vs. Arm B: fluoropyrimidine and bevacizumab) are:

H_0: the distribution of the PFS time is the same in the two treatment groups

PFS (Arm A) = PFS (Arm B)

H_1: the distribution of the PFS time is different in the two treatment groups

specifically PFS (Arm A) > PFS (Arm B)

If the hazard ratio (HR) of Arm A compared to Arm B is assumed to be constant over time, then the null and alternative hypotheses are:

H_0: HR = 1 vs. H_1: HR < 1

The formal statistical test for Cohort 1 – $BRAF^{mut}$ will be one-sided and performed at an alpha level (type I error rate) of 10%.

Cohort 2 – No Biomarker

The null and alternative hypotheses when comparing PFS between the two randomised treatments in Cohort 2 – No Biomarker (Arm A: fluoropyrimidine with bevacizumab and atezolizumab vs. Arm B: fluoropyrimidine and bevacizumab) are:

H_0: the distribution of the PFS time is the same in the two treatment groups

PFS (Arm A) = PFS (Arm B)

H_1: the distribution of the PFS time is different in the two treatment groups

PFS (Arm A) ≠ PFS (Arm B)

If the HR of Arm A compared to Arm B is assumed to be constant over time, then the null and alternative hypotheses are:

H_0: HR = 1 vs. H_1: HR ≠ 1

The formal statistical test for Cohort 2 – No Biomarker will be two-sided and performed at an alpha level (type I error rate) of 5%.

Primary Endpoint

All Cohorts

The study has co-primary endpoints within each cohort: 1) the proportion of patients with a 20% reduction in tumour size after 2 months of treatment in the Maintenance Treatment Phase; and 2) PFS evaluated according to RECIST 1.1.

The co-primary efficacy endpoints of early efficacy and PFS form a hierarchy, and PFS will be tested between treatments within cohorts that have shown adequate response in the experimental treatment arm at the preliminary response evaluation.

Tumour size will be calculated using the sum of the longest diameters of all target lesions, and reduction will be based on comparisons to the tumour assessment done at Week 16 of the Induction Treatment Phase.

The evaluation of early efficacy will take place after the predefined patient number for early response assessment after 2 months has taken place, which will likely occur at about 3 months after initiation of maintenance treatment. Early efficacy will be summarized and presented along with the 95% Clopper-Pearson confidence interval.

Unless a cohort is prematurely terminated, the co-primary endpoint of PFS will be assessed within each cohort. For the co-primary endpoint, PFS is defined as the time from randomisation into the Maintenance Treatment Phase until disease progression determined by the Investigator according to RECIST 1.1 or death from any cause, whichever occurs first. Patients without an event will be censored at the date of their last evaluable tumour assessment or, if this is not available, at the date

of randomisation. For each cohort, the primary analysis of PFS will occur when the target number of PFS events has been reached.

Within each cohort, PFS will be presented graphically for each treatment group using the Kaplan-Meier method. Estimates and the corresponding 95% confidence interval will be reported by treatment group for median survival time, and for the 4-, 6- and 12-month PFS rates.

Within each cohort, the comparison of PFS between the treatment groups will be performed using an unstratified log-rank test. In addition, a Cox regression will be performed with treatment and the stratification variables (biomarkers, geographic region and response after induction treatment) as terms in the model. The estimated hazard ratio and its corresponding 95% confidence interval will be presented.

Secondary Efficacy Endpoints

All Cohorts

The secondary efficacy endpoints for each cohort are OS, ORR, DCR, time to treatment response, duration of response and ECOG performance status.

OS is defined as the time from randomisation until death from any cause. Patients who are still alive at the time of analysis (clinical cut-off) and patients who are lost to follow-up will be censored at their last clinical assessment date.

Best overall response will be assessed for all patients after randomisation until disease progression. ORR will be calculated as the proportion of patients with a best overall response of CR or PR determined according to RECIST 1.1. ORR will be summarized and presented along with the 95% Clopper-Pearson confidence interval.

DCR will be calculated as the proportion of patients with a best overall response of CR, PR or SD as determined according to RECIST 1.1. DCR will be summarized and presented along with the 95% Clopper-Pearson confidence interval.

Time to treatment response will be calculated as the time from randomisation to the first occurrence of a documented objective response (CR or PR) determined according to RECIST 1.1.

Duration of response will be assessed for all patients after randomisation until PD. Only patients with a best overall response of CR or PR per RECIST 1.1 are considered responders. The duration of response is the time from the first assessment of CR or PR until disease progression or death from any cause, whichever occurs first.

The secondary time-to-event endpoints will be analysed by the same methods and at the same time as the primary endpoint.

Safety Endpoints

All Cohorts

Verbatim adverse event (AE) data will be mapped to Medical Dictionary for Regulatory Activities (MedDRA) thesaurus terms.

All treatment-emergent AEs occurring during or after the first dose of study medication will be summarized by treatment group in frequency tables, as follows:

- By preferred term and system organ class
- By severity of all adverse events (graded according to NCI CTCAE v4.0)

- Grade 3 – 5 AEs
- Grade 5 AEs or AEs leading to death on study treatment
- All SAEs
- AEs leading to premature discontinuation of any component of study treatment
- AEs leading to dose reduction or interruption of any component of study treatment
- AEs of special interest

The above safety data will be summarized separately for the Induction and Maintenance Treatment Phases.

Deaths reported during the study treatment period and those reported during follow-up after treatment completion/discontinuation will be summarized.

Study medication exposure will be separately summarized by number of cycles, duration, dose and dose intensity.

Vital signs data, clinical laboratory parameters, concomitant medication and subsequent anti-cancer therapy will also be summarized.

Safety data will be summarised separately for the Induction and Maintenance Treatment Phases.

Analysis for Exploratory Outcome Measures

Cohort 2 – No Biomarker - Experimental Arm Only

The exploratory efficacy endpoint of PFS in patients treated with atezolizumab is defined as the time from randomisation into the Maintenance Treatment Phase until disease progression per Investigator assessment using mRECIST or death from any cause, whichever occurs first. Patients without an event will be censored at the date of their last evaluable tumour assessment or, if this is not available, at the date of randomisation. PFS may be presented graphically using the Kaplan-Meier method. Estimates and the corresponding 95% confidence interval may be reported for the 4-, 6- and 12-month PFS rates.

All Cohorts

Biomarker analyses will be of exploratory nature only, utilizing all available data obtained from archival tumour samples from the initial diagnosis and all other tumour and blood samples collected during the study from all study patients including Supplemental Biomarker Program participants. These analyses will be of exploratory nature only, using descriptive methods with no fixed hypotheses testing.

With the ongoing analyses of the study's various biomarker-based cohorts, more information on the concordance of different biomarkers will be collected and summarized. Relevant findings will be discussed with the study's SC in order to conduct further exploratory biomarker analyses accordingly.

Interim Analyses

All Cohorts

Within each cohort, a preliminary evaluation of response will be made by the iDMC once a total of 27 patients in the experimental treatment arm of the cohort have completed a tumour assessment at Month 2 of the Maintenance Treatment Phase (see Figure 2).

In addition, the iDMC will review safety data for the first six patients treated with the experimental combination of '5-FU/LV + cetuximab + vemurafenib' and will also meet regularly to review safety data as well as OS and PFS data from all cohorts as available.

Determination of Sample Size

Approximately 1680 patients will be screened. Approximately 700 patients will be enrolled in the Induction Treatment Phase of the study in order to randomise 126 patients in Cohort 1 – $BRAF^{mut}$ and 405 patients in Cohort 2 – No Biomarker.

Within each cohort, the required sample size is based on the comparison of PFS between the treatment groups.

The sample size calculation has been based on an assumed 3-year recruitment period and the following median PFS:

Table 1: PFS Estimates per Cohort

Cohort	Median PFS (months)	
	Experimental treatment group	Control group (FP and bevacizumab)
Cohort 1 – $BRAF^{mut}$	7	4.9
Cohort 2 – No Biomarker	11.5	7.5

Cohort 1 – $BRAF^{mut}$

Only 10% of the patient population is anticipated to be $BRAF^{mut}$, and approximately 25% of $BRAF^{mut}$ patients are expected to have disease progression prior to randomisation into the Maintenance Treatment Phase. Based on these assumptions, with an assumed 1680 patients screened over 3 years, an average of approximately 3.5 $BRAF^{mut}$ patients are anticipated to be randomised into this cohort each month.

Based on a one-sided 10% test, then 96 events in the $BRAF^{mut}$ group will give approximately 65% power to detect a HR of 0.7. Randomising 126 patients using a 2:1 ratio, and assuming a 36-month recruitment period, the study duration will be approximately 36 months (from the time that the first $BRAF^{mut}$ patient is randomised into the Maintenance Treatment Phase).

Cohort 2 – No Biomarker

Approximately 90% of the patient population is anticipated to fall into this cohort, and approximately 25% of these patients are expected to have disease progression prior to randomisation into the Maintenance Treatment Phase. Based on these assumptions, with an assumed 1680 patients screened over 3 years, approximately 31.5 patients are anticipated to be randomised into this cohort each month.

Based on a two-sided 5% test, then 259 events in this cohort will give approximately 90% power to detect a HR of 0.65. Randomising 405 patients using a 2:1 ratio, and assuming an 11-month recruitment period, the study duration will be approximately 22 months (from the time that the first patient is randomised into the Maintenance Treatment Phase).

Appendix 2: Schedule of Assessments for All Patients (Screening / Baseline and Induction Treatment Phase)

					Patients who have PD during or at end of Induction Treatment Phase or who refuse Maintenance Treatment or who are not eligible for any study cohort	
	Screening / Baseline		Induction Treatment Phase [a]		Study Treatment Discontinuation Visit [b]	Post-Treatment Follow-Up Phase [c]
	≤ 28 days	≤ 7 days	Day 1 Cycle 1	Every 2 cycles (every 4 weeks)	(≤ 30 days after last dose of study treatment)	Every 3 months
Informed consent [d]	x					
Confirmation of general eligibility [e]	x	x		As required		
Demographics and medical history [f]	x					
Vital signs and weight [g]	x	x	x	x	x	
Physical examination[h]	x		x	x	x	
ECOG performance status [i]		x	x	x	x	
Concomitant medications [j]	x	x	x	x	x	
Haematology and blood chemistry [k]		x		x	x	

					Patients who have PD during or at end of Induction Treatment Phase or who refuse Maintenance Treatment or who are not eligible for any study cohort	
	Screening / Baseline		**Induction Treatment Phase [a]**		**Study Treatment Discontinuation Visit [b]**	**Post-Treatment Follow-Up Phase [c]**
	≤ 28 days	≤ 7 days	Day 1 Cycle 1	Every 2 cycles (every 4 weeks)	(≤ 30 days after last dose of study treatment)	Every 3 months
INR, aPTT (select patients) [l]		x		x		
Urinalysis (dipstick) [m]		x		x	x	
Pregnancy test [n]		x		If clinically indicated		
Tumour assessments [o]	x			Mandatory at Week 16 (end of Induction Treatment Phase)		According to local standard of care (in applicable patients only)`
Archival primary tumour tissue for biomarker assessment [p]	x					
Metastatic tumour tissue for exploratory biomarker assessment [q]	x (optional for all patients)			*At PD (Supplemental Biomarker Program only)*		
Whole blood sample [r]			x			

					Patients who have PD during or at end of Induction Treatment Phase or who refuse Maintenance Treatment or who are not eligible for any study cohort	
	Screening / Baseline		**Induction Treatment Phase [a]**		**Study Treatment Discontinuation Visit [b]**	**Post-Treatment Follow-Up Phase [c]**
	≤ 28 days	≤ 7 days	Day 1 Cycle 1	Every 2 cycles (every 4 weeks)	(≤ 30 days after last dose of study treatment)	Every 3 months
Plasma samples [r]			x	Cycles 4, 6 and 8		At time of progression (if patient has not yet progressed)
Adverse events (including SAEs) [s]	x	x	x	Every cycle	x	x (as applicable)
Study medication administration [t]			x Administered every 2 weeks			
Subsequent anti-cancer therapies (see [c])						x
Patient survival (see [c])					x	x

a. With the exception of Cycle 1, all other study visits and assessments during the Treatment Phase should be performed within ± 7 days of the scheduled date.

b. Patients who experience PD during or at the end of the Induction Treatment Phase, or who refuse to go into the Maintenance Treatment Phase or who are not eligible for any study cohort, will undergo a Study Treatment Discontinuation Visit 30 days after the last dose of study medication. These patients will then enter the Post-Treatment Follow-up Phase. All patients need to be evaluated for potential resection of metastasis at completion of the induction period. This is of particular importance for patients with liver metastases. If the patient is found to be

resectable they will undergo a Study Treatment Discontinuation Visit within 30 days after the last dose of study treatment and will then enter the Post-treatment Follow-up Phase.

c. Patients in the Post-Treatment Follow-up Phase will be followed up every 3 months during which time subsequent anti-cancer therapies will be recorded and survival assessed until the end of the study. Treatment during the Post-Treatment Follow-up Phase is at the Investigator's discretion; $BRAF^{mut}$ patients experiencing early disease progression during the Induction Treatment Phase will have the option of proceeding immediately to receive second-line treatment with 5-FU/LV, cetuximab and vemurafenib. Patients who discontinue study treatment prior to disease progression will also continue to be followed for PFS, with disease status followed according to local practice until progression or the end of the study, whichever comes first.

d. Written informed consent for participation in the study must be obtained before performing any study-specific screening tests or evaluations. However, results from routine assessments conducted prior to informed consent signature may be used as screening assessments as long as they were done within 7 days prior to informed consent signature.

e. The "All Cohort" eligibility criteria are evaluated prior to initiating the first cycle of study treatment during the Induction Treatment Phase.

f. Medical history includes clinically significant diseases, surgeries, cancer history (including prior cancer therapies and procedures), reproductive status, smoking history, use of alcohol and drugs of abuse, and all medications (e.g., prescription drugs, over-the-counter drugs, herbal or homeopathic remedies, nutritional supplements) used by the patient within 7 days prior to the Screening visit. Demographic data will include age, sex, and self-reported race/ethnicity (where permitted by federal regulations).

g. Vital signs include measurements of systolic and diastolic blood pressure while the patient is in a seated position, and temperature. During Screening, weight only required ≤ 7 days.

h. Baseline assessment requires a complete physical exam. A complete physical examination should include an evaluation of the head, eyes, ears, nose, and throat, and the cardiovascular, dermatological, musculoskeletal, respiratory, gastrointestinal, genitourinary, and neurological systems. Abnormalities identified at Screening / Baseline will be recorded as baseline conditions. At subsequent visits (or as clinically indicated), limited, symptom-directed physical examinations should be performed. Changes from Baseline, with new or worsened clinically significant abnormalities, should be reported as AEs if appropriate.

i. ECOG status assessed within 7 days prior to Day 1 of Cycle 1 (Induction Treatment Phase) for eligibility determination. See Appendix 5.

j. Concomitant medication includes any prescription medications or over-the-counter preparations used by a patient between the 7 days prior to the date of informed consent up until the date of study discontinuation. Only concomitant medications used for supportive care, to alleviate symptoms of mCRC, or to treat adverse drug reactions should be recorded on the Concomitant Medications eCRF. At subsequent visits, only changes to current medications or medications used since the last documentation of medications will be recorded. Concomitant medications for treatment of AEs related to study medication will continue to be recorded while the AE is being followed. For permitted and prohibited concomitant medications, see Section 4.4.

k. Haematology includes haemoglobin, haematocrit, platelet count, red blood cell count, white blood cell count, and differential. Blood chemistry includes ALT, AST, alkaline phosphatase, total bilirubin, total protein, albumin, blood urea nitrogen or urea, LDH, creatinine, glucose, calcium, phosphorus, sodium, potassium, chloride, and bicarbonate. Hematology and blood chemistry tests must be conducted prior to each treatment cycle, with the results available for review prior to start of treatment according to local standards for treatment management. However, only tests conducted every second treatment cycle will be recorded in the eCRF. Clinical laboratory results constituting a clinical significant AE should be recorded as such.

l. INR and aPTT only for patients receiving anticoagulants while on protocol-specified treatment.

m. Urinalysis must be performed by dipstick at Baseline and within 48 hours prior to every cycle. A 24-hour urine collection is needed in the event of proteinuria ≥ ± 2 by dipstick test.

n. Urine or blood pregnancy test, only for women of childbearing potential, including those who have had a tubal ligation. A serum pregnancy test is required within 7 days prior to start of study induction treatment, or within 14 days with a confirmatory urine pregnancy test within 7 days prior start of study induction treatment

o. Will include radiology, chest and abdominal CT or MRI, and other scans to document all sites of disease. Include upper abdomen at Baseline. Subsequent tumour assessments will be done according to standard of care at each study centre, with the exception that all patients must have a tumour assessment at the end of the Induction Treatment Phase. Tumour assessments are not required for study purposes after disease progression has been documented. Patients who discontinue study treatment during the Induction Treatment Phase prior to disease progression will also continue to be followed for progressive disease, with disease status followed according to local practice until progression or the end of the study, whichever comes first.

p. Archival tumour tissue (FFPET) block from the primary tumour obtained at the time of the initial diagnosis. Prior to performing any screening procedures, the Investigator must ensure that adequate archival tissue from a potential participant's primary tumour is available for shipping to the Sponsor's designated laboratory during the Screening Phase. If the tumour block is not available, ≥ 20 slides cut within 2 weeks of shipping to the Sponsor's designated laboratory will be accepted as an alternative. The sample must be shipped to the designated laboratory with the corresponding pathology report during the patient's Screening Phase. See Appendix 12.

q. The core biopsy of metastatic tumour at baseline is optional for all patients. It can be obtained either as part of routine care within 2 months before ICF signature or as part of study procedures after ICF signature within the Screening Phase. For patients in the Supplemental Biomarker Program (See Appendix 13), core biopsies of metastasis are also required at time of disease progression.

r. Whole blood and plasma samples will be collected from all study patients for exploratory biomarker analyses unless genomic analysis is not allowed per local regulations. In such instances, only plasma samples will be collected. All samples will be sent to a designated laboratory. Samples during treatment should be taken within 48 hours prior to study treatment Day 1 of each cycle indicated, unless otherwise specified (see Appendix 12 and Laboratory Manual).

s. After the signing of the informed consent form, and prior to Day 1 of Cycle 1 (Induction Treatment Phase), any SAEs thought to be related to a protocol-mandated intervention should be reported. Adverse events will be documented at every cycle during treatment. All patients will be followed for new AEs for 28 days following the discontinuation of study treatment. At the time of treatment discontinuation, any ongoing AE/SAE will be followed until the event resolves, the Investigator assesses the event as stable, the patient is lost to follow-up, dies or withdraws consent. Death related to disease progression is not considered to be an SAE. The Sponsor should be notified if the Investigator becomes aware of any SAE or AEs of special interest occurring after the end of the adverse event reporting period, regardless of causality.

t. 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-FU, 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.

Appendix 3: Schedule of Assessments During Maintenance Phase (Cohort 2)

	Prior to randomization	Maintenance Treatment Phase [a]	Study Treatment Discontinuation Visit [b]	Post-Treatment Follow-Up Phase [c]
	Within 3 weeks of completing Induction Treatment Phase	Every 2 cycles (every 4 weeks)	(≤ 30 days after last dose of study treatment)	Every 3 months
Assignment of cohort [d]	x			
Confirmation of cohort-specific eligibility [e]	x			
Randomisation [f]	x			
Vital signs and weight [g]		x	x	
Physical examination [h]		x	x	
ECOG performance status [i]		x	x	
Concomitant medications [j]		x	x	
Haematology and blood chemistry [k]		x	x	
INR, aPTT (select patients) [l]		According to local standard of care		
Urinalysis (dipstick) [m]		x	x	
Pregnancy test [n]		As applicable		
TSH, free T3, free T4 *(Experimental Arm only)*		Prior to Cycle 1 then every 3 cycles	X	

	Prior to randomization	Maintenance Treatment Phase [a]	Study Treatment Discontinuation Visit [b]	Post-Treatment Follow-Up Phase [c]
	Within 3 weeks of completing Induction Treatment Phase	Every 2 cycles (every 4 weeks)	(≤ 30 days after last dose of study treatment)	Every 3 months
Pulse oximetry *(Experimental Arm only)*		Prior to Cycle 1 then every 2 cycles	X	
Tuberculosis test [o]	x			
HIV, HBV, HCV serology [p]	X			
Tumour assessments [q]		According to local standard of care. Mandatory at Month 2 for First 27 patients in experimental arm of each cohort		According to local standard of care (in applicable patients only)`
Metastatic tumour tissue for exploratory biomarker assessment [r]	*Supplemental Biomarker Program only:* After completion of Induction, but prior to start of Maintenance	*Supplemental Biomarker Program only:* At time of PD		
Plasma samples [s]		Cycles 1 and 2 then every 2 cycles thereafter And at time of PD		At time of progression (if patient has not yet progressed)
Adverse events (including SAEs) [t]		Every cycle	x	x (as applicable)

	Prior to randomization	Maintenance Treatment Phase [a]	Study Treatment Discontinuation Visit [b]	Post-Treatment Follow-Up Phase [c]
	Within 3 weeks of completing Induction Treatment Phase	Every 2 cycles (every 4 weeks)	(≤ 30 days after last dose of study treatment)	Every 3 months
Study medication administration [u]		x		
Subsequent anti-cancer therapies (see [c])				x
Patient survival (see [c])			x	x

a. With the exception of Cycle 1, all other study visits and assessments during the Treatment Phase should be performed within ± 7 days of the scheduled date.

b. Patients who experience PD at any time during the Maintenance Treatment Phase, or who need to permanently discontinue study medication for any reason, will undergo a Study Treatment Discontinuation Visit 30 days after the last dose of study medication. These patients will then enter the Post-Treatment Follow-up.

c. After discontinuation of study treatment, patients will enter the Post-Treatment Follow-up Phase and will be followed up every 3 months during which time subsequent anti-cancer therapies will be recorded and survival assessed until the end of the study. Treatment during the Post-Treatment Follow-up Phase is at the Investigator's discretion, however, patients treated with atezolizumab should not receive other immunomodulatory agents for 10 weeks after study treatment discontinuation. Patients who discontinue study treatment prior to disease progression will also continue to be followed for PFS, with disease status followed according to local practice until progression or the end of the study, whichever comes first.

d. Patients completing the Induction Treatment Phase, and who have not experienced PD can then proceed to the Maintenance Treatment Phase. Depending on the patient's biomarker status (based on the archival sample from initial diagnosis), these patients will be assigned to Cohort 1 – $BRAF^{mut}$ or Cohort 2 – No Biomarker. Patients with an unknown biomarker status due to lack of determinant result (e.g. due to technical issues) can still be included in the study and will be assigned to Cohort 2 – No Biomarker.

e. The cohort-specific exclusion criteria must be assessed prior to randomization to study maintenance treatment but assessment of cohort-specific eligibility can only be completed after the biomarker analysis results from the patient's archival tumour tissue from initial diagnosis are

known. Patients found ineligible for any cohort will undergo a Study Treatment Discontinuation Visit and enter the Post-Treatment Follow-up Phase.

f. Each cohort will consist of an experimental treatment arm and a control arm. Randomised on a 2:1 (experimental:control) basis to either the experimental treatment arm or the control arm of that cohort. See Section 4.2.

g. Vital signs include measurements of systolic and diastolic blood pressure while the patient is in a seated position, and temperature. For the first infusion, the patient's vital signs (heart rate, respiratory rate, blood pressures, and temperature) should be determined within 60 minutes before the infusion, every 15 ± 5 minutes during the infusion, and 30 ± 10 minutes after the infusion. For subsequent infusions, vital signs will be collected within 60 minutes before the infusion and should be collected during or after the infusion if clinically indicated or if symptoms occurred in the prior infusion.

h. Physical examinations will be symptom-directed, and will include changes from Baseline (pre-Induction) with new or worsened clinically significant abnormalities being reported as AEs if appropriate.

i. See Appendix 5.

j. Concomitant medication includes any prescription medications or over-the-counter preparations used by a patient between the 7 days prior to the date of informed consent up until the Study Treatment Discontinuation visit. Only concomitant medications used for supportive care, to alleviate symptoms of mCRC, or to treat adverse drug reactions should be recorded on the Concomitant Medications eCRF. At subsequent visits, only changes to current medications or medications used since the last documentation of medications will be recorded. Concomitant medications for treatment of AEs related to study medication will continue to be recorded while the AE is being followed. For permitted and prohibited concomitant medications, see Section 4.4.

k. Haematology includes haemoglobin, haematocrit, platelet count, red blood cell count, white blood cell count, and differential. Blood chemistry includes ALT, AST, alkaline phosphatase, total bilirubin, total protein, albumin, blood urea nitrogen or urea, LDH, creatinine, glucose, calcium, phosphorus, sodium, potassium, chloride, and bicarbonate. Hematology and blood chemistry tests must be conducted prior to each treatment cycle, with the results available for review prior to start of treatment according to local standards for treatment management. However, only tests conducted every second treatment cycle will be recorded in the eCRF. Clinical laboratory results constituting a clinical significant AE should be recorded as such.

l. INR and aPTT only for patients receiving anticoagulants while on protocol-specified treatment.

m. Urinalysis must be performed by dipstick within 48 hours prior to every cycle. A 24-hour urine collection is needed in the event of proteinuria ≥ ± 2 by dipstick test.

n. Urine or blood pregnancy test, only for women of childbearing potential, including those who have had a tubal ligation. If urine pregnancy test is positive, it must be confirmed by a serum pregnancy test.

o. Patients with a positive tuberculosis test are not eligible for Cohort 2 and will be excluded from entering the Maintenance Phase of the study.

p. HIV testing performed in accordance with national and/or institutional guidelines. HBV serology includes HBsAg and anti-HBc. HCV serology includes anti-HCV.

q. Tumour assessments according to RECIST1.1 for Cohort 2 – No Biomarker, and additionally according to mRECIST for the experimental arm of Cohort 2 – No Biomarker. Will include radiology, chest and abdominal CT or MRI, and other scans to document all sites of disease. Tumour assessments will be done according to standard of care at each study centre, with the exception that the first 27 patients in the experimental arm of each cohort must have a tumour assessment at Month 2 of the Maintenance Treatment Phase so that the initial response of each cohort can be evaluated. Tumour assessments are not required for study purposes after disease progression has been documented. Patients who discontinue study treatment during either the Induction or Maintenance Treatment Phases prior to disease progression will also continue to be followed for progressive disease, with disease status followed according to local practice until progression or the end of the study, whichever comes first.

r. For patients in the Supplemental Biomarker Program, core biopsies of metastasis are required upon completion of induction treatment prior to initiation of maintenance treatment, and at time of disease progression (see Appendix 13).

s. Plasma samples will be collected from all patients for exploratory biomarker analyses. These samples will be sent to a designated laboratory. Samples during treatment should be taken within 48 hours prior to study treatment Day 1 of each cycle indicated, unless otherwise specified (see Appendix 12 and the Laboratory Manual).

t. Adverse events will be documented at every cycle during treatment. All patients will be followed for new AEs for 28 days following the discontinuation of study treatment. At the time of treatment discontinuation, any ongoing AE/SAE will be followed until the event resolves, the Investigator assesses the event as stable, the patient is lost to follow-up, dies or withdraws consent. Death related to disease progression is not considered to be an SAE. The Sponsor should be notified if the Investigator becomes aware of any SAE or AEs of special interest occurring after the end of the adverse event reporting period, regardless of causality.

u. Patients in the Experimental Arm will receive 5-FU or capecitabine 1,600 – 2,400 mg/m2 5-FU administered via 46-hour IV infusion and LV 400 mg/m2 administered via a 2-hour infusion given day 1 every 2 weeks; or 1000 mg/m2 b.i.d. capecitabine given days 1-14 every 2 weeks followed by a one-week treatment break. Atezolizumab at a fixed dose of 800 mg administered via 60-minute IV infusion on Day 1 of every 2-week cycle (if initial infusion is well tolerated, subsequent infusions will be done over a 30-minute time period) and bevacizumab 5 mg/kg via 15-30 minute IV infusion on Day 1 of every 2-week cycle. Patients in the Control arm will receive: 5-FU or capecitabine, dose and schedule will be according to local label, where applicable, or otherwise will be determined per the Investigator's discretion, with bevacizumab 5 mg/kg via 15-30 minute IV infusion on Day 1 of every 2-week cycle.

Appendix 4: SAS code

The following SAS code will be used to obtain the log-rank p-value from the unstratified log-rank test mentioned in section 4.11.1:

```
PROC LIFETEST data=dataset METHOD=KM CONFTYPE=LOGLOG;
TIME pfstime*censor(1);
STRATA treat / test=logrank;
RUN;
* pfstime represents variable containing event/censor times;
* censor represents censoring variable (1=censored, 0=event);
* treat represents treatment group variable;
Further options to control the output may be added.
```

The following SAS code will be used for the logistic regression mentioned in section 4.11.2.2:

```
PROC LOGISTIC DATA= dataset;
CLASS treat (ref='FP+Bev')strate1 strate2 strate3 strate4/ param=ref;
MODEL response (event='1') = treat strate1 strate2 / alpha=0.05;
RUN;
* response represents the response variable;
* treat represents the treatment group;
* strate1, strate2, strate3, strate4 represents the categorical covariates
related to stratification factors as per clinical data based for region and
as per eCRF data for tumor response;
Further options to control the output may be added.
```

The following SAS code will be used to obtain the hazard ratio and corresponding confidence interval from the Cox Model with treatment as single covariate mentioned in section 4.11.40:

```
PROC PHREG data=dataset;
CLASS treat;
MODEL pfstime*censor(1)=treat /RL TIES=EXACT;
RUN;
* pfstime represents variable containing event/censor times;
* censor represents censoring variable (1=censored, 0=event);
* treat represents treatment group variable;
Further options to control the output may be added.
```

The following SAS code will be used to obtain the hazard ratio and corresponding confidence interval from the adjusted Cox Model mentioned in section 4.11.4:

```
PROC PHREG data=dataset;
CLASS treat strate1 strate2 strate3 strate4;
MODEL pfstime*censor(1)=treat stratum1 stratum2 stratum3 stratum4 /RL
TIES=EXACT;
RUN;
* pfstime represents variable containing event/censor times;
* censor represents censoring variable (1=censored, 0=event);
* treat represents treatment group variable;
* strate1, strate2, strate3, strate4 represents the categorical covariates
related to stratification factors;
Further options to control the output may be added.
```

The following SAS code will be used for the logistic regression with treatment as single covariate mentioned in section 4.11.4:

```
PROC LOGISTIC DATA= dataset;
CLASS treat (ref='FP+Bev') / param=ref;
MODEL response (event='1') = treat / alpha=0.05;
RUN;
* response represents the response variable;
* treat represents the treatment group;
Further options to control the output may be added.
```

Appendix 5 : List of Outputs

1. LIST OF OUTPUTS: TABLES

Table Number	Table Title	Phase	Population	Primary analysis	Final Analysis
	Patient Disposition				
14.1.1.1	Patient Disposition For Induction Treatment Phase	ITP	ALL	X	
14.1.1.2	Patient Disposition For Maintenance Treatment Phase	MTP	MTP	X	X
14.1.2.1	Major Protocol Deviations For Induction Treatment Phase	ITP	ITP	X	
14.1.2.2	Major Protocol Deviations For Maintenance Treatment Phase	MTP	MTP	X	X
	Demographics and Baseline Characteristics				
14.1.3.1	Summary of Baseline and Demographic Characteristics	ITP	ITP	X	
14.1.3.2	Summary of Baseline and Demographic Characteristics	MTP	MTP	X	
14.1.3.3	Summary of Baseline Biomarker Status	MTP	MTP	X	
14.1.4.1	Tumor Response Status (RECIST 1.1) at end of induction (eCRF data)	ITP	ITP	X	
14.1.5	Randomization by Country and Study Center	MTP	MTP		
14.1.6	Stratification Factors as per IxRS	MTP	MTP		
14.1.7.1	Tumor Response Status (RECIST 1.1) at end of induction (eCRF data)	MTP	MTP	X	
14.1.7.2	Tumor response (RECIST 1.1) at end of induction as per IxRS versus eCRF data	MTP	MTP	X	
14.1.8.1	Summary of colorectal cancer history	ITP	ITP	X	
14.1.8.2	Summary of colorectal cancer history	ITP	MTP	X	
14.1.9	RECIST Tumor-Specific Characteristics at Baseline	MTP	MTP	X	
14.1.10.1	Medical History	ITP	ITP	X	
14.1.10.2	Medical History	ITP	MTP	X	
14.1.11.1	Summary of Prior Anti-Cancer Treatments/Procedures	ITP	ITP	X	
14.1.11.2	Summary of Prior Anti-Cancer Treatments/Procedures	ITP	MTP	X	
14.1.12	Prior Medications	ITP	ITP	X	
14.1.13.1	Concomitant Medications during the induction phase	ITP	ITP	X	
14.1.13.2	Concomitant Medications during the Maintenance phase	MTP	SAF	X	X

Table Number	Table Title	Phase	Population	Primary analysis	Final Analysis
14.1.14.1	Concomitant Radiotherapy during the Induction phase	ITP	ITP	X	
14.1.14.2	Concomitant Radiotherapy during the Maintenance phase	MTP	SAF	X	X
14.1.15.1	Concomitant colorectal cancer surgery during the Induction phase	ITP	ITP	X	
14.1.15.2	Concomitant colorectal cancer surgery during the Maintenance phase	MTP	SAF	X	X
	Exposure				
14.1.16.1	Summary of Total Number of Cycles Initiated during ITP	ITP	ITP	X	
14.1.16.2	Summary of drug exposure during ITP	ITP	ITP	X	
14.1.17.1	Summary of overall Duration of Treatment and Number of cycles Initiated during MTP	MTP	SAF	X	X
14.1.17.2	Summary of drug exposure during MTP	MTP	SAF	X	X
14.1.17.3	Summary of Cycles delayed during MTP	MTP	SAF	X	X
14.1.17.4	Summary of cycles delayed (at the cycle level) during MTP	MTP	SAF	X	X
	Efficacy				
14.2.1.1	Summary of Progression Free Survival – Primary Analysis (Surgery Censored)	MTP	MTP	X	X
14.2.1.2	Progression Free Survival: Hazard Ratio	MTP	MTP	X	X
14.2.1.3.1	Summary of Progression Free Survival by Region	MTP	MTP	X	X
14.2.1.3.2	Summary of Progression Free Survival by Tumor Response at end of ITP (based on eCRF data)	MTP	MTP	X	X
14.2.1.3.3	Summary of Progression Free Survival by Tumor Colon Location	MTP	MTP	X	X
14.2.1.3.4	Summary of Progression Free Survival by RAS Status	MTP	MTP	X	X
14.2.1.3.5	Summary of Progression Free Survival by Microsatellite Stability Status	MTP	MTP	X	X
14.2.1.3.6	Summary of Progression Free Survival by RAS Status for MSS patients	MTP	MTP	X	X
14.2.1.3.7	Summary of Progression Free Survival by Tumor Colon Location for RAS wt patients	MTP	MTP	X	X
14.2.1.3.8	Summary of Progression Free Survival by Tumor Colon Location for RAS mt patients	MTP	MTP	X	X
14.2.1.3.9	Summary of Progression Free Survival by Tumor Colon Location for MSS patients	MTP	MTP	X	X
14.2.2.1	Summary of Progression Free Survival - Sensitivity Analyses (Surgery not Censored)	MTP	MTP	X	X
14.2.2.2	Progression Free Survival: Hazard Ratio - Sensitivity Analyses (Surgery not Censored)	MTP	MTP	X	X
14.2.3.1	Summary of Progression Free Survival On-Treatment - Sensitivity Analyses	MTP	MTP	X	X

Table Number	Table Title	Phase	Population	Primary analysis	Final Analysis
14.2.3.2	Progression Free Survival On-Treatment: Hazard Ratio - Sensitivity Analyses	MTP	MTP	X	X
14.2.4.1	Summary of PFS Considering the First 259 Events - Sensitivity Analyses	MTP	MTP	X	X
14.2.4.2	PFS: Hazard Ratio Considering the First 259 Events - Sensitivity Analyses	MTP	MTP	X	X
14.2.5.1	Summary of PFS Considering the First 405 Patients - Sensitivity Analyses	MTP	MTP	X	X
14.2.5.2	PFS: Hazard Ratio Considering the First 405 Patients - Sensitivity Analyses	MTP	MTP	X	X
14.2.6	Summary of Progression Free Survival according to mRECIST	MTP	MTP	X	X
14.2.7.1	Summary of Overall Survival	MTP	MTP	X	X
14.2.7.2	Overall Survival: Hazard Ratio	MTP	MTP	X	X
14.2.7.3.1	Summary of Overall Survival by Region	MTP	MTP	X	X
14.2.7.3.2	Summary of Overall Survival by Tumor Response at end of ITP (based on eCRF data)	MTP	MTP	X	X
14.2.7.3.3	Summary of Overall Survival by Tumor Colon Location	MTP	MTP	X	X
14.2.7.3.4	Summary of Overall Survival by RAS Status	MTP	MTP	X	X
14.2.7.3.5	Summary of Overall Survival by Microsatellite Stability Status	MTP	MTP	X	X
14.2.7.3.6	Summary of Overall Survival by RAS Status for MSS patients	MTP	MTP	X	X
14.2.7.3.7	Summary of Overall Survival by Tumor Colon Location for RAS wt patients	MTP	MTP	X	X
14.2.7.3.8	Summary of Overall Survival by Tumor Colon Location for RAS mt patients	MTP	MTP	X	X
14.2.7.3.9	Summary of Overall Survival by Tumor Colon Location for MSS patients	MTP	MTP	X	X
14.2.8.1	Summary of Overall Response Rate (main definition)	MTP	MTP	X	X
14.2.8.2.1	Summary of Overall Response Rate (main definition) by Region	MTP	MTP	X	X
14.2.8.2.2	Summary of Overall Response Rate (main definition) by Tumor Response at end of ITP (based on eCRF data)	MTP	MTP	X	X
14.2.8.2.3	Summary of Overall Response Rate (main definition) by Tumor Colon Location	MTP	MTP	X	X
14.2.8.2.4	Summary of Overall Response Rate (main definition) by RAS Status	MTP	MTP	X	X
14.2.8.2.5	Summary of Overall Response Rate (main definition) by Microsatellite Stability Status	MTP	MTP	X	X
14.2.8.2.6	Summary of Overall Response Rate (main definition) by RAS Status for MSS patients	MTP	MTP	X	X
14.2.8.2.7	Summary of Overall Response Rate (main definition) by Tumor Colon Location for RAS wt patients	MTP	MTP	X	X

Table Number	Table Title	Phase	Population	Primary analysis	Final Analysis
14.2.8.2.8	Summary of Overall Response Rate (main definition) by Tumor Colon Location for RAS mt patients	MTP	MTP	X	X
14.2.8.2.9	Summary of Overall Response Rate (main definition) by Tumor Colon Location for MSS patients	MTP	MTP	X	X
14.2.8.2.10	Summary of Overall Response Rate (main definition) by ECOG performance status (0 vs 1/2)	MTP	MTP	X	X
14.2.8.2.11	Summary of Overall Response Rate (main definition) by Initial AJCC/UICC stage (stage III, stage IV)	MTP	MTP	X	X
14.2.8.2.12	Summary of Overall Response Rate (main definition) by age category In years (<65, >=65)	MTP	MTP	X	X
14.2.8.2.13	Summary of Overall Response Rate (main definition) by liver as metastatic site (yes, no)	MTP	MTP	X	X
14.2.8.2.14	Summary of Overall Response Rate (main definition) by number of metastatic sites at screening (<2, >=2)	MTP	MTP	X	X
14.2.8.2.15	Summary of Overall Response Rate (main definition) by gender	MTP	MTP	X	X
14.2.8.2.16	Summary of Overall Response Rate (main definition) by cancer type (colon, rectal)	MTP	MTP	X	X
14.2.8.2.17	Summary of Overall Response Rate (main definition) by initial diagnosis (synchronous vs metachronous)	MTP	MTP	X	X
14.2.8.3	Summary of Overall Response Rate (secondary definition)	MTP	MTP	X	X
14.2.8.4.1	Summary of Overall Response Rate (secondary definition) by Region	MTP	MTP	X	X
14.2.8.4.2	Summary of Overall Response Rate (secondary definition) by Tumor Response at end of ITP (based on eCRF data)	MTP	MTP	X	X
14.2.8.4.3	Summary of Overall Response Rate (secondary definition) within right or left colon	MTP	MTP	X	X
14.2.8.4.4	Summary of Overall Response Rate (secondary definition) by RAS mutation status	MTP	MTP	X	X
14.2.8.4.5	Summary of Overall Response Rate (secondary definition) by MSI-H or MSS status	MTP	MTP	X	X
14.2.8.4.6	Summary of Overall Response Rate (secondary definition) by RAS mutation status for MSS patients	MTP	MTP	X	X
14.2.8.4.7	Summary of Overall Response Rate (secondary definition) within right or left colon for RAS wt patients	MTP	MTP	X	X
14.2.8.4.8	Summary of Overall Response Rate (secondary definition) within right or left colon for RAS mt patients	MTP	MTP	X	X
14.2.8.4.9	Summary of Overall Response Rate (secondary definition) within right or left colon for MSS	MTP	MTP	X	X

Table Number	Table Title	Phase	Population	Primary analysis	Final Analysis
	patients				
14.2.8.4.10	Summary of Overall Response Rate (secondary definition) by ECOG performance status (0 vs 1/2)	MTP	MTP	X	X
14.2.8.4.11	Summary of Overall Response Rate (secondary definition) by Initial AJCC/UICC stage (stage III, stage IV)	MTP	MTP	X	X
14.2.8.4.12	Summary of Overall Response Rate (secondary definition) by age category In years (<65, >=65)	MTP	MTP	X	X
14.2.8.4.13	Summary of Overall Response Rate (secondary definition) by liver as metastatic site (yes, no)	MTP	MTP	X	X
14.2.8.4.14	Summary of Overall Response Rate (secondary definition) by number of metastatic sites at screening (<2, >=2)	MTP	MTP	X	X
14.2.8.4.15	Summary of Overall Response Rate (secondary definition) by gender	MTP	MTP	X	X
14.2.8.4.16	Summary of Overall Response Rate (secondary definition) by cancer type (colon, rectal)	MTP	MTP	X	X
14.2.8.4.17	Summary of Overall Response Rate (secondary definition) by initial diagnosis (synchronous vs metachronous)	MTP	MTP	X	X
14.2.8.5	Overall Response Rate (ORR): Odds Ratio	MTP	MTP	X	X
14.2.9.1	Summary of Disease Control Rate (main definition)	MTP	MTP	X	X
14.2.9.2	Summary of Disease Control Rate (secondary definition)	MTP	MTP	X	X
14.2.9.3	Disease Control Rate (DCR): Odds Ratio	MTP	MTP	X	X
14.2.10.1	Summary of Duration of Response and Time to Response (main definition)	MTP	MTP	X	X
14.2.10.2	Summary of Duration of Response and Time to Response (secondary definition)	MTP	MTP	X	X
14.2.11.1	Summary of Progression Free Survival 2	MTP	MTP	X	X
14.2.11.2	Progression Free Survival 2: Hazard Ratio	MTP	MTP	X	X
14.2.12.1	Summary of ECOG Performance Status over time	MTP	MTP	X	X
14.2.12.2	Shift from baseline to ECOG Performance Status at end of MTP	MTP	MTP	X	X
	Adverse Events				
14.3.1.1.1	Treatment Emergent Adverse Events (TEAEs) during ITP: Overall Summary	ITP	ITP	X	
14.3.1.1.2	Treatment Emergent Adverse Events (TEAEs) during MTP: Overall Summary	MTP	SAF	X	X
14.3.1.1.3	Post Induction Treatment Adverse Events (AEs): Overall Summary	Post-	ITP who	X	

Table Number	Table Title	Phase	Population	Primary analysis	Final Analysis
		Treatment	completed study treatment discontinuation visit		
14.3.1.1.4	Post Maintenance Treatment Adverse Events (AEs): Overall Summary	Post-Treatment	SAF who completed study treatment discontinuation visit	X	X
14.3.1.2.1	Treatment Emergent Adverse Events by SOC and PT and by Worst Intensity during ITP	ITP	ITP	X	
14.3.1.2.2	Treatment Emergent Adverse Events by SOC and PT and by Worst Intensity during MTP	MTP	SAF	X	X
14.3.1.2.3	Treatment Emergent AESI by Categories, SOC, PT and by Worst Intensity during MTP	MTP	SAF	X	X
14.3.1.2.4	Serious Treatment Emergent AESI by Categories, SOC, PT and by Worst Intensity during MTP	MTP	SAF	X	X
14.3.1.3.1	Treatment Emergent Adverse Events Related to Any Study Drug by SOC and PT during ITP	ITP	ITP	X	
14.3.1.3.2	Treatment Emergent Adverse Events Related to FOLFOX by SOC and PT during ITP	ITP	ITP	X	
14.3.1.3.3	Treatment Emergent Adverse Events Related to 5-FU/LV by SOC and PT during ITP	ITP	ITP	X	
14.3.1.3.4	Treatment Emergent Adverse Events Related to bevacizumab by SOC and PT during ITP	ITP	ITP	X	
14.3.1.3.5	Treatment Emergent Adverse Events Related to Any Study Drug by SOC and PT during MTP	MTP	SAF	X	X
14.3.1.3.6	Treatment Emergent Adverse Events Related to 5-FU/LV by SOC and PT during MTP	MTP	SAF	X	X
14.3.1.3.7	Treatment Emergent Adverse Events Related to capecitabine by SOC and PT during MTP	MTP	SAF	X	X
14.3.1.3.8	Treatment Emergent Adverse Events Related to atezolizumab by SOC and PT during MTP	MTP	SAF	X	X
14.3.1.3.9	Treatment Emergent Adverse Events Related to bevacizumab by SOC and PT during MTP	MTP	SAF	X	X
14.3.1.4.1	Treatment Emergent Adverse Events Leading to Discontinuation of Any Study Drug by SOC and PT during ITP	ITP	ITP	X	
14.3.1.4.2	Treatment Emergent Adverse Events Leading to Discontinuation of FOLFOX by SOC and PT during ITP	ITP	ITP	X	
14.3.1.4.3	Treatment Emergent Adverse Events Leading to Discontinuation of 5-FU/LV by SOC and	ITP	ITP	X	

Table Number	Table Title	Phase	Population	Primary analysis	Final Analysis
	PT during ITP				
14.3.1.4.4	Treatment Emergent Adverse Events Leading to Discontinuation of bevacizumab by SOC and PT during ITP	ITP	ITP	X	
14.3.1.4.5	Treatment Emergent Adverse Events Leading to Discontinuation of Any Study Drug by SOC and PT during MTP	MTP	SAF	X	X
14.3.1.4.6	Treatment Emergent Adverse Events Leading to Discontinuation of fluorpyrimidines by SOC and PT during MTP	MTP	SAF	X	X
14.3.1.4.7	Treatment Emergent Adverse Events Leading to Discontinuation of atezolizumab by SOC and PT during MTP	MTP	SAF	X	X
14.3.1.4.8	Treatment Emergent Adverse Events Leading to Discontinuation of bevacizumab by SOC and PT during MTP	MTP	SAF	X	X
14.3.1.5.1	Treatment Emergent Adverse Events Leading to Dose Reduction or Interruption of Any Study Drug by SOC and PT during ITP	ITP	ITP	X	
14.3.1.5.2	Treatment Emergent Adverse Events Leading to Dose Reduction or Interruption of FOLFOX by SOC and PT during ITP	ITP	ITP	X	
14.3.1.5.3	Treatment Emergent Adverse Events Leading to Dose Reduction or Interruption of 5-FU/LV by SOC and PT during ITP	ITP	ITP	X	
14.3.1.5.4	Treatment Emergent Adverse Events Leading to Dose Reduction or Interruption of bevacizumab by SOC and PT during ITP	ITP	ITP	X	
14.3.1.5.5	Treatment Emergent Adverse Events Leading to Dose Reduction or Interruption of Any Study Drug by SOC and PT during MTP	MTP	SAF	X	X
14.3.1.5.6	Treatment Emergent Adverse Events Leading to Dose Reduction or Interruption of fluoropyrimidines by SOC and PT during MTP	MTP	SAF	X	X
14.3.1.5.7	Treatment Emergent Adverse Events Leading to Dose Reduction or Interruption of atezolizumab by SOC and PT and by Worst Intensity during MTP	MTP	SAF	X	X
14.3.1.5.8	Treatment Emergent Adverse Events Leading to Dose Reduction or Interruption of bevacizumab by SOC and PT and by Worst Intensity during MTP	MTP	SAF	X	X
14.3.1.6.1	Treatment Emergent Adverse Events of Grade 3 or More by SOC and PT during ITP	ITP	ITP	X	
14.3.1.6.2	Treatment Emergent Adverse Events of Grade 3 or More by SOC and PT during MTP	MTP	SAF	X	X

Table Number	Table Title	Phase	Population	Primary analysis	Final Analysis
14.3.1.7.1	Serious Treatment Emergent Adverse Events by SOC and PT during ITP	ITP	ITP	X	
14.3.1.7.2	Serious Treatment Emergent Adverse Events by SOC and PT during MTP	MTP	SAF	X	X
14.3.1.8.1	Serious Treatment Emergent Adverse Events Related to Any Study Drug by SOC and PT during ITP	ITP	ITP	X	
14.3.1.8.2	Serious Treatment Emergent Adverse Events Related to FOLFOX by SOC and PT during ITP	ITP	ITP	X	
14.3.1.8.3	Serious Treatment Emergent Adverse Events Related to 5-FU/LV by SOC and PT during ITP	ITP	ITP	X	
14.3.1.8.4	Serious Treatment Emergent Adverse Events Related to bevacizumab by SOC and PT during ITP	ITP	ITP	X	
14.3.1.8.5	Serious Treatment Emergent Adverse Events Related to Any Study Drug by SOC and PT during MTP	MTP	SAF	X	X
14.3.1.8.6	Serious Treatment Emergent Adverse Events Related to fluoropyrimidines by SOC and PT during MTP	MTP	SAF	X	X
14.3.1.8.7	Serious Treatment Emergent Adverse Events Related to FOLFOX by SOC and PT during MTP	MTP	SAF	X	X
14.3.1.8.8	Serious Treatment Emergent Adverse Events Related to atezolizumab by SOC and PT during MTP	MTP	SAF	X	X
14.3.1.8.9	Serious Treatment Emergent Adverse Events Related to bevacizumab by SOC and PT during MTP	MTP	SAF	X	X
14.3.1.9.1	Treatment Emergent Adverse Events with Fatal Outcome by SOC and PT during ITP	ITP	ITP	X	
14.3.1.9.2	Treatment Emergent Adverse Events with Fatal Outcome by SOC and PT during MTP	MTP	SAF	X	X
14.3.1.10	Treatment Emergent AESI based on eCRF Categories during MTP	MTP	SAF	X	X
14.3.1.11	Serious Treatment Emergent Adverse Events AESI based on eCRF Categories during MTP	MTP	SAF	X	X
	Deaths				
14.3.1.12.1	Deaths within 30 days from last day of treatment of ITP and Reason	ITP	ITP	X	

Table Number	Table Title	Phase	Population	Primary analysis	Final Analysis
14.3.1.12.2	Deaths within 30 days from last day of treatment of MTP and Reason	MTP	MTP	X	X
14.3.1.12.3	Deaths within 30 days from last day of treatment of MTP and Reason	MTP	SAF	X	X
14.3.1.12.4	Post Induction Treatment Deaths and Reason	Post-Treatment	ITP who completed study treatment discontinuation visit	X	
14.3.1.12.5	Post Maintenance Treatment Deaths and Reason	Post-Treatment	MTP who completed study treatment discontinuation visit	X	X
	Laboratory Parameters				
14.3.4.1.1	Shift table (baseline versus worst on-treatment) during ITP for CTC gradable Hematology parameters	ITP	ITP	X	
14.3.4.1.2	Shift table (baseline versus worst on-treatment) during MTP for CTC gradable Hematology parameters	MTP	SAF	X	X
14.3.4.2.1	Shift table (baseline versus worst on-treatment) during ITP for CTC gradable Blood Chemistry parameters	ITP	ITP	X	
14.3.4.2.2	Shift table (baseline versus worst on-treatment) during MTP for CTC gradable Blood Chemistry parameters	MTP	SAF	X	X
14.3.4.3.1	Shift table (baseline versus worst on-treatment) during ITP for CTC gradable Coagulation parameters	ITP	ITP	X	
14.3.4.3.2	Shift table (baseline versus worst on-treatment) during MTP for CTC gradable Coagulation parameters	MTP	SAF	X	X
14.3.4.4.1	Shift table (baseline versus worst on-treatment) during ITP for non CTC gradable Hematology parameters	ITP	ITP	X	
14.3.4.4.2	Shift table (baseline versus worst on-treatment) during MTP for non CTC gradable Hematology parameters	MTP	SAF	X	X
14.3.4.5.1	Shift table (baseline versus worst on-treatment) during ITP for non CTC gradable Blood	ITP	ITP	X	

Table Number	Table Title	Phase	Population	Primary analysis	Final Analysis
	Chemistry parameters				
14.3.4.5.2	Shift table (baseline versus worst on-treatment) during MTP for non CTC gradable Blood Chemistry parameters	MTP	SAF	X	X
14.3.4.6	Shift table (baseline versus worst on-treatment) during MTP for non CTC gradable Thyroid parameters	MTP	SAF	X	X
14.3.4.7.1	Shift table (baseline versus worst on-treatment) during ITP for Urinalysis Protein Dipstick	ITP	ITP	X	
14.3.4.7.2	Shift table (baseline versus worst on-treatment) during MTP for Urinalysis Protein Dipstick	MTP	SAF	X	X
	Other Safety Data				
14.3.5.1	Summary of vital signs Over Time during ITP	ITP	ITP	X	
14.3.5.2	Summary of vital signs Over Time during MTP	MTP	SAF	X	X
14.3.6	Summary of blood oxygen saturation Over Time during MTP	MTP	SAF	X	X

2. LIST OF OUTPUTS: FIGURES

Figure Number	Figure Title	Phase	Population	Primary analysis	Final Analysis
	Efficacy				
14.1.1	CONSORT flow Diagram for All Screened Patients	All	Screened	X	X
14.1.2	CONSORT flow Diagram for Patients Randomized in Cohort 2	MTP	MTP	X	X
14.2.1.1	Kaplan Meier Plot of Progression Free Survival - Primary Analysis (Surgery Censored)	MTP	MTP	X	X
14.2.1.2	Kaplan Meier Plot of Progression Free Survival - Sensitivity Analysis (Surgery not Censored)	MTP	MTP	X	X
14.2.1.3	Kaplan Meier Plot of Progression Free Survival On-Treatment - Sensitivity Analysis	MTP	MTP	X	X
14.2.1.4	Kaplan Meier Plot of PFS considering the first 259 events - Sensitivity Analysis	MTP	MTP	X	X
14.2.1.5	Kaplan Meier Plot of PFS considering the first 405 patients - Sensitivity Analysis	MTP	MTP	X	X
14.2.1.6	Kaplan Meier plot of PFS according to mRECIST - Experimental Group	MTP	MTP	X	X
14.2.1.7.1	Kaplan Meier Plot of Progression Free Survival by Region	MTP	MTP	X	X
14.2.1.7.2	Kaplan Meier Plot of Progression Free Survival by Tumor Response at end of ITP (based on eCRF data)	MTP	MTP	X	X

Figure Number	Figure Title	Phase	Population	Primary analysis	Final Analysis
14.2.1.7.3	Kaplan Meier Plot of Progression Free Survival by Tumor Colon Location	MTP	MTP	X	X
14.2.1.7.4	Kaplan Meier Plot of Progression Free Survival by RAS Status	MTP	MTP	X	X
14.2.1.7.5	Kaplan Meier Plot of Progression Free Survival by Microsatellite Stability Status	MTP	MTP	X	X
14.2.1.7.6	Kaplan Meier Plot of Progression Free Survival by RAS Status for MSS patients	MTP	MTP	X	X
14.2.1.7.7	Kaplan Meier Plot of Progression Free Survival by Tumor Colon Location for RAS wt patients	MTP	MTP	X	X
14.2.1.7.8	Kaplan Meier Plot of Progression Free Survival by Tumor Colon Location for RAS mt patients	MTP	MTP	X	X
14.2.1.7.9	Kaplan Meier Plot of Progression Free Survival by Tumor Colon Location for MSS patients	MTP	MTP	X	X
14.2.1.8	PFS: Proportional Hazard Assumption - Model Checking	MTP	MTP	X	
14.2.1.9.1	Forest Plot of Hazard Ratio for Progression Free Survival by baseline characteristics subgroup	MTP	MTP	X	X
14.2.1.9.2	Forest Plot of Hazard Ratio for Progression Free Survival by biomarker subgroup	MTP	MTP	X	X
14.2.1.10	Kaplan Meier Plot with Reverse Censoring	MTP	MTP	X	
14.2.2.1	Kaplan Meier Plot of Overall Survival	MTP	MTP	X	X
14.2.2.2.1	Kaplan Meier Plot of Overall Survival by Region	MTP	MTP	X	X
14.2.2.2.2	Kaplan Meier Plot of Overall Survival by Tumor Response at end of ITP (based on eCRF data)	MTP	MTP	X	X
14.2.2.2.3	Kaplan Meier Plot of Overall Survival by Tumor Colon Location	MTP	MTP	X	X
14.2.2.2.4	Kaplan Meier Plot of Overall Survival by RAS Status	MTP	MTP	X	X
14.2.2.2.5	Kaplan Meier Plot of Overall Survival by Microsatellite Stability Status	MTP	MTP	X	X
14.2.2.2.6	Kaplan Meier Plot of Overall Survival by RAS Status for MSS patients	MTP	MTP	X	X
14.2.2.2.7	Kaplan Meier Plot of Overall Survival by Tumor Colon Location for RAS wt patients	MTP	MTP	X	X
14.2.2.2.8	Kaplan Meier Plot of Overall Survival by Tumor Colon Location for RAS mt patients	MTP	MTP	X	X
14.2.2.2.9	Kaplan Meier Plot of Overall Survival by Tumor Colon Location for MSS patients	MTP	MTP	X	X
14.2.2.3.1	Forest plot of Hazard Ratio for Overall Survival by baseline characteristics subgroup	MTP	MTP	X	X
14.2.2.3.2	Forest plot of Hazard Ratio for Overall Survival by biomarker subgroup	MTP	MTP	X	X
14.2.3	Waterfall Plot of Best Percentage Change from Baseline in Sum of Diameter	MTP	MTP	X	
14.2.4.1	Forest Plot of Odds Ratio for Overall Response Rate by baseline characteristics subgroup	MTP	MTP	X	X
14.2.4.2	Forest Plot of Odds Ratio for Overall Response Rate by biomarker subgroup	MTP	MTP	X	X
14.2.5.1	Kaplan Meier Plot of Progression Free Survival 2	MTP	MTP	X	X

3. LIST OF OUTPUTS: LISTINGS

Listing Number	Listing Title	Phase	Population	Primary analysis	Final Analysis
16.2.1.1	Patient disposition and Study Termination Information	ITP	ITP	X	X
16.2.1.2	Patient who discontinue treatment due to Adverse Event	ITP	ITP	X	X
16.2.2	Major Protocol Deviations	ITP/MTP	ITP	X	X
16.2.3	Analysis Population	ITP/MTP	ITP	X	
	Demographics and Baseline Characteristics				
16.2.4.1	Demographics and Baseline Characteristics	ITP/MTP	ITP	X	
16.2.4.2	Serology Values	MTP	MTP	X	
16.2.4.3	Tuberculosis Test Values	MTP	MTP	X	
16.2.4.4	Baseline Biomarker Status	MTP	MTP	X	
16.2.4.5	Randomization Stratification Factors as per IxRS and eCRF	MTP	MTP	X	
16.2.4.6	Colorectal Cancer History	ITP	ITP	X	
16.2.4.7	Medical history	ITP	ITP	X	
16.2.4.8	Prior Anti-Cancer Therapy	ITP	ITP	X	
16.2.4.9	Cancer Radiotherapy: Prior and On-Study	ITP/MTP	ITP	X	X
16.2.4.10	Colorectal Cancer Surgery : Prior and On-Study	ITP/MTP	ITP	X	X
16.2.4.11	Prior and Concomitant medications	ITP/MTP	ITP	X	X
16.2.4.12	Subsequent anti-cancer therapies - Post-treatment Follow-up Phase	Post-Treatment	ITP	X	X
	Drug Administration				
16.2.5.1	Study Drug Administration for 5-FU	ITP/MTP	ITP	X	X
16.2.5.2	Study Drug Administration for Leucovorin	ITP/MTP	ITP	X	X
16.2.5.3	Study Drug Administration for Oxaliplatin during ITP	ITP	ITP	X	
16.2.5.4	Study Drug Administration for bevacizumab	ITP/MTP	ITP	X	X

Listing Number	Listing Title	Phase	Population	Primary analysis	Final Analysis
16.2.5.5	Drug exposure during ITP	ITP	ITP	X	
16.2.5.6	Study Drug Administration for capecitabine during MTP	MTP	SAF	X	X
16.2.5.7	Study Drug Administration for atezolizumab during MTP	MTP	SAF	X	X
16.2.5.8	Drug Exposure during MTP	MTP	SAF	X	X
	Efficacy				
16.2.6.1	Progression Free Survival – Primary Analysis (Surgery Censored)	MTP	MTP	X	X
16.2.6.2	Progression Free Survival – Sensitivity Analysis (Surgery not Censored)	MTP	MTP	X	X
16.2.6.3	Individual Tumor Assessment and Overall Response as per RECIST v1.1	ITP/MTP	ITP	X	X
16.2.6.4	Progression Free Survival On-Treatment	MTP	MTP	X	X
16.2.6.5	Progression Free Survival Considering the First 259 Events	MTP	MTP	X	X
16.2.6.6	Individual Tumor Assessment and Overall Response as per mRECIST– Experimental Group	ITP/MTP	MTP	X	X
16.2.6.7	PFS in treated patients with Atezolizumab according to mRECIST – Experimental Group	MTP	MTP	X	X
16.2.6.8	Best Overall Response, Time to Response and Duration of Response	MTP	MTP	X	X
16.2.6.9	Overall Survival	MTP	MTP	X	X
16.2.6.10	Progression Free Survival 2	MTP	MTP	X	X
16.2.6.11	ECOG performance status	ITP/MTP	ITP	X	X
	Safety				
16.2.7.1	Adverse Events	ITP/MTP/ Post-treatment	ITP	X	X
16.2.7.2	Grade 5 Adverse Events or any Adverse Events with fatal outcome	ITP/MTP/ Post-treatment	ITP	X	X
16.2.7.3	Adverse Events Leading to Treatment Discontinuation	ITP/MTP/ Post-treatment	ITP	X	X
16.2.7.4	Adverse events of Special Interest as reported on eCRF	MTP/ Post-treatment	MTP	X	X
16.2.7.5	Deaths	ITP/MTP/	ITP	X	X

Listing Number	Listing Title	Phase	Population	Primary analysis	Final Analysis
		Post-treatment			
16.2.8.1.	Laboratory Values	ITP/MTP	ITP	X	X
16.2.8.2	Laboratory Abnormalities	ITP/MTP	ITP	X	X
16.2.8.3	Urinalysis: Urine Protein Dipstick	ITP/MTP	ITP	X	X
16.2.8.4	Urinalysis: 24 Hour Urine Protein	ITP/MTP	ITP	X	X
16.2.8.5	Pregnancy Test	ITP/MTP	ITP	X	X
16.2.9	Vital Signs	ITP/MTP	ITP	X	X

STATISTICAL ANALYSIS PLAN

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

COHORT 3

PROTOCOL NUMBER: MO29112

COHORT 3 STUDY DRUGS: bevacizumab (RO4876646)
pertuzumab (RO4368451)
trastuzumab (RO0452317)

VERSION NUMBER: 1.0

IND NUMBER: N/A

EUDRACT NUMBER: 2014-001017-61

SPONSOR: F. Hoffmann-La Roche Ltd

PLAN PREPARED BY: [redacted], Cytel, Inc

DATE FINAL: 09th May 2019

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HISTORY CHANGE

Version	Date	Changes
Final 1.0		N/A

LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	adverse event
AESI	adverse events of special interest
BMI	body mass index
$BRAF^{mut}$	BRAF mutation
BSA	body surface area
CR	complete response
CSR	clinical study report
eCRF	electronic Case Report Form
EU	European Union
HER2	human epidermal growth factor receptor 2
HER2+	human epidermal growth factor receptor 2 positive
ICH	International Conference on Harmonization
iDMC	Independent Data Monitoring Committee
IHC	immunohistochemistry
ITP	Induction Treatment Phase
IxRS	interactive voice or web-based response system
mCRC	metastatic Colorectal Cancer
MedDRA	Medical Dictionary for Regulatory Activities
MSI-H	high microsatellite instability
MSS	microsatellite stable
MTP	Maintenance Treatment Phase
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NGS	next generation sequencing
PD	progressive disease
PFS	progression free survival
PR	partial response
SAP	statistical analysis plan
SC	Steering Committee
SD	stable disease
TEAE	treatment emergent adverse event

1. BACKGROUND

The study is a randomized, multi-center, active-controlled, open-label, parallel-group clinical study of biomarker-driven maintenance treatment for first-line metastatic colorectal cancer (mCRC) patients. All patients will receive induction treatment with FOLFOX and bevacizumab. Induction treatment will be followed by maintenance treatment with chemotherapy combined with targeted therapy within one of several maintenance treatment cohorts. Only those patients who experience disease response or disease control during induction and who are not assessed as resectable at completion of induction will proceed to further treatment in the Maintenance Treatment Phase (MTP) of the study. Patients will be assigned to a maintenance treatment cohort based on their primary tumour biomarker results. The primary study objective within each cohort is to evaluate progression-free survival (PFS).

Maintenance treatment cohorts may be added or modified over the course of the study. This SAP describes planned analyses of patients who were assigned, or would have been assigned, to maintenance treatment Cohort 3 based on their primary tumour biomarker profile. Given that only 5 patients were randomized into Cohort 3, only few listings will be provided. The corresponding SAP is therefore abbreviated.

Analyses of patients assigned to all other MODUL cohorts will be described in SAPs applicable to each specific cohort.

A Steering Committee (SC) is responsible for overseeing the general conduct of the study.

In addition, an independent Data Monitoring Committee (iDMC) is responsible for evaluating the safety of the patients participating in the trial at regular intervals throughout the study. The iDMC makes recommendations as to whether cohort recruitment should continue based on benefit-risk evaluations that include efficacy as well as safety data. To minimize the impact of such reviews on efficacy endpoint analyses, efficacy data included in these reviews has to be specified by the iDMC at a preceding iDMC meeting and has to be documented in the iDMC meeting minutes.

2. STUDY DESIGN

Patients continuing from the Induction Treatment Phase (ITP) to the Maintenance Treatment Phase are assigned to a maintenance treatment cohort based on their primary tumour biomarker status. Following eligibility assessment for their assigned cohort, eligible patients are randomized to the experimental or control arm within their cohort.

The study was initiated with 2 maintenance treatment cohorts, Cohorts 1 and 2. Two additional cohorts, Cohorts 3 and 4, were added with protocol amendment 5 (protocol version 6).

In this open-label study, all patients will receive 8 cycles induction treatment that is considered standard in many countries and that has been shown to improve outcomes in the first-line setting. Treatment during the ITP, 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

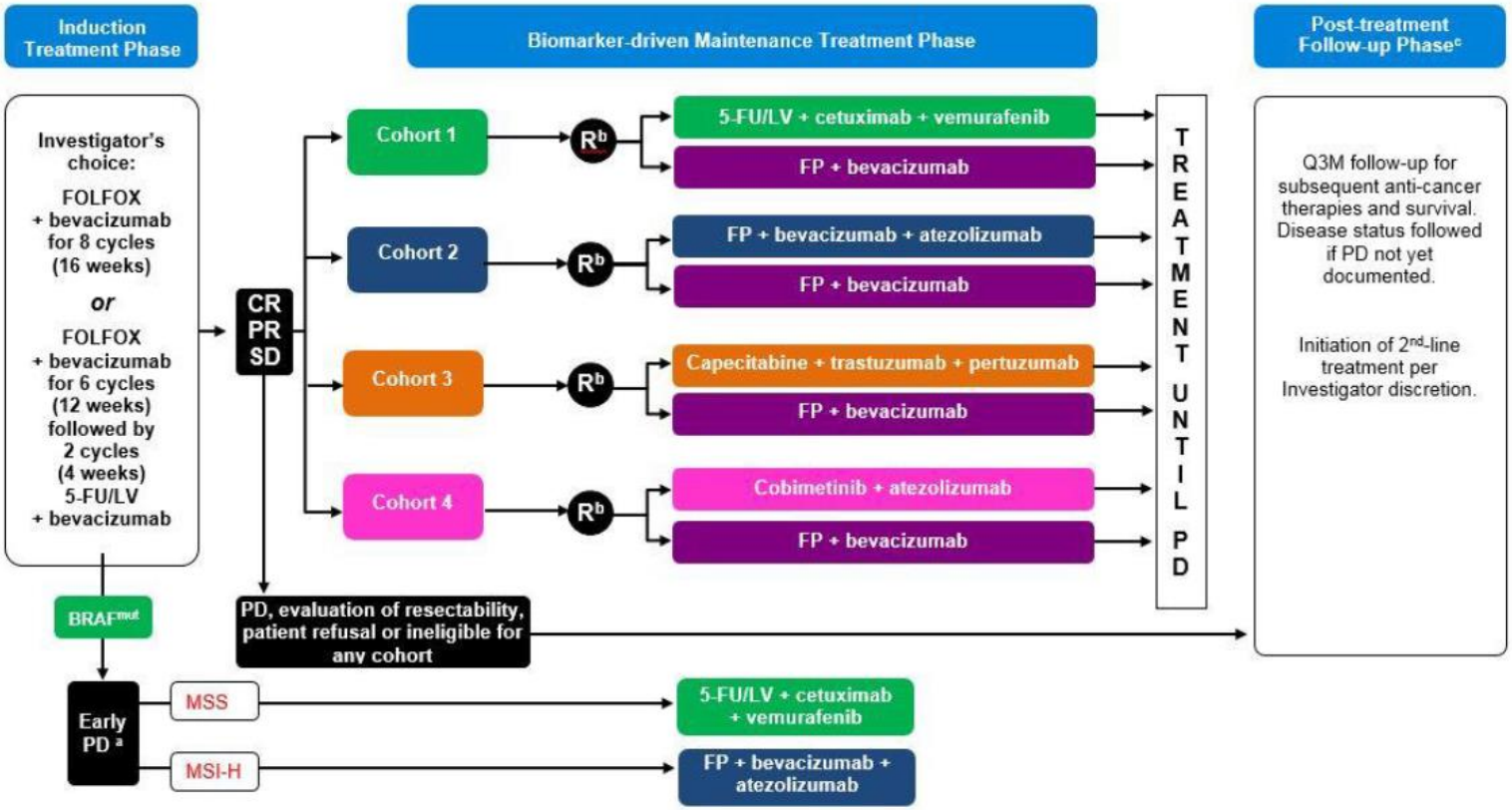
- Six 2-week cycles of FOLFOX in combination with bevacizumab, followed by two 2-week cycles of 5-FU/LV with bevacizumab

Patients who prematurely discontinue study treatment for any reason during the ITP, who experience progressive disease (PD) at any time during or at the end of the ITP, who are evaluated as resectable at the end of ITP, who refuse to proceed to the MTP or who are not eligible for any maintenance cohort will undergo a study treatment discontinuation visit and enter post-treatment follow-up. Patients who experience disease control or tumor response to induction treatment will continue to the randomized MTP of the study wherein the effects of experimental and control groups will be compared. Patients in screening after June 28, 2016, were assigned to Cohort 3 if their primary tumour was HER2+. (Of note: HER2+ is defined as 'Amplified (>=5CN)' as per FMI next generation sequencing (NGS). To be enrolled in Cohort 3, amplified samples should be tested by HER IHC and have IHC>=0. Otherwise, patients were to be checked for Cohort 4 eligibility). Treatment in each cohort is shown in Figure 1.

Table 1: Biomarker Profile by Cohort

	Biomarker profile	
	Patients in Screening Prior June 28, 2016	Patients in Screening After June 28, 2016
Cohort 1	$BRAF^{mut}$	$HER2\text{-}/MSS/BRAF^{mut}/RAS^{wt}$
Cohort 2	$BRAF^{wt}$ or biomarker status unknown	Closed to patients screened after June 3, 2016
Cohort 3	Not applicable	HER2+
Cohort 4	Not applicable	$HER2\text{-}/MSI\text{-}H$; $HER2\text{-}/MSS/BRAF^{wt}$; $HER2\text{-}/MSS/BRAF^{mut}/RAS^{mut}$

Figure 1: Study Design as of protocol version 6



FP = fluoropyrimidine (5-FU/LV or capecitabine); 5-FU/LV = 5-fluorouracil/leucovorin; MSI -H= high microsatellite instability; MSS = microsatellite stable

a. Patients who progress early and who are not $BRAF^{mut}$ will enter the Post-treatment Follow-up Phase with initiation of 2nd-line treatment per Investigator discretion

b. Randomization stratified by: Cohorts 1 and 2- region (EU, Americas, Africa or Asia), induction treatment response (CR/PR vs. SD); Cohort 3- induction treatment response (CR/PR vs. SD), HER2 IHC (IHC0/ IHC1+/IHC2+ vs. IHC3+); Cohort 4- region (EU vs. rest of world), induction treatment response (CR/PR vs. SD), microsatellite stability (MSI-H vs. MSS), RAS status (wild-type KRAS and NRAS vs. mutant KRAS and/or NRAS)

c. Patients discontinuing study treatment for any reason during the Induction or Maintenance Treatment Phases will enter the Post-treatment Follow-up Phase.

Primary objective of this study:

The primary study objective within each cohort is to evaluate PFS.

An iDMC is responsible for regularly reviewing safety data.

2.1 PROTOCOL SYNOPSIS

The Protocol version 8 synopsis is provided in Appendix 1. For additional details, see the Schedule of Assessments in Appendix 2.

2.2 OUTCOME MEASURES

The outcome measures are listed in protocol synopsis (Appendix 1).

2.3 DETERMINATION OF SAMPLE SIZE

Before study enrolment was closed prematurely, approximately 1820 patients were planned for enrolment in the Induction Treatment Phase of the study in order to randomise 90 patients in Cohort 3, with around 6% of patients assumed to be eligible for Cohort 3 based on biomarker status. Cohort 3 was closed to accrual with 5 patients randomized (ie, prior to reaching the target sample size).

The estimated proportion of patients enrolled into the study that are eligible for cohort 3 is based on published reports (*Seo et 2014).* Approximately 25% of all patients enrolled are expected to have disease progression prior to randomisation into the Maintenance Treatment Phase (Roche, data on file). Inputs used in cohort-specific sample size calculations are provided in Table 2.

Table 2: Sample Size Determination per Cohort

	Cohort 3
Percent of study population eligible for cohort based on biomarker status	6%
Percent of patients eligible for cohort based on biomarker status expected to have disease progression prior to randomization	25%
Average randomization rate (pts/month) [a]	2.5
Estimated median PFS [b] (months) - Experimental group	11.5
Estimated median PFS [b] (months) - Control group	7.5
Hazard ratio (HR)	0.65
Number of expected PFS events	69
Statistical test	1-sided
Alpha level	10%
Power	65%
Randomized patients	90
Randomization ratio (experimental vs control)	2:1
Recruitment period (months)	36

	Cohort 3
Time to primary analysis of PFS (months) [c]	43
a. Based on 1,820 patients screened over the entire recruitment period b. Per RECIST 1.1 c. Time from first patient randomised in cohort	

2.4 ANALYSIS TIMING

Cohort 3 will not reach its target sample size (final n=5). As originally planned for cohorts reaching their target number of PFS events (applies to Cohort 2 only), an update analysis of efficacy and safety parameters will be conducted based on 24 months survival follow-up after the clinical cut-off date for the primary analysis. The cut-off date for the Cohort 2 primary analysis was May 31, 2017 so the Cohort 2 update analysis will be conducted based on a cut-off date of May 31, 2019. The primary analysis for cohort 3 will be conducted at the same time as the Cohort 2 update analysis (i.e. based on the same cut-off date of May 31, 2019).

The final analysis of cohort 3, which will consist of updating disposition and death information, will take place after the end of the study. End of study is defined as the date when all study patients have discontinued study treatment and completed the adverse event reporting period. Given the small sample size; only few listings will be provided for each analysis (no summary tables). The outputs to be provided for the analyses (primary or final) are listed in Appendix 4.

Analysis for cohorts other than cohort 3 is not covered in this SAP and will be documented in separate SAPs.

3. STUDY CONDUCT

3.1 RANDOMIZATION ISSUES

Patients will be assigned to a cohort based on the results of biomarker assessments conducted on archival primary tumour tissue obtained during their initial CRC diagnosis. Once assigned to a cohort, patients will be randomized on a 2:1 basis to either the experimental treatment group or the control group of that cohort. Randomization in Cohort 3 will be stratified by HER2 IHC result (IHC0/IHC1+/IHC2+ vs IHC3+) and by patient response after the Induction Treatment Phase (CR/PR vs. SD).

3.2 INDEPENDENT REVIEW FACILITY

Not applicable.

3.3 DATA MONITORING

An iDMC is responsible for:

- evaluating the safety of the patients participating in the trial at regular intervals throughout the study,
- making recommendations as to whether cohort recruitment should continue based on benefit-risk evaluations that include efficacy as well as safety data. To minimize the impact of such reviews on efficacy endpoint analyses, efficacy data included in these

reviews has to be specified by the iDMC at a preceding iDMC meeting and has to be documented in the iDMC meeting minutes.

4. STATISTICAL METHODS

Only listings will be provided.

4.1 DEFINITION OF TREATMENT PHASE

In this study, there are 3 treatment phases:

1. Patients are treated first in the Induction Treatment Phase (ITP) for a planned duration of 8 cycles, i.e. 16 weeks.

2. If they do not experience any progressive disease before or at the end of the ITP, are not considered resectable at the end of the ITP and do not withdraw from the study and are still eligible for any cohort, they are randomized and treated in the Maintenance Treatment Phase (MTP).

3. If they discontinue study treatment for any reason during the Induction or Maintenance Treatment Phases, do not withdraw from the study and are still alive, they enter the Post-Treatment Follow-up Phase.

4.1.1 Induction Treatment Phase (ITP)

ITP is defined as the time from first study drug administration until

- the day before the randomization for patients continuing treatment in the MTP
- the last assessment date otherwise

The first day of treatment in the ITP is defined as the earliest day of a non-null administration of any induction phase treatment.

The last day of treatment in the ITP is defined as the last day of the last initiated cycle of the induction phase, or as the death day if the patient died in between. A two-week cycle duration is assumed.

Baseline evaluations for the ITP will be those performed not earlier than 28 days prior to the first day of treatment in the induction phase, unless otherwise stated. The latest available assessment up to start of the first day of treatment in the induction phase will be considered as baseline. For laboratory examinations, weight, vital signs and ECOG PS, assessments performed on the first day of treatment of the ITP will be assumed to have been performed before drug was given and, thus, will be considered as baseline evaluations.

On-treatment evaluations for the ITP will be post baseline evaluations performed until

- the day before the randomization for patients continuing treatment in the MTP
- (including) the study treatment discontinuation visit within 30 days after last day of treatment of the ITP (as defined above), for patients not randomized in the MTP.

4.1.2 Maintenance Treatment Phase (MTP)

MTP is defined as the time from randomization into MTP until (including) the study treatment discontinuation visit in the MTP.

The first day of treatment in the MTP is defined as the earliest day of a non-null administration of any maintenance phase treatments.

The last day of treatment in the MTP is defined as the last day of the last initiated cycle of the maintenance phase, or as the death day if the patient died in between. A two-week cycle duration is assumed.

Baseline evaluations for the MTP will be those performed prior to the first day of treatment in the maintenance, unless otherwise stated. The latest available assessment prior to the first day of treatment in the maintenance phase will be considered as baseline for safety assessments. For laboratory examinations, weight and vital signs, assessments performed on the first day of treatment of the MTP will be assumed to have been performed before drug was given and, thus, will be considered as baseline evaluations. For subjects randomized but not treated in the MTP, the latest available assessment before or on randomization date (including assessments from ITP) will be considered as baseline for the MTP.

For efficacy assessments, the latest available assessment prior or on the randomization date will be considered as baseline.

On-Treatment evaluations for the MTP will be evaluations performed on or after the first day of treatment in the MTP within 30 days from last day of treatment in the maintenance phase. On-treatment laboratory will be all values collected after the first day of treatment in the maintenance phase and within 30 days from last day of treatment in the maintenance phase (as defined above). For adverse events, treatment emergent adverse events (TEAEs) will be events occurring on or after the first day of treatment in the MTP within 30 days (for patients in control group) and 90 days (for patients in experimental group) from last day of treatment in the maintenance phase (as defined above).

4.2 DATA CONVENTION

All data will be listed (e.g. pre-treatment serious adverse events).

Age at informed consent (IC) {in years} = (date of informed consent – date of birth) / 365.25

Body surface area (BSA) will be recalculated based on the height and weight of the patient using the following formula:

BSA (m^2) = ([Height {cm} x Weight {kg}] / 3600)^{½}

Body mass index (BMI) will be calculated using the following formula:

BMI (kg/m^2) = Weight {kg} / Height^2 {m}

4.3 COMPUTING ENVIRONMENT

All statistical analyses will be performed using SAS statistical software (Version 9.2 or newer version), unless otherwise noted.

4.4 GRADING AND CODING OF ADVERSE EVENTS, LABORATORY PARAMETERS AND MEDICATIONS

Adverse events and relevant Medical History data fields (i.e. prior symptoms / AEs) will be coded using the most recent version of Medical Dictionary for Regulatory Activities (MedDRA) dictionary available at the time of analysis.

Dictionary versions used will be displayed in analysis outputs.

4.5 ADUSTMENTS FOR COVARIATES

Not applicable.

4.6 SUBGROUP ANALYSIS

Not applicable.

4.7 ANALYSIS POPULATIONS

The following patient populations will be evaluated and used for presentation and analysis of the data.

4.7.1 All Population

ALL Population: The ALL population consists of all screened patients with HER2+ biomarker profile enrolled after June 28, 2016.

Induction Treatment Phase (ITP) Population: all patients included in the ALL Population and who are treated in the ITP, i.e. who received at least one non-null dose of any study medications during the ITP. The ITP population is the main population to be used to summarize ITP data and Post Induction Treatment data. ITP population will be the main population for the data listings; the 3 following groups will be displayed in listings: patients randomized in the experimental group of MTP, patients randomized in the control group of MTP, patients not randomized into MTP.

4.7.2 Randomized Population

Maintenance Treatment Phase (MTP) Population is defined as all patients randomized into the Cohort 3 MTP of the study, irrespective of whether or not they received study medication. Patients will be allocated to the treatment group into which they were randomized (as per interactive voice or web-based response system [IxRS]).

4.7.3 Safety Population

Not applicable.

4.7.4 Per Protocol (PP) Population

Not applicable.

4.7.5 Pharmacokinetic-Evaluable Population

Not applicable.

4.7.6 Biomarker-Evaluable Population

Not applicable.

4.8 ANALYSIS OF STUDY CONDUCT

This SAP focuses only on the description of the analysis required for cohort 3 data.

4.8.1 Patient Disposition

Patient disposition (including the tumor response status at the end of ITP) and study termination information will be listed on ITP population.

4.8.2 Protocol Deviations

No outputs will be provided.

4.9 ANALYSIS OF TREATMENT GROUP COMPARABILITY

4.9.1 Demographics and Baseline Disease Characteristics

Baseline and demographic characteristics (age, sex, ethnicity, race, smoking status, alcohol use, height, weight, BMI, BSA, female reproductive status) will be listed on ITP population.

4.9.2 Medical History

No outputs will be provided.

4.9.3 Prior and Concomitant Medications

No outputs will be provided.

4.9.4 Subsequent Anti-Cancer Therapy

No outputs will be provided.

4.10 EFFICACY ANALYSIS

PFS is defined as the time from randomization into the MTP until documented disease progression as per investigator assessment using Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 or death from any cause, whichever occurs first. If no progression / death is observed at the time of clinical cut-off or by the date of any on-study colorectal anti-cancer surgery with palliative or curative intent, patients will be censored at the date of the last evaluable tumor assessment or date of randomization, whichever comes last.

(Of note: (i) Progressive disease are identified by the Overalll Response='PD', even if solely based on symptomatic deterioration, (ii) Only surgery occurring between baseline tumor assessment for MTP and PFS events are considered for censoring PFS)

PFS time will be listed on MTP population.

No other efficacy endpoints will be listed.

4.11 PHARMACOKINETIC AND PHARMACODYNAMIC ANALYSES

Not applicable

4.12 SAFETY ANALYSES

4.12.1 Exposure of Study Medication

Listing on exposure will be provided for ITP and MTP separately.

Table 3: Exposure Definitions for Induction Treatments

	FOLFOX	5-FU/LV	bevacizumab
Number of cycles	sum of all cycles in which at least one non-null dose of FOLFOX has been administered	sum of all cycles in which at least one non-null dose of 5-FU and LV has been administered. Of note, consider only cycles where oxaliplatin is not administered concomitantly with 5-FU/LV.	sum of all cycles in which at least one non-null dose of bevacizumab has been administered
Duration of dosing (weeks) (1)	[min (last date of FOLFOX+13, death date) – first FOLFOX dosing date+1] / 7 or If FOLFOX-4 or FOLFOX-7 or modified FOLFOX-7 is administered in the last cycle initiated [min (last date of FOLFOX +12, death date) – first FOLFOX dosing date+1] / 7	max (min(last date of 5-FU+13, death date), min(last date of LV+13, death date)) – min (first date of 5-FU, first date of LV) +1] / 7 Of note, consider only records/cycles where oxaliplatin is not administered concomitantly with 5-FU/LV.	[min (last date of bevacizumab +13, death date)) – (first bevacizumab dosing date in the induction) +1] / 7

(1) According to the proposed formula, the duration of dosing may be overestimated in case patients discontinued treatment prior to the end of the last cycle.

Table 4: Exposure Definitions for Maintenance

	capecitabine	**5-FU or LV**	**bevacizumab**	**trastuzumab**	**pertuzumab**
Number of cycle	The sum of all cycles in which at least one non-null dose of <*treatment*> has been administered			The sum of all cycles in which at least one non-null dose of <*treatment*> has been administered	
Duration of dosing (weeks) [1]	[min (last dosing date of <treatment> + x, death date)) – (first <treatment> dosing date in the maintenance) +1] / 7 Where x=6 for capecitabine, x=13 for 5FU, LV, bevacizumab, x=20 for trastuzumab, pertuzumab For 5-FU and LV, last dosing date of treatment will be replaced by the first dosing date of the last administration				
Actual dose	<treatment> dose administered (in mg) as collected on the dosing eCRF page Unit: mg				
Planned dose	<treatment> planned dose (in mg) as collected on the dosing eCRF page Unit: mg				
Normalized dose	dose / recalculated BSA[2] Unit: mg/m^2		dose / weight[3] Unit: mg/kg	dose / weight[3] Unit: mg/kg	NA

	capecitabine	5-FU or LV	bevacizumab	trastuzumab	pertuzumab
Cumulative dose	The cumulative dose will be derived for each records as below: (end date of administration - start date of administration +1) * normalized actual dose for the record * 2 Cumulative dose= sum of cumulative dose across all records Unit: mg/m2	sum of the all <treatment > normalized actual doses (in mg/m^2) administered in all cycles	sum of the all bevacizumab normalized actual doses (in mg/kg) administered in all cycles	sum of the all trastuzumab normalized actual doses (in mg/kg) administered in all cycles	sum of the all of pertuzumab actual doses (in mg) administered in all cycles
Dose intensity	Cumulative dose / (duration of dosing *7) Unit: $mg/m^2/day$	Cumulative dose / duration of dosing Unit: $mg/m^2/week$	Cumulative dose / duration of dosing Unit: mg/kg/week	Cumulative dose / duration of dosing Unit: mg/kg/week	Cumulative dose / (duration of dosing * 7) Unit: mg/day
Planned dose intensity	CPD/(duration of dosing *7)	CPD/duration of dosing	CPD/duration of dosing Unit: mg/kg/week	CPD/duration of dosing Unit:	CPD/(duration of dosing*7) Unit: mg/day

	Unit: mg/m^2/day	Unit: mg/m^2/week		mg/kg/week	
Relative dose intensity (RDI) (%)	100 * (dose intensity) / (planned dose intensity)				

(1) According to the proposed formula, the duration of dosing may be overestimated in case patients discontinued treatment prior to the end of the last cycle.
(2) The BSA will be recalculated based on the height and weight (see point 3 for identification of weight) of the patient using the formula as mentioned in section 4.3.
(3) The baseline weight will be used as reference. If the last available weight of the patient prior to or on the cycle start has changed by 10% or greater (i.e. patient has gained or lost more than 10% of their body weight since baseline) the patient new weight will be set as the baseline weight and will be used at the patient current and subsequent cycles. If a patient weight has changed by 10% or greater at a later cycle, then this new weight will be set as the base weight as aforementioned.

4.12.2 Adverse Events

Adverse events variables are defined in Table 5.

Table 5: Adverse Events Definitions

Variable	Definition
Treatment Emergent Adverse Events (TEAEs) for the induction treatment phase [(1)]	Any adverse events (serious and non-serious) with an onset date on (only if the "Event occurred prior to first study drug administration" from the AE eCRF page is not checked) or after the first day of treatment of the ITP and up to the: • first day of treatment of the MTP (excluding) if it occurs within the 30 days from last day of treatment of induction treatment for patients treated with maintenance treatment • within 30 days from last day of treatment of induction treatment (as defined in section 4.1.1), for patients not treated with maintenance treatment or for patients treated with maintenance treatment but with first day of treatment of MTP being more than 30 days after last day of treatment of ITP.
TEAEs for the maintenance treatment phase[(1)]	Any adverse events (serious and non-serious) with an onset date on (only if the "Event occurred prior to first study drug administration" from the AE eCRF page is not checked) or after the first day of treatment of the MTP and up to 30 days (for patients in control group) and 90 days (for patients in experimental group) from the last day of treatment of MTP (as defined in section 4.1.2)
Post induction treatment Adverse Events	Any adverse events (serious and non-serious): • with an onset date more than 30 days after the last day of treatment of the ITP (as defined in section 4.1.1) for patients not treated with maintenance treatment. • with an onset date more than 30 days after the last day of treatment of the ITP and prior the first day of treatment of the MTP, for patients treated with maintenance treatment with first day of treatment of MTP being more than 30 days after last day of treatment of ITP..
Post maintenance treatment Adverse events	Any adverse events (serious and non-serious) with an onset date more than 30 days (for patients in control group) and more than 90 days (for patients in experimental group) after the last day of treatment of the MTP (as defined in section 4.1.2) (as defined in section 4.1.2).
Adverse Events NCI CTCAE grade	The adverse events grade will be the one with tick box checked for "AE most extreme NCI CTCAE grade"
Serious Adverse Events	Any adverse events qualified as "serious" by the investigator.

Adverse Events with fatal outcome	Any adverse events with outcome of “Fatal”.
Adverse events related to <FOLFOX, bevacizumab, FP, trastuzumab, pertuzumab>	Any adverse events with an “AE suspected to be caused by study drug <FOLFOX, bevacizumab, FP, trastuzumab, pertuzumab > as ‘Yes’. For AE suspected to be caused by FOLFOX while starting in the maintenance phase, the unique text ‘“AE considered related to Folfox”‘ has been reported in the comment field ‘
Adverse events leading to <FOLFOX, bevacizumab, FP, trastuzumab, pertuzumab> discontinuation	Any adverse events with an “Action taken with <FOLFOX, bevacizumab, FP, trastuzumab, pertuzumab > due to SAE/AE” of “drug withdrawn”
Adverse events of Special Interest (AESI) as reported on eCRF	AESIs will be selected based on the tick box from the eCRF.

(1) Of note, in case an event has an incomplete or missing start date, which consequently prevents its allocation to only one treatment phase of the study, the event will be allocated to both the induction and maintenance phase. Refer to section 4.13 for further details.

By-patient listings will be provided for all adverse events AEs on ITP population.

4.12.3 Death

One listing will be generated for deaths based on the ITP population and including appropriate flagging of study phase (ITP and MTP) and on-treatment/post-treatment deaths (i.e. within 30 days from last day of treatment/more than 30 days from last day of treatment).

All deaths information (including reason and date) will be retrieved from the Study Completion/Early Discontinuation eCRF page.

4.12.4 Laboratory Data

No outputs will be provided.

4.12.5 Vital Signs

No outputs will be provided.

4.12.6 Other Safety Assessment

No outputs will be provided for other safety assessment (eg. pregnancy test).

4.13 MISSING DATA

Imputation of partial/missing death date will be done as follows:

- If the date is completely missing, then the day of "Last known to be alive" +1 will be used
- If only day is missing and year and month are same as "Last known to be alive", then the day of "Last known to be alive"+1 will be used otherwise the 1st day of the month will be used
- If day and month are missing and year is same as "Last known to be alive", then the "Last known to be alive"+1 will be used, otherwise 1st of January will be used

Partially missing dates for adverse events (AEs) will be imputed as follows. Of note, imputation of missing/partial AE date will be done only to identify treatment emergent AEs.

AE onset dates

- Partially missing onset dates will be imputed as follows
  - When only Day is missing:
    - If Month & Year of the onset date are the same as Month & Year of the first day of treatment of the induction/maintenance treatment phase, the imputed onset date will be imputed as the minimum of the first day of treatment of the induction/maintenance treatment phase and the AE resolution date (imputed if needed).
    - Otherwise, the missing day will be replaced by "1".
  - When Day & Month are missing:
    - If Year of the onset date is the same as Year of the induction/maintenance treatment phase, the imputed onset date will be imputed as the minimum of the first day of treatment of the induction/maintenance treatment phase and the AE resolution date (imputed if needed).
    - Otherwise, the missing Day & Month will be replaced by "01JAN".

- Complete missing onset dates for AEs will be imputed by first day of treatment of the induction/maintenance treatment phase and the AE will be considered as treatment emergent, unless the end date of the AE (imputed if needed) or the end year of the AE (if day and month are missing) is entered and is before the year of the first treatment administration of the induction/maintenance treatment phase.

AE resolution dates

- Incomplete resolution dates will be replaced by the last day of the month (if day is missing only), if not resulting in a date later than the date of patient's death. In the latter case the date of death will be used to impute the incomplete resolution date
- In all other cases the incomplete resolution date will not be imputed

Of note, the above rules may allow allocation of an event to both the ITP and MTP treatment phase.

The original incomplete, missing or partial dates will be presented in the listings, not the imputed dates.

4.14 INTERIM ANALYSES

No formal interim analyses on PFS or OS are planned.

5. REFERENCES

Seo AN, Kwak Y, Kim DW, et al. HER2 status in colorectal cancer: its clinical significance and the relationship between HER2 gene amplification and expression. PLoS One. 2014 May 30;9(5):e98528. doi: 10.1371/journal.pone.0098528. eCollection 2014.

Ron Brookmeyer and John Crowley, A Confidence Interval for the Median Survival Time. Biometrics Vol. 38, No. 1 (Mar., 1982), 29-41

Appendix 1: Protocol Synopsis

Objectives

Efficacy Objectives

The primary efficacy objective of the study is to evaluate progression-free survival (PFS) within each maintenance treatment cohort.

Secondary efficacy objectives include the evaluation of efficacy through other endpoints:

- Overall survival (OS)
- Overall response rate (ORR)
- Disease control rate (DCR)
- Time to treatment response (TTR)
- Duration of response (DoR)
- Change in Eastern Cooperative Oncology Group (ECOG) performance status

Safety Objectives

Additional objectives for this study are to assess the safety of each treatment including:

- the 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

Adverse events (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 modified RECIST (mRECIST) in patients treated with atezolizumab

The exploratory biomarker objectives for 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)
- Explore and correlate microbiome with other biomarkers, baseline characteristics and clinical outcome

Study Design

Description of Study

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). The primary study endpoint is PFS according to RECIST 1.1 within each cohort. Secondary endpoints include other efficacy measurements and safety. In addition, exploratory outcomes will focus on the correlations between biomarkers and study outcomes.

Patients with mCRC who have not received any prior chemotherapy in the metastatic setting are eligible for entry. The study will enrol patients in Europe, Asia, Africa, and South America.

For an individual patient, the study will consist of a Screening Phase (≤ 28 days), a 4-month Induction Treatment Phase, a Maintenance Treatment Phase, and finally follow-up during the Post-Treatment Follow-up Phase.

Potential patients will undergo screening assessments to determine study eligibility within 28 days prior to starting study induction treatment. Results from routine assessments conducted prior to informed consent signature may be used as screening assessments as long as they were done within

7 days prior to informed consent signature. The primary tumour tissue block prepared at the time of the initial diagnosis will be used for biomarker assessment for maintenance treatment cohort assignment (see Appendix 17). If the tumour block is not available, ≥ 20 slides cut from the primary tumour sample will be accepted as an alternative. The sample (block or slides) must be shipped to the designated laboratory and confirmation of sample receipt by the laboratory must be obtained before the patient may be enrolled in the study.

All patients enrolled in the study will be asked to give written informed consent to provide blood samples for exploratory biomarker analyses and to allow all available residual samples of tumour, blood and plasma samples collected in the study be used for additional exploratory biomarker research using the Roche Clinical Sample Repository (RCR). No additional sampling is required for RCR samples. Prior to May 2018, an optional metastatic tumour sample was collected from all study patients. In addition, patients at selected centres were able to participate in an optional Supplemental Biomarker Program (described in Appendix 18). As of May 2018, collection of the optional baseline metastatic tumour sample has been discontinued and the Supplemental Biomarker Program has been closed. Baseline metastatic tumour samples and Supplemental Biomarker Program samples collected up to this time point may still be used for exploratory biomarker analyses.

Eligible patients will enter a 4-month Induction Treatment Phase. Treatment during this phase, based on Investigator's choice (see Appendix 6), 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

During the Induction Treatment Phase, patients will be assessed for AEs at every cycle. Clinical laboratory assessments will be conducted at each cycle, however results from tests conducted every second treatment cycle only will be collected in the case report form (CRF). Physical examinations and documentation of concomitant medications will be done every two treatment cycles. 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 prematurely discontinue study treatment for any reason during the Induction Treatment Phase, or who experience PD at any time during or at the end of the Induction Treatment Phase, or who refuse to proceed to the Maintenance Treatment Phase or who are not eligible for any study cohort will undergo a Study Treatment Discontinuation Visit within 30 days after the last dose of study treatment and will then enter the Post-Treatment Follow-up Phase. All patients need to be evaluated for potential resection of metastasis at completion of the induction period. This is of particular importance for patients with liver metastases. If the patient is found to be resectable they will undergo a Study Treatment Discontinuation Visit within 30 days after the last dose of study treatment and will then enter the Post-Treatment Follow-up Phase. Patients completing induction treatment who do not have progressive disease and whose disease has not become resectable can proceed to the Maintenance Treatment Phase. Informed consent based on the information specific to the assigned maintenance cohort will be obtained prior to the conduct of any cohort-specific screening assessments (unless the study site has chosen to conduct informed consent including information for induction regimens and all potential maintenance regimens prior to study entry).

Each maintenance treatment cohort will consist of a cohort-specific experimental treatment arm and a standard control arm of fluoropyrimidine (5-FU/LV or capecitabine) and bevacizumab. At completion of the Induction Treatment Phase of the study, patients continuing to the biomarker-driven Maintenance Treatment Phase will be assigned to a maintenance treatment cohort based on the biomarker profile determined from their primary tumour tissue. Biomarkers considered in maintenance

treatment assignment include presence or absence of HER2 overexpression (HER2+ or HER2- respectively), microsatellite stability status (microsatellite stable [MSS] or high microsatellite instability [MSI-H]), wild-type or mutated BRAF gene ($BRAF^{wt}$ or $BRAF^{mut}$ respectively), and presence or absence of RAS pathway mutation (RAS^{wt} or RAS^{mut} respectively; see Appendix 17 for the biomarker-based cohort assignment decision tree). Patients will be randomised within their assigned cohort on a 2:1 (experimental:control) basis to either the experimental treatment arm or the control arm of that cohort and will begin treatment within 3 weeks of completing induction treatment. Randomisation will be stratified according to specific biomarkers identified for each cohort, by geographical region, and/or by patient response after the Induction Treatment Phase (CR/PR vs. SD). Stratification variables applicable to each cohort are described in Section 4.2 of the protocol.

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 (see Figure 1).

Cohort 1

Biomarker profile (all patients screened prior to June 3, 2016): $BRAF^{mut}$

*Biomarker profile (all patients screened after June 3, 2016): **HER2-/MSS/$BRAF^{mut}$/RAS^{wt}***

5-FU/LV with cetuximab and vemurafenib

vs.

Fluoropyrimidine (5-FU/LV or capecitabine) and bevacizumab

Cohort 2 - CLOSED TO ENROLMENT

(No patients screened after June 3, 2016 will be assigned to this cohort)

*Biomarker profile: **$BRAF^{wt}$***

Fluoropyrimidine (5-FU/LV or capecitabine) with bevacizumab and atezolizumab

vs.

Fluoropyrimidine (5-FU/LV or capecitabine) and bevacizumab

Cohort 3

*Biomarker profile: **HER2+***

Capecitabine with trastuzumab and pertuzumab

vs.

Fluoropyrimidine (5-FU/LV or capecitabine) and bevacizumab

Cohort 4 - CLOSED TO ENROLMENT

(As of February 12, 2018, no further patients are assigned to this cohort. See protocol Section 3.1.2.4.)

*Biomarker profiles: **HER2-/MSI-H; HER2-/MSS/$BRAF^{wt}$; HER2-/MSS/$BRAF^{mut}$/RAS^{mut}***

Cobimetinib and atezolizumab

vs.

Fluoropyrimidine (5-FU/LV or capecitabine) and bevacizumab

See Appendix 17 for additional information on biomarker testing and biomarker-based cohort assignment.

Study Enrolment and Cohort Status Update:

- Accrual to Cohort 2 was completed in November 2016.

- Study enrolment and accrual into Cohort 4 were suspended in February 2018 as a result of an unfavourable benefit-risk evaluation of Cohort 4 by the independent Data Monitoring Committee (iDMC). Accrual to Cohort 4 was not re-opened after February 2018 due to iDMC recommendations. See protocol Section 3.1.2.4.
- Cohort assignment and randomization of any patients who were already enrolled and eligible for Cohorts 1 and 3 were continued following the February 2018 suspension of study enrolment.
- No new or modified cohorts have been identified for addition to the study. In the absence of a cohort with broad biomarker eligibility criteria (i.e. to replace Cohort 4), the majority of patients would not be eligible for maintenance cohort assignment. For this reason, study enrolment will not be re-opened following the February 2018 suspension.

All Cohorts

No other anti-cancer therapy is permitted during the study with the following exceptions:

- local ablation for liver metastases during Induction Treatment Phase only and only if there are other non-ablated sites of measurable disease that have been followed from baseline tumour assessment (i.e. prior to start of induction treatment)
- radiotherapy for pain control during the either Induction or Maintenance Treatment Phases

For all patients who are not receiving atezolizumab, study maintenance treatment will continue until disease progression (based on Investigator's assessment), unacceptable toxicity, initiation of another anti-cancer therapy, patient or physician decision to discontinue, or patient death, whichever occurs first.

For all patients who are receiving atezolizumab, study maintenance treatment may continue after the first tumour assessment showing progression per RECIST 1.1 as long as patients meet the following criteria as assessed by the Investigator:

- Evidence of clinical benefit
- Absence of symptoms and signs (including worsening of laboratory values, e.g. new or worsening hypercalcaemia) indicating unequivocal progression of disease
- No decline in ECOG performance status that can be attributed to disease progression
- Absence of tumour progression at critical anatomical sites (e.g. leptomeningeal disease) that cannot be managed by protocol-allowed medical interventions

Treatment should be discontinued if the next follow-up tumour assessment continues to demonstrate progression per RECIST 1.1 (as compared to the assessment at the end of induction treatment). If the next tumour assessment does not show progression per RECIST 1.1, the patient may continue maintenance treatment until such time as the treatment continuation criteria above are no longer met and/or two sequential tumour assessments show progression per RECIST 1.1.

Atezolizumab treated patients may be discontinued from study treatment for the following reasons other than loss of clinical benefit or persistent progression: unacceptable toxicity, initiation of another anti-cancer therapy, patient or physician decision to discontinue, or patient death, whichever occurs first.

Efficacy, safety and tolerability will be assessed during the entire Maintenance Treatment Phase. While receiving study treatment during the Maintenance Treatment Phase, patients will be assessed for AEs and concomitant medications at every treatment cycle. Clinical laboratory assessments will be conducted at every cycle. For regimens with two week treatment cycles, clinical laboratory results from every second treatment cycle only will be collected in the CRF. For regimens with three week treatment cycles (such as Cohort 3 experimental regimen), clinical laboratory results from every cycle will be collected in the CRF. Physical examinations will be done every treatment cycle (regimens with three week cycles) or every two treatment cycles (regimens with two week cycles). Additional safety

reviews (safety run-ins) will be conducted by the iDMC, when necessary, for a prespecified number of initial patients receiving experimental combinations with inadequate prior safety experience to assure appropriate dosing (e.g., as required for the initial patients treated with the experimental combination of '5-FU/LV + cetuximab + vemurafenib'). Up to and including May 31, 2019, disease status will be evaluated during the Maintenance Treatment Phase as compared to the tumour assessment at the end of induction treatment and in accordance with RECIST 1.1 (see Appendix 10) for all patients, and additionally according to mRECIST (see Appendix 11) for patients treated with atezolizumab. Tumour assessments will be conducted every eight weeks. After May 31, 2019, disease status will no longer be collected for study analyses and should be evaluated according to local practice. Schedules of Assessments for each cohort are provided in Appendices 2 to 5.

Patients who discontinue study treatment for any reason during the Maintenance Treatment Phase will undergo a Study Treatment Discontinuation Visit within 30 days after the last dose of study treatment and will then enter the Post-Treatment Follow-up Phase.

Patients who prematurely discontinue treatment during the Induction Treatment Phase, who did not proceed to the Maintenance Treatment Phase or who discontinue treatment during the Maintenance Treatment Phase, will be followed for new AEs for 28 days (patients discontinuing before maintenance treatment and patients treated in all maintenance cohort control arms and Cohort 1 experimental arm) or 90 days (patients treated in experimental arms of Cohorts 2, 3 and 4 only) following the discontinuation of study treatment. At the time of treatment discontinuation, any ongoing AE/SAE will be followed until the event resolves, the Investigator assesses the event as stable, or the patient is lost to follow-up, dies or withdraws consent. The Sponsor should be notified if the Investigator becomes aware of any SAE or AEs of special interest occurring after the end of the adverse event reporting period if the event is believed to be related to prior study treatment.

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. Before May 31, 2019, patients will be followed every 3 months during the Post-Treatment Follow-up Phase for subsequent anti-cancer therapies, survival, and AEs (as applicable) including therapy-specific safety assessments (e.g., investigations for squamous cell carcinoma in patients who received vemurafenib) (see Appendices 1 to 5). After May 31, 2019, patients in Cohorts 2 and 3 who have completed the adverse event reporting period and, if applicable, cohort-specific post-treatment follow-up safety assessments will be discontinued from the study. Cohorts 2 and 3 patients who have completed the adverse event reporting period (and cohort-specific post-treatment follow-up safety assessments if applicable) prior to May 31, 2019 will be discontinued at their Post-Treatment Follow-up visit within the 3 months prior to and including May 31, 2019. See protocol Section 5.3.1 for adverse event reporting periods and post-treatment follow-up safety assessments. All patients in Cohorts 1 and 4 will continue in the Post-Treatment Follow-up Phase until the end of the study. Refer to Appendix 19 for management of patients in each cohort based on their study status on May 31, 2019.

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 (patients discontinuing during the Induction Treatment Phase) or every eight weeks (patients discontinuing during the Maintenance Treatment Phase) until progression or May 31, 2019, whichever comes first. After May 31, 2019, disease status will no longer be collected for any study patient. Disease assessments in any patient who has not yet progressed as of May 31, 2019 should thereafter be conducted according to local practice.

Second-line treatment during the Post-Treatment Follow-up Phase is at the Investigator's discretion. However, patients who received atezolizumab should not receive other immunomodulatory agents for 10 weeks after maintenance treatment discontinuation.

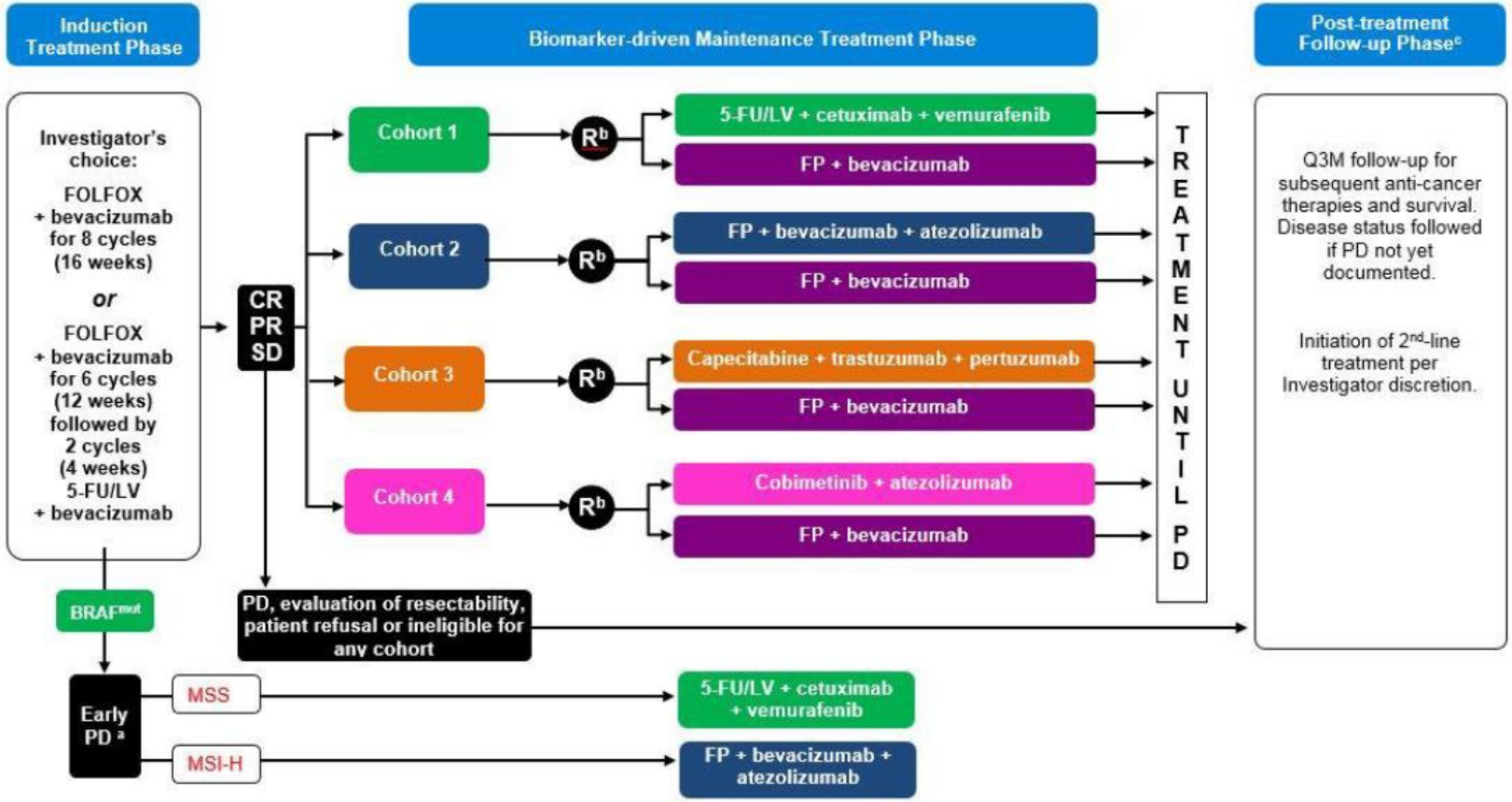
BRAF^{mut} Patients and Early Disease Progression

BRAF^{mut} patients experiencing early disease progression during induction treatment will have the option of proceeding immediately to receive second-line treatment with 5-FU/LV, cetuximab and vemurafenib if their primary tumour is MSS, or with a fluoropyrimidine (5-FU/LV or capecitabine), bevacizumab, and atezolizumab if their primary tumour is MSI-H.

If a patient previously indicated to have a BRAF^{mut} primary tumour (e.g. according to local testing) progresses prior to the availability of results from the study primary tumour biomarker testing, the Investigator may request an expedited biomarker report from the sponsor's Medical Monitor to confirm BRAF^{mut} status and to obtain MS status. Such patients will be allocated to the appropriate second-line treatment and may begin treatment following approval from the Medical Monitor.

Early progressing BRAF^{mut} patients receiving 5-FU/LV, cetuximab and vemurafenib as second-line treatment will be followed for safety and efficacy in accordance with the Maintenance Treatment Phase Schedule of Assessments (including eligibility, biomarker sampling and post-treatment follow-up) for Cohort 1 (see Appendix 2) and will be managed according to protocol recommendations and requirements for the experimental arm of Cohort 1. Early progressing BRAF^{mut} patients receiving a fluoropyrimidine (5-FU/LV or capecitabine), bevacizumab, and atezolizumab as second-line treatment will be followed for safety and efficacy in accordance with the Maintenance Treatment Phase Schedule of Assessments (including eligibility, biomarker sampling and post-treatment follow-up) for Cohort 2 (see Appendix 3) and will be managed according to protocol recommendations and requirements for the experimental arm of Cohort 2. This includes continuation of therapy beyond progression per RECIST 1.1 as described for Maintenance Treatment Phase patients receiving atezolizumab.

Figure 1: Study Design



FP = fluoropyrimidine (5-FU/LV or capecitabine); 5-FU/LV = 5-fluorouracil/leucovorin; MSI -H= high microsatellite instability; MSS = microsatellite stable

a. Patients who progress early and who are not BRAF^{mut} will enter the Post-treatment Follow-up Phase with initiation of 2nd-line treatment per Investigator discretion

b. Randomization stratified by: Cohorts 1 and 2- region (EU, Americas, Africa or Asia), induction treatment response (CR/PR vs. SD); Cohort 3- induction treatment response (CR/PR vs. SD), HER2 IHC (IHC0/ IHC1+/IHC2+ vs. IHC3+); Cohort 4- region (EU vs. rest of world), induction treatment response (CR/PR vs. SD), microsatellite stability (MSI-H vs. MSS), RAS status (wild-type KRAS and NRAS vs. mutant KRAS and/or NRAS)

c. Patients discontinuing study treatment for any reason during the Induction or Maintenance Treatment Phases will enter the Post-treatment Follow-up Phase.

Study Conduct

A Steering Committee (SC) will be responsible for overseeing the general conduct of the study. An iDMC will be responsible for evaluating the safety of the patients participating in the trial at regular intervals throughout the study. This includes ongoing evaluation of benefit-risk balance based on accumulating safety and, as warranted, efficacy data. The iDMC will make recommendations as to whether cohort recruitment should continue based on each interim evaluation. In addition, when necessary due to the nature of prior experience with a particular experimental regimen, the iDMC will conduct a safety run-in review of a pre-specified number of initial patients (e.g. as conducted for the initial patients treated with '5-FU/LV + cetuximab + vemurafenib'). Safety run-ins deemed necessary for additional cohorts will be specified in the protocol. The schedule of iDMC reviews will be determined by the iDMC and described in the iDMC Charter. Additional data are provided in the respective SC and iDMC Charters.

Number of Patients

Before study enrolment was closed prematurely, approximately 1,820 patients were expected to be screened and approximately 1,400 patients were expected to be enrolled in the Induction Treatment Phase of the study in order to randomise the target sample size in each maintenance cohort. This included 405 patients in Cohort 2. Accrual into Cohort 4 was terminated prior to reaching the target sample size. Due to early closure of study enrolment, target sample sizes will not be reached for Cohorts 1 and 3.

Screening procedures

For comparability reasons, only the archival primary tumour sample from the original diagnosis will be used for the biomarker assessment which determines treatment assignment during the Maintenance Treatment Phase, as this material will be available for all patients. To be eligible for the study, patients must have an archival primary tumour sample for biomarker assessment for cohort assignment. If the tumour block is not available, ≥ 20 slides cut from the primary tumour sample will be accepted as an alternative. The sample (block or slides) must be shipped to the designated lab with confirmation of sample receipt provided by the laboratory prior to study enrolment. Biomarker analyses for cohort assignment will be conducted during the Induction Treatment Phase and these results will only be available during the Induction Treatment Phase and not during Screening. Patients with an adequate tumour sample but with unknown biomarker status due to lack of determinant result (e.g. due to technical issues) may still be included in the study depending on the addition of future cohorts.

For enrolment into the study, patients who do not meet the study eligibility criteria (screen failures) may be re-screened within 7 days of the date they are determined to be screen failures. Re-screening of a patient > 7 days after screen failure is allowed only with prior approval from the Medical Monitor. Patients cannot be re-screened for the study more than once.

Target Population

The target study population consists of patients with mCRC who have not received any prior chemotherapy in the metastatic setting. Cohort-specific target populations are further defined by specific biomarker profiles.

The "All Cohort" eligibility criteria are evaluated prior to initiating the first cycle of study treatment during the Induction Treatment Phase. Cohort-specific exclusion criteria must be assessed within 3 weeks of completing Induction Treatment Phase. Biomarker assessments will be completed prior to randomisation, as the results of the biomarker assessments are required to identify the intended cohort in order to complete the appropriate cohort-specific eligibility assessments.

Inclusion Criteria

Patients must meet the following criteria for study entry:

All Cohorts

Patient Status

1. Have provided written informed consent prior to any study specific procedures
2. Willing and able to comply with the protocol
3. ≥ 18 years of age
4. ECOG status of ≤ 2 (see Appendix 8)
5. At least 16 weeks of life expectancy at time of entry into the study

Disease-related

6. Histologically confirmed CRC with mCRC confirmed radiologically
7. Measurable, unresectable disease according to RECIST 1.1
8. No prior chemotherapy for CRC in the metastatic setting
9. Archival tumour formalin-fixed paraffin-embedded tissue (FFPET) block from the primary tumour obtained at the time of the initial diagnosis must be shipped to the Sponsor's designated laboratory with sample receipt confirmed by the laboratory. If the tumour block is not available, ≥ 20 slides cut from the primary tumour sample will be accepted as an alternative (see Appendix 17). The slides must be shipped with receipt confirmed by the Sponsor's designated laboratory prior to study enrolment.

Exclusion Criteria

Patients who meet any of the following criteria will be excluded from study entry:

All Cohorts

Other Prior or Current Treatments

1. Less than 6 months from completion of any prior neoadjuvant or adjuvant chemotherapy or radiotherapy
2. Prior or current treatment with bevacizumab or any other anti-angiogenic drug (i.e. anti-VEGF or vascular endothelial growth factor receptor [VEGFR] therapies or tyrosine kinase inhibitors)
3. Current or recent (within 10 days of start of study induction treatment) use of aspirin (> 325 mg/day), clopidogrel (> 75 mg/day), therapeutic oral or parenteral anticoagulants, or thrombolytic agents for therapeutic purposes.

   Note: The use of full-dose oral or parenteral anticoagulants is permitted as long as the international normalised ratio (INR) or activated partial thromboplastin time (aPTT) is within therapeutic limits (according to the medical standard of the institution) and the patient has been on a stable dose of anticoagulants for at least two weeks prior to the start of study induction treatment. Prophylactic use of anticoagulants is allowed.
4. Requirement for treatment with any medicinal product that contraindicates the use of any of the study medications, may interfere with the planned treatment, affects patient compliance or puts the patient at high risk for treatment-related complications
5. Treatment with any other investigational agent within 28 days or 5 investigational agent half-lives (whichever is longer) prior to the start of study induction treatment

Haematological, Biochemical and Organ Function

6. Inadequate haematological function indicated by one or more of the following:
   - Absolute neutrophil count (ANC) < 1.5 x 10^9/L
   - Platelet count < 100 x 10^9/L
   - Haemoglobin < 9 g/dL (patients may have transfusions and/or growth factors to attain adequate haemoglobin)
7. Inadequate liver function indicated by one or more of the following:
   - Total bilirubin ≥ 1.5 x upper limit of normal (ULN)
   - Aspartate transaminase (AST) or alanine aminotransferase (ALT) ≥ 2.5 x ULN (≥ 5 x ULN in patients with known liver metastases)
   - Alkaline phosphatase (ALP) ≥ 2 x ULN (≥ 5 x ULN in patients with known liver metastases)
8. Inadequate renal function indicated by one or more of the following:
   - Serum creatinine > 1.25 x ULN or calculated creatinine clearance < 50 ml/min
   - Urine dipstick for proteinuria ≥ 2+ unless a 24-hour urine protein < 1 g of protein is demonstrated
9. INR > 1.5 or aPTT > 1.5 x ULN within 7 days prior to the start of study induction treatment for patients not receiving anti-coagulation. For patients, receiving anticoagulants INR and aPTT must be within the medical standard of enrolling institution.

   The use of full-dose oral or parenteral anticoagulants is permitted as long as the INR or aPTT is within therapeutic limits (according to the medical standard of the enrolling institution) and the patient has been on a stable dose of anticoagulants for at least two weeks prior to the start of study induction treatment.

General Criteria

10. Active infection requiring intravenous antibiotics at the start of study induction treatment
11. Previous or concurrent malignancy, except for adequately treated basal or squamous cell skin cancer, *in situ* cervical cancer, or other cancer for which the patient has been disease-free for five years prior to study entry
12. Evidence of any other disease, neurologic or metabolic dysfunction, physical examination finding or laboratory finding giving reasonable suspicion of a disease or condition that contraindicates the use of any of the study medications, puts the patient at higher risk for treatment-related complications or may affect the interpretation of study results
13. Inadequately controlled hypertension (defined as systolic blood pressure > 150 mmHg and/or diastolic blood pressure > 100 mmHg)
14. Prior history of hypertensive crisis or hypertensive encephalopathy
15. Clinically significant (i.e. active) cardiovascular disease, for example cerebrovascular accidents ≤ 6 months prior to start of study induction treatment, myocardial infarction ≤ 6 months prior to study enrolment, unstable angina, New York Heart Association (NYHA) Functional Classification Grade 2 or greater congestive heart failure, or serious cardiac arrhythmia uncontrolled by medication or potentially interfering with protocol treatment
16. History or evidence upon physical or neurological examination of central nervous system (CNS) disease (e.g. seizures) unrelated to cancer unless adequately treated with standard medical therapy
17. Significant vascular disease (e.g. aortic aneurysm requiring surgical repair or recent arterial thrombosis) within 6 months of start of study induction treatment
18. Any previous venous thromboembolism > National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) Grade 3 within 12 months prior to start of study induction treatment

19. Active, symptomatic or untreated CNS metastases; CNS disease other than supratentorial or cerebellar metastases (i.e. patients with metastases to midbrain, pons, medulla or spinal cord are excluded); history of or known carcinomatous meningitis.

    Note: Treatment of brain metastases, either by surgical or radiation techniques, must have been completed > 4 weeks prior to start of study induction treatment. Patients requiring anticonvulsants or corticosteroids for symptom control and patients with evidence of interim progression between the completion of CNS-directed therapy and study baseline disease assessments are excluded from the study.

    Note: Patients without measurable disease outside the CNS are excluded from the study.

20. History of haemoptysis ≥ Grade 2 (defined as ≥ 2.5 mL bright red blood per episode) within 1 month of start of study induction treatment
21. History or evidence of inherited bleeding diathesis or significant coagulopathy at risk of bleeding (i.e. in the absence of therapeutic anticoagulation)
22. Surgical procedure (including open biopsy, surgical resection, wound revision, or any other major surgery involving entry into a body cavity) or significant traumatic injury within 28 days prior to start of study induction treatment, or anticipation of need for major surgical procedure during the course of the study
23. Minor surgical procedure including placement of a vascular access device, within 2 days of start of study induction treatment
24. History of abdominal fistula, gastrointestinal (GI) perforation, intra-abdominal abscess or active GI bleeding within 6 months prior to start of study induction treatment
25. Serious, non-healing wound, active ulcer, or untreated bone fracture
26. Known hypersensitivity to any component of any of the study induction or maintenance treatment medications
27. History of severe allergic, anaphylactic, or other hypersensitivity reactions to chimeric or humanised antibodies or fusion proteins
28. Known dihydropyrimidine dehydrogenase (DPD) deficiency
29. Pregnancy or lactation. A serum pregnancy test is required within 7 days prior to start of study induction treatment, or within 14 days with a confirmatory urine pregnancy test within 7 days prior start of study induction treatment
30. For women who are not post-menopausal (< 12 months of non-therapy-induced amenorrhea) or surgically sterile (absence of ovaries and/or uterus): refusal to use a highly effective contraceptive method (i.e. with a failure rate of < 1% per year such as sexual abstinence, hormonal implants, combined oral contraceptives, vasectomised partner), during both the Induction and Maintenance Treatment Phases and for at least 7 months after the last dose of study medication. Periodic abstinence [e.g., calendar, ovulation, symptothermal, postovulation methods] and withdrawal are not acceptable methods of contraception. A combination of male condom with cap, diaphragm or sponge with spermicide (double barrier methods) is not considered highly effective, birth control methods. Acceptable methods of contraception may include total abstinence in cases where the lifestyle of the patient ensures compliance. A vasectomised partner is a highly effective birth control method provided that partner is the sole sexual partner of the MODUL trial participant and that the vasectomised partner has received medical assessment of the surgical success. Some of the study-related medication, such as vemurafenib may decrease the plasma exposure of those hormonal contraceptives predominantly metabolised by CYP3A4. In these cases, the use of an alternate highly effective method of contraception must be considered.
31. For men: refusal to use a highly effective contraceptive method (i.e. with a failure rate of < 1% per year such as vasectomy, sexual abstinence or female partner use of hormonal implants or combined oral contraceptives) during both the Induction and Maintenance Treatment Phases and for a period of at least 6 months after the last dose of study medication. Periodic abstinence [e.g., calendar, ovulation, symptothermal, postovulation methods] and withdrawal are not acceptable

methods of contraception. A combination of male condom with either cap, diaphragm or sponge with spermicide (double barrier methods) is not considered highly effective, birth control methods. Acceptable methods of contraception may include total abstinence in cases where the lifestyle of the patient ensures compliance. A vasectomised MODUL trial participant is a highly effective birth control method provided that the MODUL trial participant has received medical assessment of the surgical success. Men must also agree not to donate sperm for at least 6 months after their last dose of study drug.

Cohort-Specific Exclusion Criteria

The following criteria will be assessed following biomarker-based cohort assignment:

Additional criteria for Cohort 1

1. Have not provided informed consent to participate in Cohort 1.

   Note: At study centers where a single informed consent form is used, informed consent to participate in any maintenance cohort will have already been provided at study entry. Patients enrolled at centers using two informed consent forms must provide maintenance cohort-specific consent after cohort assignment and prior to cohort-specific eligibility assessments other than eligibility assessments already conducted as part of routine care.

2. Inability to swallow pills.
3. Refractory nausea and vomiting, malabsorption, external biliary shunt or significant bowel resection that would preclude adequate absorption.
4. History or presence of clinically significant ventricular or atrial dysrhythmias ≥ NCI CTCAE Grade 2
5. Corrected QT (QTc) interval ≥ 450 msec as assessed within 3 weeks prior to randomization, long QT syndrome, uncorrectable electrolyte abnormalities (including magnesium) or requirement for medicinal products known to prolong the QT interval
6. For women who are not post-menopausal (< 12 months of non-therapy-induced amenorrhea) or surgically sterile (absence of ovaries and/or uterus): refusal to use an alternate highly effective contraceptive method (i.e. with a failure rate of < 1% per year such as sexual abstinence, vasectomised partner) other than hormonal contraceptives, during both the Induction and Maintenance Treatment Phases and for at least 7 months after the last dose of study medication. Vemurafenib may decrease the plasma exposure of those hormonal contraceptives predominantly metabolised by CYP3A4.
7. ECOG PS > 2.

   Note: Due to the potential risks associated with treatment in the experimental arm of Cohort 1, patients with ECOG PS = 2 and a low body mass index (BMI) must be judged by the Investigator as adequately physically fit to receive treatment with 5-FU/LV + cetuximab + vemurafenib to be considered eligible. See protocol Section 4.3.2.2.2.

Additional criteria for Cohort 2

1. Have not provided informed consent to participate in Cohort 2

   Note: At study centers where a single informed consent form is used, informed consent to participate in any maintenance cohort will have already been provided at study entry. Patients enrolled at centers using two informed consent forms must provide maintenance cohort-specific consent after cohort assignment and prior to cohort-specific eligibility assessments other than eligibility assessments already conducted as part of routine care.

2. Known hypersensitivity or allergy to Chinese hamster ovary cell products
3. History of autoimmune disease including but not limited to myasthenia gravis, myositis, autoimmune hepatitis, systemic lupus erythematosus, rheumatoid arthritis, inflammatory bowel

disease, vascular thrombosis associated with antiphospholipid syndrome, Wegener's granulomatosis, Sjögren's syndrome, Guillain-Barré syndrome, multiple sclerosis, vasculitis, or glomerulonephritis (see Appendix 9 for a more comprehensive list of autoimmune diseases)

Patients with the following are eligible:

- a history of autoimmune-related hypothyroidism on a stable dose of thyroid replacement hormone
- controlled Type 1 diabetes mellitus on a stable insulin regimen
- eczema, psoriasis, lichen simplex chronicus, or vitiligo with dermatologic manifestations only (e.g. patients with psoriatic arthritis would be excluded) are permitted provided that they meet the following conditions:
  - rash must cover less than 10% of body surface area (BSA)
  - disease is well controlled prior to randomization and only requires low potency topical steroids
  - no acute exacerbations of underlying condition within the previous 12 months (not requiring PUVA [psoralen plus ultraviolet A radiation], methotrexate, retinoids, biologic agents, oral calcineurin inhibitors, high potency or oral steroids)

4. Prior allogeneic bone marrow transplantation or prior solid organ transplantation
5. History of idiopathic pulmonary fibrosis (including pneumonitis), drug-induced pneumonitis, organizing pneumonia (i.e., bronchiolitis obliterans, cryptogenic organizing pneumonia), or evidence of active pneumonitis on most recent chest imaging (CT scan or MRI)

   Note: History of radiation pneumonitis in the radiation field (fibrosis) is permitted.
6. Positive test for human immunodeficiency virus (HIV)
7. Active hepatitis B (defined as having a positive hepatitis B surface antigen [HBsAg] test prior to randomization) or hepatitis C

   Note: Patients with past hepatitis B virus (HBV) infection or resolved HBV infection (defined as having a negative HBsAg test and a positive antibody to hepatitis B core antigen [anti-HBc] antibody test) are eligible.

   Patients positive for hepatitis C virus (HCV) antibody are eligible only if polymerase chain reaction (PCR) is negative for HCV RNA.
8. Active tuberculosis
9. Severe infection within 4 weeks prior to start of maintenance treatment including, but not limited to, hospitalization for complications of infection, bacteremia, or severe pneumonia; has signs or symptoms of significant infection or has received oral or IV antibiotics within 2 weeks prior to start of maintenance treatment.

   Note: Patients receiving prophylactic antibiotics (e.g. for prevention of a urinary tract infection or chronic obstructive pulmonary disease) are eligible.
10. Administration of a live, attenuated vaccine within 4 weeks prior to start of study maintenance treatment or anticipation that such a live attenuated vaccine will be required during the study
11. Prior treatment with CD137 agonists, anti-CTLA4, anti-PD-1, or anti-PD-L1 therapeutic antibody or pathway-targeting agents
12. Treatment with systemic immunostimulatory agents (including but not limited to interferons or interleukin-2) within 4 weeks or five half-lives of the drug, whichever is longer, prior to start of study maintenance treatment
13. Treatment with systemic corticosteroids or other systemic immunosuppressive medications (including but not limited to prednisone, dexamethasone, cyclophosphamide, azathioprine, methotrexate, thalidomide, and anti-tumour necrosis factor [TNF] agents) within 2 weeks prior to

start of study maintenance treatment, or requirement for systemic immunosuppressive medications during the trial.

Note: The use of inhaled corticosteroids for chronic obstructive pulmonary disease (≤ 10 mg oral prednisone or equivalent), mineralocorticoids (e.g., fludrocortisone) for patients with orthostatic hypotension, and low-dose supplemental corticosteroids for adrenocortical insufficiency are allowed.

Patients who have received acute, low-dose (≤ 10 mg oral prednisone or equivalent), systemic immunosuppressant medications may be enrolled in the study after discussion with and approval by the Medical Monitor.

14. If receiving a RANKL inhibitor (e.g. denosumab), unwilling to adopt alternative treatment such as (but not limited to) bisphosphonates, while receiving atezolizumab.

Additional criteria for Cohort 3

1. Have not provided informed consent to participate in Cohort 3

   Note: At study centers where a single informed consent form is used, informed consent to participate in any maintenance cohort will have already been provided at study entry. Patients enrolled at centers using two informed consent forms must provide maintenance cohort-specific consent after cohort assignment and prior to cohort-specific eligibility assessments other than eligibility assessments already conducted as part of routine care.

2. Inability to swallow pills
3. Left ventricular ejection fraction (LVEF) < 50% as assessed after completion of induction treatment by either 2D echocardiogram (ECHO) or multiple-gated acquisition (MUGA) (ECHO is the preferred method).
4. Clinically significant cardiovascular disease, including unstable angina, history of or active congestive heart failure of ≥ NYHA Grade 2, history of or ongoing serious cardiac arrhythmia requiring treatment (except for controlled atrial fibrillation and/or paroxysmal supraventricular tachycardia).
5. Current uncontrolled hypertension (systolic > 150 mmHg and/or diastolic > 100 mmHg) with or without medication
6. Current dyspnoea at rest due to complications of advanced malignancy or other disease requiring continuous oxygen therapy
7. Insulin-dependent diabetes
8. Current known infection with HIV, HBV, or HCV (active infection or carriers)
9. Requirement for concurrent use of the antiviral agent sorivudine (antiviral) or chemically related analogues, such as brivudine
10. Malabsorption syndrome, disease significantly affecting gastrointestinal function, resection of the stomach or small bowel, or ulcerative colitis
11. Known hypersensitivity to murine proteins

Additional Criteria for Cohort 4

1. Have not provided informed consent to participate in Cohort 4

   Note: At study centers where a single informed consent form is used, informed consent to participate in any maintenance cohort will have already been provided at study entry. Patients enrolled at centers using two informed consent forms must provide maintenance cohort-specific consent after cohort assignment and prior to cohort-specific eligibility assessments other than eligibility assessments already conducted as part of routine care.

2. Inability to swallow medications
3. Known hypersensitivity or allergy to Chinese hamster ovary cell products

4. History of autoimmune disease including but not limited to myasthenia gravis, myositis, autoimmune hepatitis, systemic lupus erythematosus, rheumatoid arthritis, inflammatory bowel disease, vascular thrombosis associated with antiphospholipid syndrome, Wegener's granulomatosis, Sjögren's syndrome, Guillain-Barré syndrome, multiple sclerosis, vasculitis, or glomerulonephritis (see Appendix 9 for a more comprehensive list of autoimmune diseases)

   Patients with the following are eligible:

   - a history of autoimmune-related hypothyroidism on a stable dose of thyroid replacement hormone
   - controlled Type 1 diabetes mellitus on a stable insulin regimen
   - eczema, psoriasis, lichen simplex chronicus, or vitiligo with dermatologic manifestations only (e.g. patients with psoriatic arthritis would be excluded) are permitted provided that they meet the following conditions:
     - rash must cover less than 10% of body surface area (BSA)
     - disease is well controlled prior to randomization and only requires low potency topical steroids
     - no acute exacerbations of underlying condition within the previous 12 months (not requiring PUVA [psoralen plus ultraviolet A radiation], methotrexate, retinoids, biologic agents, oral calcineurin inhibitors, high potency or oral steroids)
5. History of idiopathic pulmonary fibrosis (including pneumonitis), drug-induced pneumonitis, organizing pneumonia (i.e., bronchiolitis obliterans, cryptogenic organizing pneumonia), or evidence of active pneumonitis on most recent chest imaging (CT scan or MRI)

   Note: History of radiation pneumonitis in the radiation field (fibrosis) is permitted.
6. Malabsorption condition that would alter the absorption of orally administered medications
7. Amylase or lipase ≥ 1.5 × ULN within 14 days prior to maintenance treatment initiation
8. Serum albumin < 2.5 g/dL
9. LVEF < institutional lower limit of normal or < 50%, whichever is lower.
10. Poorly controlled hypertension, defined as a blood pressure consistently above 150/90 mmHg despite optimal medical management.
11. Uncontrolled pleural effusion, pericardial effusion or ascites requiring repeated drainage more than once every 28 days. Indwelling drainage catheters (e.g. PleurX®) are allowed.
12. Unstable angina, new onset angina within last 3 months, myocardial infarction within last 6 months and current congestive heart failure ≥ NYHA Grade 2
13. History of stroke, reversible ischemic neurological defect, or transient ischemic attack within 6 months prior to initiation of maintenance treatment
14. History or evidence of intracranial hemorrhage or spinal cord hemorrhage
15. Evidence of clinically significant vasogenic edema
16. Any hemorrhage or bleeding event ≥ NCI CTCAE Grade 3 within 28 days prior to initiation of maintenance treatment
17. History or evidence of retinal pathology on ophthalmologic examination that is considered a risk factor for central serous retinopathy, retinal vein occlusion, or neovascular macular degeneration

    Patients will be excluded if they currently have any of the following risk factors for retinal vein occlusion:

    - Uncontrolled glaucoma with intra ocular pressure ≥ 21 mmHg
    - Uncontrolled hypercholesterolemia > 300 mg/dL or 7.75 mmol/L
    - Uncontrolled hypertriglyceridemia > 300 mg/dL or 3.42 mmol/L
    - Fasting hyperglycemia > 160 mg/dL or 8.9 mmol/L

18. Positive HIV test
19. Active hepatitis B (defined as having a positive HBsAg test prior to randomization) or hepatitis C

    Note: Patients with past HBV infection or resolved HBV infection (defined as having a negative HBsAg test and a positive anti-HBc antibody test) are eligible.

    Patients positive for HCV antibody are eligible only if PCR is negative for HCV RNA.
20. Active tuberculosis
21. Severe infection within 4 weeks prior to start of maintenance treatment including, but not limited to, hospitalization for complications of infection, bacteremia, or severe pneumonia; has signs or symptoms of significant infection or has received oral or IV antibiotics within 2 weeks prior to start of maintenance treatment.

    Note: Patients receiving prophylactic antibiotics (e.g. for prevention of a urinary tract infection or chronic obstructive pulmonary disease) are eligible.
22. Prior allogeneic bone marrow transplantation or prior solid organ transplantation
23. Administration of a live, attenuated vaccine within 4 weeks prior to start of study maintenance treatment or anticipation that such a live attenuated vaccine will be required during the study
24. Prior treatment with CD137 agonists, anti-CTLA4, anti-PD-1, or anti-PD-L1 therapeutic antibody or pathway-targeting agents
25. Prior treatment with a MEK or ERK inhibitor
26. Treatment with systemic immunostimulatory agents (including but not limited to interferons or interleukin-2) within 4 weeks or five half-lives of the drug, whichever is longer, prior to start of study maintenance treatment
27. Treatment with systemic corticosteroids or other systemic immunosuppressive medications (including but not limited to prednisone, dexamethasone, cyclophosphamide, azathioprine, methotrexate, thalidomide, and anti-TNF agents) within 2 weeks prior to start of study maintenance treatment, or requirement for systemic immunosuppressive medications during the trial.

    Note: The use of inhaled corticosteroids for chronic obstructive pulmonary disease (≤ 10 mg oral prednisone or equivalent), and mineralocorticoids (e.g., fludrocortisone) for patients with orthostatic hypotension, and low-dose supplemental corticosteroids for adrenocortical insufficiency are allowed.

    Note: Patients who have received acute, low-dose (≤ 10 mg oral prednisone or equivalent), systemic immunosuppressant medications (e.g. a one-time dose of dexamethasone for nausea) may be enrolled in the study after discussion with and approval by the Medical Monitor.
28. If receiving a RANKL inhibitor (e.g. denosumab), unwilling to adopt alternative treatment such as (but not limited to) bisphosphonates, while receiving atezolizumab.
29. Consumption of foods, supplements or drugs that are potent CYP3A4 enzyme inducers or inhibitors ≤ 7 days before initiation of study maintenance treatment or expected concomitant use during maintenance treatment. These include St. John's wort or hyperforin (potent CYP3A4 enzyme inducer) and grapefruit juice (potent cytochrome P450 CYP3A4 enzyme inhibitor).

Length of Study

Study recruitment started in April 2015. Patient screening was temporarily suspended beginning in June 2016 for the addition of maintenance Cohorts 3 and 4. Screening and enrolment were again suspended in February 2018 to accommodate closure of accrual to Cohort 4. Study enrolment will not be re-opened. The entire study duration is estimated to be approximately 5 years.

End of Study

The end of the study is defined as the date when all study patients have discontinued study treatment and completed the adverse event reporting period and, if applicable, cohort-specific post-treatment follow-up safety assessments (see protocol Section 5.3.1 for adverse event reporting periods and post-treatment follow-up safety assessments). After this, the trial will end and no further data will be collected in the clinical database for this study.

Continued access to Roche investigational medicinal products (IMPs) used in the study will be in accordance with the Roche Global Policy on Continued Access to Investigational Medicinal Product.

Efficacy Outcome Measures

All Cohorts

Efficacy outcome measures will be assessed within each cohort (experimental arm vs. control arm) during the Maintenance Treatment Phase.

Primary

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

Secondary

- 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. Response will be determined by the Investigator according to RECIST 1.1 based on comparisons to the tumour assessment done at the end of the Induction Treatment Phase.
- DCR (defined as CR, PR or SD) during the Maintenance Treatment Phase. Response will be determined by the Investigator according to RECIST 1.1 based on comparisons to the tumour assessment done at the end 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

Safety Outcome Measures

All Cohorts

The safety outcome measures for this study are as follows:

- Incidence, nature and severity of all adverse events (graded according to NCI CTCAE v4.0)
- Incidence and nature of all Grade 3 – 5 AEs
- Grade 5 AEs or AEs leading to death on study treatment
- All SAEs
- Incidence and reasons for any premature discontinuation of any component of study treatment

- Incidence and reasons for any dose reductions or interruptions of any component of study treatment
- AEs of special interest
- Clinically significant changes in laboratory values

Adverse events 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 Outcome Measures

Cohorts 2 and 4- Experimental Arms Only

PFS in patients treated with atezolizumab defined as the time from randomisation into the Maintenance Treatment Phase until disease progression per Investigator assessment using mRECIST or death from any cause, whichever occurs first.

All Cohorts

The exploratory biomarker and microbiome outcome measures for this study include molecular markers/marker profiles and efficacy and/or safety outcomes. Efficacy outcomes considered for this analysis may include, but are not limited to, ORR, PFS and OS, as appropriate. Biomarkers, biomarker profiles and microbiomes may be assessed using various methodologies including, but not limited to, immunohistochemistry (single and multiplex), RNA and DNA analysis (e.g polymerase chain reaction; next generation sequencing; and mutation, expression and microsatellite instability analyses) of tumour and blood samples collected from all study patients as well as additional tumour samples and stool samples collected from patients participating in the Supplemental Biomarker Program.

Study Treatment

Induction Treatment Phase

All Cohorts

All patients will receive 4 months of study treatment in the Induction Treatment Phase. Treatment during this phase, based on Investigator's choice, will be either:

- eight 2-week cycles of 5-FU/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

and should be in accordance with locally approved prescribing information including any recommendations for pre-treatment (i.e. antiemetic therapies). The Investigator will select the FOLFOX regimen (e.g. FOLFOX-4, FOLFOX-6, modified FOLFOX-6, FOLFOX-7 or modified FOLFOX-7; see Appendix 6) also in accordance with local standards.

Maintenance Treatment Phase

All Cohorts

Each cohort will contain an experimental treatment arm based specifically on the patient's biomarker status based on the patient's archival tumour sample from the initial diagnosis (see Appendix 17 for additional details on cohort assignment). Patients with an adequate tumour sample but with unknown

biomarker status due to lack of determinant result (e.g. due to technical issues) may still be eligible depending on the addition of future cohorts. Each cohort will also include a control treatment arm containing a fluoropyrimidine and bevacizumab. Maintenance treatment will begin within 3 weeks of completing induction treatment.

For patients in Cohorts 1 and 3, and the control arms of Cohorts 2 and 4, study treatment during the Maintenance Treatment Phase will continue until disease progression (based on Investigator's assessment according to RECIST 1.1), unacceptable toxicity, initiation of another anti-cancer therapy, patient or physician decision to discontinue, or patient death, whichever occurs first.

For patients randomised to the experimental arms of Cohorts 2 and 4 (i.e. patients who are receiving atezolizumab), study treatment during the Maintenance Treatment Phase may continue after the first tumour assessment showing progression per RECIST 1.1 as long as they meet the following criteria as assessed by the Investigator:

- Evidence of clinical benefit
- Absence of symptoms and signs (including worsening of laboratory values, e.g. new or worsening hypercalcaemia) indicating unequivocal progression of disease
- No decline in ECOG performance status that can be attributed to disease progression
- Absence of tumour progression at critical anatomical sites (e.g. leptomeningeal disease) that cannot be managed by protocol-allowed medical interventions

Treatment should be discontinued if the next follow-up tumour assessment continues to demonstrate progression per RECIST 1.1 (as compared to the assessment at the end of induction treatment). If the next tumour assessment does not show progression per RECIST 1.1, the patient may continue maintenance treatment until such time as the treatment continuation criteria above are no longer met and/or two sequential tumour assessments show progression per RECIST 1.1.

Atezolizumab treated patients may be discontinued from study treatment during the Maintenance Phase for the following reasons other than loss of clinical benefit or persistent progression: unacceptable toxicity, initiation of another anti-cancer therapy, patient or physician decision to discontinue, or patient death, whichever occurs first.

Dose reductions or interruptions of IMPs are only allowed as recommended in the applicable Investigator's Brochure. If any drug of any study treatment regimen in either the Induction or Maintenance Treatment Phase is discontinued or held for > 21 days, approval from the Medical Monitor will be required before treatment can be re-initiated. If Medical Monitor approval is not obtained, the patient will come off all study treatment and will enter the Post-Treatment Follow-up Phase.

All Cohorts - Control Arms

The maintenance treatment regimen is the same for the control arms of all cohorts.

Fluoropyrimidine (5-FU/LV or capecitabine): dose and schedule will be according to local label, where applicable, or otherwise will be determined per the Investigator's discretion. Administration should be according to local prescribing information.

Bevacizumab: 5 mg/kg via 15 – 30 minute IV infusion on Day 1 of every 2-week cycle. Bevacizumab should be prepared and administered in accordance with local prescribing information.

Cohort 1 – Experimental Arm

Patients assigned to the experimental arm of Cohort 1 with an ECOG PS = 2 and a low BMI must be carefully assessed by the Investigator for physical fitness adequate for receipt of this regimen prior to initiating treatment. Such patients must be closely monitored through the maintenance treatment period.

5-FU: The first six patients in this cohort received 1,600 mg/m² 5-FU administered via 46-hour IV infusion, in combination with LV 400 mg/m² administered via 2-hour infusion, on Day 1 of every 2-week cycle. Subsequent patients in this cohort will receive 1,600 – 2,400 mg/m² 5-FU administered via 46-hour IV infusion (IV bolus is not permitted), in combination with LV 400 mg/m² administered via 2-hour infusion, on Day 1 of every 2-week cycle.

Cetuximab: The dose and scheduling of cetuximab is 500 mg/m² via IV infusion on Day 1 of every 2-week cycle. Cetuximab must be administered in hospital under the supervision of a physician experienced in the use of antineoplastic medicinal products. Cetuximab must be administered via infusion pump or syringe pump at a rate not exceeding 5 mg/min for the first administration and 10 mg/min for subsequent administrations. Close monitoring is required during the infusion and for at least 1 hour after the end of the infusion. Availability of resuscitation equipment must be ensured. Prior to the first infusion of cetuximab, patients must receive premedication with an antihistamine and a corticosteroid. This premedication is recommended prior to all subsequent infusions. Refer to cetuximab Package Insert (Appendix 14).

Vemurafenib: The dose and scheduling of vemurafenib is 960 mg b.i.d by mouth. Vemurafenib should be taken at approximately the same times each day, the first dose is to be taken in the morning and the second dose is to be taken approximately 12 hours later in the evening. Each dose should always be taken in the same manner i.e. either with or without a meal. Missed doses will not be made up.

Note: A safety run-in review of the first six patients treated with the experimental combination of '5-FU/LV + cetuximab + vemurafenib' was conducted in February 2016. The iDMC recommended that patients allocated to this regimen may now receive 5-FU at doses up to 2,400 mg/m². The iDMC will continue to monitor initial patients in this regimen treated with 5-FU doses ≥ 1,600 mg/m² and have also recommended that patients with ECOG PS = 2 and a low BMI be carefully assessed by the Investigator for physical fitness adequate for receipt of this regimen.

Cohort 2 - Experimental Arm

Fluoropyrimidine (5-FU/LV or capecitabine): 1,600 – 2,400 mg/m² 5-FU administered via 46-hour IV infusion (IV bolus is not permitted) on Day 1 of every 2-week cycle, and LV 400 mg/m² administered via a 2-hour infusion on day 1 every 2 weeks; or 1000 mg/m² twice-daily capecitabine (b.i.d.) by mouth given days 1-14 every 2 weeks followed by a one-week treatment break.

Bevacizumab: The dose and schedule of bevacizumab is 5 mg/kg via 15 – 30 minute IV infusion on Day 1 of every 2-week cycle. Bevacizumab should be prepared and administered in accordance with local prescribing information. Patients may be at risk of developing infusion / hypersensitivity reactions with bevacizumab. Close observation of the patient during and following the administration of bevacizumab is recommended as expected for any infusion of a therapeutic humanised monoclonal antibody. If a reaction occurs, the infusion should be discontinued and appropriate medical therapies should be administered. A systematic premedication is not warranted.

Atezolizumab: Atezolizumab is administered at a fixed dose of 800 mg via 60-minute IV infusion on Day 1 of every 2-week cycle. Atezolizumab must be administered in hospital under the supervision of a physician experienced in the use of antineoplastic medicinal products. For the first infusion, the patient's vital signs (heart rate, respiratory rate, blood pressures, and temperature) should be determined within 60 minutes before the infusion, every 15 ± 5 minutes during the infusion, and 30 ± 10 minutes after the infusion. For subsequent infusions, vital signs will be collected within 60 minutes before the infusion and should be collected during or after the infusion if clinically indicated or if symptoms occurred in the prior infusion. If the initial infusion is well tolerated, subsequent infusions will be done over a 30-minute time period. No premedication is indicated for the first dose of atezolizumab. Patients who experience an infusion-related reaction with Cycle 1 of atezolizumab may receive premedication with antihistamines or

antipyretics/analgesics (e.g. acetaminophen) for subsequent infusions. The rate of atezolizumab infusion should be modified in the event of an infusion-related reaction.

Cohort 3 - Experimental Arm

Capecitabine, trastuzumab and pertuzumab will be administered according to the doses and schedules described below. For the first treatment cycle, pertuzumab should be administered on Day 1, followed by the first dose of trastuzumab and capecitabine on Day 2. If the administration of all three agents is well tolerated in the first treatment cycle, they may be given sequentially on Day 1 (pertuzumab and trastuzumab should not be mixed in the same infusion bag) in subsequent cycles thereafter. If a patient cannot tolerate all three drugs given on the same day, pertuzumab should continue to be delivered on Day 1, with trastuzumab and capecitabine delivered on Day 2 for subsequent treatment cycles.

Capecitabine: 1000 mg/m^2 twice-daily capecitabine (b.i.d.; for a total daily dose of 2000 mg/m^2) by mouth given days 1-14 every 2 weeks followed by a one-week treatment break administered in accordance with local prescribing information. See Appendix 7 for capecitabine dose calculations by body surface area with corresponding tablet counts.

Trastuzumab: Trastuzumab is administered by IV infusion on Day 1 of every 3-week treatment cycle at an initial loading dose of 8 mg/kg followed by 6 mg/kg for subsequent doses. Trastuzumab must be administered in hospital under the supervision of a physician experienced in the use of antineoplastic medicinal products. The first infusion should be delivered over 90 minutes followed by a 60 minute observation period. If the first infusion is well tolerated without infusion-associated AEs, the second and subsequent infusions may be delivered over 30 minutes with an observation period of 30 minutes. Longer infusion and/or observation times can be maintained if there is any doubt about tolerability. No premedication will be allowed for the first dose of trastuzumab. Premedication may be administered for subsequent cycles at the discretion of the treating physician. The rate of trastuzumab infusion should be modified in the event of an infusion-related reaction.

Pertuzumab: Pertuzumab is administered by IV infusion on Day 1 of each 3-week treatment cycle at an initial fixed loading dose of 840 mg followed by 420 mg for subsequent doses. Pertuzumab must be administered in hospital under the supervision of a physician experienced in the use of antineoplastic medicinal products. The first infusion should be delivered over 60 minutes followed by a 60 minute observation period. The observation period for subsequent infusions may be between 30 and 60 minutes if the first infusion is well tolerated without infusion-associated AEs. No premedication will be allowed for the first dose of pertuzumab. Premedication may be administered for subsequent cycles at the discretion of the treating physician. The rate of pertuzumab infusion should be modified in the event of an infusion-related reaction.

Cohort 4 - Experimental Arm

In an Urgent Safety Measure Letter dated July 25, 2018, the Sponsor advised investigators to strongly consider discontinuing treatment in any Cohort 4 patients receiving experimental treatment. Investigators were advised to discuss appropriate next treatment options, including combination treatment with a fluoropyrimidine plus bevacizumab, with patients discontinuing experimental treatment. Please refer to protocol Section 3.1.2.4 for further details of the basis for Sponsor decisions for Cohort 4 and management of ongoing patients randomized to the experimental arm.

Cobimetinib: Cobimetinib is administered orally at a dose of 60 mg for 3 weeks followed by a 1 week treatment break (21/7 schedule). Treatment cycle length in this arm is 2 weeks. Cobimetinib will be administered daily every day of each odd numbered 2-week treatment cycle, and for the first 7 days only of each even numbered 2-week treatment cycle. Cobimetinib should be taken at the same time every day with or without food. If a dose is missed or vomiting occurs when a dose is taken, dosing should be resumed at the next scheduled dose.

Atezolizumab: Atezolizumab is administered at a fixed dose of 840 mg via 60-minute IV infusion on Day 1 of every 2-week cycle. Atezolizumab must be administered in hospital under the supervision of a physician experienced in the use of antineoplastic medicinal products. For anaphylaxis precautions, see Appendix 16. For the first infusion, the patient's vital signs (heart rate, respiratory rate, blood pressures, and temperature) should be determined within 60 minutes before the infusion, every 15 ± 5 minutes during the infusion, and 30 ± 10 minutes after the infusion. For subsequent infusions, vital signs will be collected within 60 minutes before the infusion and should be collected during or after the infusion if clinically indicated or if symptoms occurred in the prior infusion. If the initial infusion is well tolerated, subsequent infusions will be done over a 30-minute time period. No premedication is indicated for the first dose of atezolizumab. Patients who experience an infusion-related reaction with Cycle 1 of atezolizumab may receive premedication with antihistamines or antipyretics/analgesics (e.g. acetaminophen) for subsequent infusions. The rate of atezolizumab infusion should be modified in the event of an infusion-related reaction.

Post-Treatment Follow-up Phase

All Cohorts

Second-line treatment during the Post-Treatment Follow-up Phase is at the Investigator's discretion. However, patients who received atezolizumab should not receive other immunomodulatory agents for 10 weeks after maintenance treatment discontinuation.

$BRAF^{mut}$ Patients and Early Disease Progression

Exceptionally, $BRAF^{mut}$/MSS patients experiencing early disease progression during the induction treatment will have the option of proceeding immediately to receive second-line treatment with 5-FU/LV, cetuximab and vemurafenib. These patients will be followed for safety and efficacy in accordance with the Maintenance Treatment Phase Schedule of Assessments (including eligibility, biomarker sampling and post-treatment follow-up) for Cohort 1 (see Appendix 2) and will be managed according to protocol recommendations and requirements for the experimental arm of Cohort 1.

Similarly, $BRAF^{mut}$/MSI-H patients experiencing early disease progression during induction treatment will have the option of proceeding immediately to receive second-line treatment with a fluoropyrimidine (5-FU/LV or capecitabine), bevacizumab, and atezolizumab. These patients will be followed for safety and efficacy in accordance with the Maintenance Treatment Phase Schedule of Assessments (including eligibility, biomarker sampling and post-treatment follow-up) for Cohort 2 (see Appendix 3) and will be managed according to protocol recommendations and requirements for the experimental arm of Cohort 2.

Investigational Medicinal Products

The IMPs used in this study include:

- all non-fluoropyrimidine agents comprising the experimental arms of each maintenance treatment cohort (i.e. cetuximab and vemurafenib in Cohort 1, bevacizumab and atezolizumab in Cohort 2, trastuzumab and pertuzumab in Cohort 3, cobimetinib and atezolizumab in Cohort 4)
- bevacizumab in the Induction Treatment Phase
- bevacizumab in the control arms of each maintenance treatment cohort
- cetuximab, vemurafenib, bevacizumab and atezolizumab administered as optional second-line treatments to early progressing $BRAF^{mut}$ patients

Non-Investigational Medicinal Products

Non-IMPs used in this study include all fluoropyrimidine agents (i.e. 5-FU and capecitabine) and leucovorin administered during the Induction and Maintenance Treatment Phases and as optional

second-line treatment to early progressing BRAF^{mut} patients. Oxaliplatin administered as part of induction treatment is also considered a non-IMP.

Statistical Methods

All Cohorts

The cohorts will be based on different biomarkers (see Appendix 17), with each cohort consisting of an experimental treatment arm and a control arm. The inclusion of a control group allows discrimination of patient outcomes caused by the experimental treatment from outcomes caused by other factors. Randomisation avoids systematic differences (bias) between the groups with respect to known or unknown baseline variables that could affect outcome. The treatment for patients in the control arms represents standard of care.

The primary objective of the study is to evaluate PFS per RECIST 1.1 within each cohort.

Provided the iDMC does not recommend discontinuation of enrolment to a cohort or enrolment is not otherwise discontinued prior to a cohort reaching its target sample size, the primary analysis will occur for each cohort when the target number of PFS events has been reached. Secondary endpoints will also be summarised at this time. Analyses of any cohort closed to accrual before its target sample size is reached will be described in an SAP and will depend on accrual at the time of closure.

Update on statistical analysis plans and cohort status following premature closure of study enrolment: Accrual to Cohort 2 was completed in November 2016. Accrual to Cohort 4 was closed in February 2018 due to iDMC recommendations as a result of an unfavourable benefit-risk evaluation (see protocol Section 3.1.2.4). Study enrolment was suspended at the time of discontinuation of accrual to Cohort 4 (February 2018) and will remain permanently closed to further enrolment. Cohorts 1, 3 and 4 will not reach their target sample size. As originally planned for cohorts reaching their target number of PFS events (applies to Cohort 2 only), an update analysis of efficacy and safety parameters will be conducted based on 24 months survival follow-up after the clinical cut-off date (CCOD) for the primary analysis. The CCOD for the Cohort 2 primary analysis was May 31, 2017. The Cohort 2 update analysis will be conducted based on a CCOD of May 31, 2019. The primary analysis for cohorts 1, 3 and 4 will be conducted at the same time as the Cohort 2 update analysis (i.e. based on the same CCOD of May 31, 2019).

The final study analysis for all cohorts will be conducted after all patients in the study have discontinued study treatment and completed the adverse event reporting period and any applicable post-treatment follow-up safety assessments (see protocol Section 5.3.1 for adverse event reporting periods and post-treatment follow-up safety assessments). Data will be summarised using appropriate summary statistics: mean, standard deviation, median, quartiles and range (minimum and maximum) for continuous variables, and number and percentage for categorical variables.

Analysis Populations

For each cohort, the Intent-To-Treat (ITT) Population will include patients entered into the Maintenance Treatment Phase of the study, irrespective of whether or not they received study medication. In this population, patients will be allocated to the study maintenance treatment into which they were randomised. The ITT Population will be used for all efficacy analyses.

The Per Protocol Population will not be defined for this study but major protocol violations will be listed.

The Safety Population will include all patients who received at least one dose of study medication during the Induction or Maintenance Treatment Phases. Patients will be allocated to the treatment regimen that they actually received. The Safety Population will be used for all safety analyses.

Statistical Hypotheses

Cohorts 1 and 3

The null and alternative hypotheses when comparing PFS between the two randomised treatments in Cohort 1 (Arm A: 5-FU/LV with cetuximab and vemurafenib vs. Arm B: fluoropyrimidine and bevacizumab) and in Cohort 3 (Arm A: capecitabine with trastuzumab and pertuzumab vs. Arm B: fluoropyrimidine and bevacizumab) are:

H_0: the distribution of the PFS time is the same in the two treatment groups

PFS (Arm A) = PFS (Arm B)

H_1: the distribution of the PFS time is different in the two treatment groups

specifically PFS (Arm A) > PFS (Arm B)

If the hazard ratio (HR) of Arm A compared to Arm B is assumed to be constant over time, then the null and alternative hypotheses are:

H_0: HR = 1 vs. H_1: HR < 1

Due to the relatively low prevalence of mCRC patients with HER2+ or $BRAF^{mut}$ disease, the formal statistical tests for Cohorts 1 and 3 will be one-sided and performed at an alpha level (type I error rate) of 10%.

Cohorts 2 and 4

The null and alternative hypotheses when comparing PFS between the two randomised treatments in Cohort 2 (Arm A: fluoropyrimidine with bevacizumab and atezolizumab vs. Arm B: fluoropyrimidine and bevacizumab) and in Cohort 4 (Arm A: cobimetinib with atezolizumab vs. Arm B: fluoropyrimidine and bevacizumab) are:

H_0: the distribution of the PFS time is the same in the two treatment groups

PFS (Arm A) = PFS (Arm B)

H_1: the distribution of the PFS time is different in the two treatment groups

PFS (Arm A) ≠ PFS (Arm B)

If the HR of Arm A compared to Arm B is assumed to be constant over time, then the null and alternative hypotheses are:

H_0: HR = 1 vs. H_1: HR ≠ 1

The formal statistical tests for Cohorts 2 and 4 will be two-sided and performed at an alpha level (type I error rate) of 5%.

Primary Endpoint

All Cohorts

The primary efficacy endpoint of PFS is defined as the time from randomisation into the Maintenance Treatment Phase until disease progression per Investigator assessment using RECIST 1.1 or death from any cause, whichever occurs first. Tumour size will be calculated using the sum of the longest diameters of all target lesions, and reduction will be based on comparisons to the tumour assessment done at the end of the Induction Treatment Phase.

Patients without an event will be censored at the date of their last evaluable tumour assessment or, if this is not available, at the date of randomisation. For each cohort, the primary analysis of PFS will occur when the target number of PFS events has been reached.

Within each cohort, PFS will be presented graphically for each treatment group using the Kaplan-Meier method. Estimates and the corresponding 95% confidence interval will be reported by treatment group for median survival time, and for the 4-, 6- and 12-month PFS rates.

Within each cohort, the comparison of PFS between the treatment groups will be performed using an unstratified log-rank test. In addition, a Cox regression will be performed with treatment and applicable stratification variables (biomarkers, geographic region and/or response after induction treatment) as terms in the model. The estimated hazard ratio and its corresponding 95% confidence interval will be presented.

The timing and methods of the primary efficacy endpoint analyses for any cohort closed to accrual before its target sample size is reached may differ from above. These will be described in the SAP applicable to the cohort and will depend on accrual at the time of early closure.

Secondary Efficacy Endpoints

All Cohorts

The secondary efficacy endpoints for each cohort are OS, ORR, DCR, TTR, DoR and ECOG performance status.

OS is defined as the time from randomisation until death from any cause. Patients who are still alive at the time of analysis (clinical cut-off) and patients who are lost to follow-up will be censored at their last clinical assessment date.

Best overall response will be assessed for all patients after randomisation until disease progression. ORR will be calculated as the proportion of patients with a best overall response of CR or PR determined according to RECIST 1.1. ORR will be summarised and presented along with the 95% Clopper-Pearson confidence interval.

DCR will be calculated as the proportion of patients with a best overall response of CR, PR or SD as determined according to RECIST 1.1. DCR will be summarised and presented along with the 95% Clopper-Pearson confidence interval.

TTR will be calculated as the time from randomisation to the first occurrence of a documented objective response (CR or PR) determined according to RECIST 1.1.

DoR will be assessed for all patients after randomisation until PD. Only patients with a best overall response of CR or PR per RECIST 1.1 are considered responders. The duration of response is the time from the first assessment of CR or PR until disease progression or death from any cause, whichever occurs first.

The secondary time-to-event endpoints will be analysed by the same methods and at the same time as the primary endpoint.

ECOG performance status will be summarised over time.

Safety Endpoints

All Cohorts

Verbatim adverse event (AE) data will be mapped to Medical Dictionary for Regulatory Activities (MedDRA) thesaurus terms.

All treatment-emergent AEs occurring during or after the first dose of study medication will be summarised by treatment group in frequency tables, as follows:

- By preferred term and system organ class
- By severity of all adverse events (graded according to NCI CTCAE v4.0)
- Grade 3 – 5 AEs
- Grade 5 AEs or AEs leading to death on study treatment

- All SAEs
- AEs leading to premature discontinuation of any component of study treatment
- AEs leading to dose reduction or interruption of any component of study treatment
- AEs of special interest

The above safety data will be summarised separately for the Induction and Maintenance Treatment Phases overall and by individual maintenance treatment cohort.

Deaths reported during the study treatment period and those reported during follow-up after treatment completion/discontinuation will be summarised.

Study medication exposure will be separately summarised by number of cycles, duration, dose and dose intensity.

Vital signs data, clinical laboratory parameters, concomitant medication and subsequent anti-cancer therapy will also be summarised.

Analysis for Exploratory Outcome Measures

Cohorts 2 and 4 - Experimental Arms Only

The exploratory efficacy endpoint of PFS in patients treated with atezolizumab is defined as the time from randomisation into the Maintenance Treatment Phase until disease progression per Investigator assessment using mRECIST or death from any cause, whichever occurs first. Patients without an event will be censored at the date of their last evaluable tumour assessment or, if this is not available, at the date of randomisation. PFS may be presented graphically using the Kaplan-Meier method. Estimates and the corresponding 95% confidence interval may be reported for the 4-, 6- and 12-month PFS rates.

All Cohorts

Biomarker analyses will be of exploratory nature only, utilizing all available data obtained from archival tumour samples from initial diagnoses, all tumour and blood samples collected during the study (including additional tumour samples collected from Supplemental Biomarker Program participants), and stool samples collected during the study from Supplemental Biomarker Program participants. These analyses will be of exploratory nature only, using descriptive methods with no fixed hypotheses testing.

With the ongoing analyses of the study's various biomarker-based cohorts, more information on the concordance of different biomarkers will be collected and summarised. Relevant findings will be discussed with the study's SC in order to conduct further exploratory biomarker analyses accordingly.

Interim Analyses

The iDMC will evaluate accumulating safety and efficacy data within each cohort to assure these data continue to support an early positive benefit-risk ratio and to confirm that continued enrolment into each cohort is appropriate. The amount of efficacy data to be assessed in a given cohort will be determined by the iDMC at a preceding iDMC meeting. Details of this process are described in the iDMC charter. Decisions on what efficacy data have to be evaluated for each cohort will be documented in the iDMC meeting minutes. In addition, the iDMC will review data from any safety run-in patients required for an experimental regimen (e.g. as conducted for the initial patients treated with the experimental combination of '5-FU/LV + cetuximab + vemurafenib'). These safety run-ins will be specified in the protocol.

Determination of Sample Size

Before study enrolment was closed prematurely, approximately 1,820 patients were expected to be screened and approximately 1,400 patients were expected to be enrolled in the Induction Treatment Phase of the study in order to randomise the planned number of patients in each of the maintenance

cohorts (see Table 1). Cohort 2 reached its target sample size and was closed to further accrual. Cohort 4 was closed to accrual with 99 patients randomized (i.e. prior to reaching the target sample size per Table 1). Due to early closure of study enrolment, target sample sizes will not be reached in Cohort 1 (final n=60) or Cohort 3 (final n=5).

Within each cohort, the required sample size is based on the comparison of PFS between the treatment groups and an assumed recruitment period of 11 months for Cohorts 2 and 4. Median PFS assumed for each cohort and treatment arm are shown in Table 1.

Table 1: PFS and Sample Size Estimates per Cohort

Cohort	Median PFS (months)		Target Sample Size
	Experimental treatment group	Control group (FP and bevacizumab)	
Cohort 1	7	4.9	126
Cohort 2	11.5	7.5	405
Cohort 3	11.5	7.5	90
Cohort 4	11.5	7.5	405

Additional details of the sample size calculation inputs are found in the statistical section of the protocol.

Appendix 2: Schedule of Assessments for All Patients (Screening / Baseline and Induction Treatment Phase)

					Patients who have PD during or at end of Induction Treatment Phase or who refuse Maintenance Treatment or who are not eligible for any study cohort	
	Screening / Baseline		Induction Treatment Phase [a]		Study Treatment Discontinuation Visit [b]	Post-Treatment Follow-Up Phase [c]
	≤ 28 days	≤ 7 days	Day 1 Cycle 1	Every 2 cycles (every 4 weeks)	(≤ 30 days after last dose of study treatment)	Every 3 months *until May 31, 2019 (see Appendix 19)*
Informed consent [d]	x					
Confirmation of general eligibility [e]	x	x		As required		
Demographics and medical history [f]	x					
Vital signs and weight [g]	x	x	x	x	x	
Physical examination[h]	x		x	x	x	
ECOG performance status [i]		x	x	x	x	
Concomitant medications [j]	x	x	x	x	x	
Haematology and blood chemistry [k]		x		x	x	
INR, aPTT (select patients) [l]		x		x		
Urinalysis (dipstick) [m]		x		x	x	
Pregnancy test [n]		x		If clinically indicated		
Tumour assessments [o]	x			Mandatory at end of Induction Treatment Phase		According to local standard of care until disease progression

					Patients who have PD during or at end of Induction Treatment Phase or who refuse Maintenance Treatment or who are not eligible for any study cohort	
	Screening / Baseline		Induction Treatment Phase [a]		Study Treatment Discontinuation Visit [b]	Post-Treatment Follow-Up Phase [c]
	≤ 28 days	≤ 7 days	Day 1 Cycle 1	Every 2 cycles (every 4 weeks)	(≤ 30 days after last dose of study treatment)	Every 3 months *until May 31, 2019 (see Appendix 19)*
Archival primary tumour tissue for biomarker assessment [p]	x					
Metastatic tumour tissue for exploratory biomarker assessment [q] Collection of these samples discontinued as of May 2018	No sample collection			No sample collection Supplemental Biomarker Program CLOSED		
Whole blood sample [r]			x			
Plasma samples [r]			x	Cycles 4, 6 and 8		At time of progression (if patient has not yet progressed)
Stool sample Supplemental Biomarker Program closed as of May 2018. Collection of these samples has been discontinued.	No sample collection Supplemental Biomarker Program CLOSED				No sample collection Supplemental Biomarker Program CLOSED	
Adverse events (including SAEs) [s]	x	x	x	Every cycle	x	x (as applicable)
Study medication administration [t]			x Administered every 2 weeks			

					Patients who have PD during or at end of Induction Treatment Phase or who refuse Maintenance Treatment or who are not eligible for any study cohort	
	Screening / Baseline		Induction Treatment Phase [a]		Study Treatment Discontinuation Visit [b]	Post-Treatment Follow-Up Phase [c]
	≤ 28 days	≤ 7 days	Day 1 Cycle 1	Every 2 cycles (every 4 weeks)	(≤ 30 days after last dose of study treatment)	Every 3 months *until May 31, 2019 (see Appendix 19)*
Subsequent anti-cancer therapies (see [c])						x
Patient survival (see [c])					x	x

a. With the exception of Cycle 1, all other study visits and assessments should be performed within ± 7 days of the scheduled date.

b. Patients who experience PD during or at the end of the Induction Treatment Phase, or who refuse to go into the Maintenance Treatment Phase or who are not eligible for any study cohort, will undergo a Study Treatment Discontinuation Visit within 30 days after the last dose of study medication. These patients will then enter the Post-Treatment Follow-up Phase. All patients need to be evaluated for potential resection of metastasis at completion of the induction period. This is of particular importance for patients with liver metastases. If the patient is found to be resectable they will undergo a Study Treatment Discontinuation Visit within 30 days after the last dose of study treatment and will then enter the Post-Treatment Follow-up Phase.

c. Patients in the Post-Treatment Follow-up Phase will be followed up every 3 months after their Study Treatment Discontinuation Visit. During post-treatment follow-up subsequent anti-cancer therapies will be recorded and survival assessed up to May 31, 2019 only. Refer to Appendix 19 for management of patients based on their study status on May 31, 2019. Treatment during the Post-Treatment Follow-up Phase is at the Investigator's discretion; $BRAF^{mut}$/MSS patients experiencing early disease progression during induction treatment will have the option of proceeding immediately to receive second-line treatment with 5-FU/LV, cetuximab and vemurafenib; $BRAF^{mut}$/MSI-H patients experiencing early disease progression during induction treatment will have the option of proceeding immediately to receive second-line treatment with a fluoropyrimidine (5-FU/LV or capecitabine), bevacizumab and atezolizumab. See Section 3.1.1.1 for further details including if disease progression occurs prior to availability of study biomarker test results in a patient with a previous BRAF mutation-positive result (e.g. by local test). Patients who discontinue study treatment during the Induction Treatment Phase prior to disease progression will also continue to be followed for PFS, with disease status followed according to local practice until progression or May 31, 2019, whichever comes first. Disease status will not be collected for the study after May 31, 2019.

d. Written informed consent for participation in the study must be obtained before performing any study-specific screening tests or evaluations and before shipping primary tumour blocks or slides to the Sponsor-designated laboratory. However, results from routine assessments conducted

prior to informed consent signature may be used as screening assessments as long as they were done within 7 days prior to informed consent signature.

e. The “All Cohort” eligibility criteria are evaluated prior to initiating the first cycle of study treatment during the Induction Treatment Phase.

f. Medical history includes clinically significant diseases, surgeries, cancer history (including prior cancer therapies and procedures), reproductive status, smoking history, use of alcohol and drugs of abuse, and all medications (e.g., prescription drugs, over-the-counter drugs, herbal or homeopathic remedies, nutritional supplements) used by the patient within 7 days prior to the Screening visit. Demographic data will include age, sex, and self-reported race/ethnicity (where permitted by federal regulations).

g. Vital signs include measurements of systolic and diastolic blood pressure while the patient is in a seated position, and temperature. During Screening, weight only required ≤ 7 days.

h. Baseline assessment requires a complete physical exam. A complete physical examination should include an evaluation of the head, eyes, ears, nose, and throat, and the cardiovascular, dermatological, musculoskeletal, respiratory, gastrointestinal, genitourinary, and neurological systems. Abnormalities identified at Screening / Baseline will be recorded as baseline conditions. At subsequent visits (or as clinically indicated), limited, symptom-directed physical examinations should be performed. Changes from Baseline, with new or worsened clinically significant abnormalities, should be reported as AEs if appropriate.

i. ECOG status assessed within 7 days prior to Day 1 of Cycle 1 (Induction Treatment Phase) for eligibility determination. See Appendix 8.

j. Concomitant medication includes any prescription medications or over-the-counter preparations used by a patient between the 7 days prior to the date of informed consent up until the date of study discontinuation. Only concomitant medications used for supportive care, to alleviate symptoms of mCRC, or to treat adverse drug reactions should be recorded on the Concomitant Medications eCRF. At subsequent visits, only changes to current medications or medications used since the last documentation of medications will be recorded. Concomitant medications for treatment of AEs related to study medication will continue to be recorded while the AE is being followed. For permitted and prohibited concomitant medications, see Section 4.4.

k. Haematology includes haemoglobin, haematocrit, platelet count, red blood cell count, white blood cell count, and differential. Blood chemistry includes ALT, AST, alkaline phosphatase, total bilirubin, total protein, albumin, blood urea nitrogen or urea, LDH, creatinine, glucose, calcium, phosphorus, sodium, potassium, chloride, and bicarbonate. Hematology and blood chemistry tests must be conducted prior to each treatment cycle, with the results available for review prior to start of treatment according to local standards for treatment management. However, only tests conducted every second treatment cycle will be recorded in the eCRF. Clinical laboratory results constituting a clinically significant AE should be recorded as such.

l. INR and aPTT are required for all patients at screening but only for patients receiving anticoagulants while on protocol-specified treatment.

m. Urinalysis must be performed by dipstick at Baseline and within 48 hours prior to every cycle. A 24-hour urine collection is needed in the event of proteinuria ≥ ± 2 by dipstick test.

n. Urine or blood pregnancy test, only for women of childbearing potential (i.e. not post-menopausal as indicated by < 12 months of non-therapy-induced amenorrhea, nor surgically sterile [absence of ovaries and/or uterus]), including those who have had a tubal ligation. A serum pregnancy test is required within 7 days prior to start of study induction treatment, or within 14 days with a confirmatory urine pregnancy test within 7 days prior start of study induction treatment

o. Will include radiology, chest and abdominal CT or MRI, and other scans to document all sites of disease. Include upper abdomen at Baseline. A CT or MRI scan of the brain is required if there is clinical suspicion of CNS metastases at screening/Baseline or at any time during the Induction Treatment Phase. Subsequent tumour assessments will be done according to standard of care at each study centre, with the exception that all patients must have a tumour assessment at the end of the Induction Treatment Phase. Tumour assessments are not required for study purposes after disease progression has been documented. Patients who discontinue study treatment during the Induction Treatment Phase prior to disease progression will also continue to be followed for progressive disease, with disease status followed according to local practice until progression or May 31, 2019, whichever comes first. After May 31, 2019, disease status will not be collected for the study.

p. Archival tumour tissue (FFPET) block from the primary tumour obtained at the time of the initial diagnosis. If the tumour block is not available, ≥ 20 slides cut from the primary tumour sample will be accepted as an alternative. Before a patient can be enrolled, the sample (block or slides) must be shipped to the designated laboratory with the corresponding pathology report and receipt of the shipment must be confirmed by the laboratory. See Appendix 17.

q. Collection of the optional core biopsy of metastatic tumours was discontinued as of May 2018 (See Appendix 18).

r. Whole blood and plasma samples will be collected from all study patients for exploratory biomarker analyses unless genomic analysis is not allowed per local regulations. In such instances, only plasma samples will be collected. All samples will be sent to a designated laboratory. Samples during treatment should be taken within 48 hours prior to study treatment Day 1 of each cycle indicated, unless otherwise specified (see Appendix 17 and Laboratory Manual).

s. After the signing of the informed consent form, and prior to Day 1 of Cycle 1 (Induction Treatment Phase), any SAEs thought to be related to a protocol-mandated intervention should be reported. Adverse events will be documented at every cycle during treatment. All patients will be followed for new AEs for 28 days following the discontinuation of study treatment. At the time of treatment discontinuation, any ongoing AE/SAE will be followed until the event resolves, the Investigator assesses the event as stable, the patient is lost to follow-up, dies or withdraws consent. Death related to disease progression is not considered to be an SAE. The Sponsor should be notified if the Investigator becomes aware of any SAE or AEs of special interest occurring after the end of the adverse event reporting period if the event is believed to be related to prior study treatment.

t. 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-FU, 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.

Appendix 3: Schedule of Assessments During Maintenance Phase (Cohort 3)

	Prior to randomization	Maintenance Treatment Phase [a]	Study Treatment Discontinuation Visit [b]	Post-Treatment Follow-Up Phase [c]
	Within 3 weeks of completing Induction Treatment Phase	Control arm: every 2 two-week cycles Experimental arm: every 3-week cycle	(≤ 30 days after last dose of study treatment)	Every 3 months *until May 31, 2019 (see Appendix 19)*
Assignment of cohort [d]	x			
Cohort- specific informed consent	x (sites using 2 consent forms only)			
Confirmation of cohort-specific eligibility [e]	x			
Randomisation [f]	x			
Vital signs and weight [g]		x	x	
Physical examination [h]		x	x	
ECOG performance status [i]		x	x	
Concomitant medications [j]		Every cycle	x	
Haematology and blood chemistry [k]		Every cycle	x	
INR, aPTT (select patients) [l]		According to local standard of care		
Urinalysis (dipstick) [m]		Every cycle	x	
Pregnancy test [n]	Experimental arm only	Experimental arm: Cycles 4, 7, 10, 13, 16, 19, 22, 25 and every third cycle thereafter Control arm: If clinically indicated	Experimental arm only	Experimental arm only: until 7 months from last trastuzumab/pertuzumab
HIV, HBV, HCV serology [o]	x			

	Prior to randomization	Maintenance Treatment Phase [a]	Study Treatment Discontinuation Visit [b]	Post-Treatment Follow-Up Phase [c]
	Within 3 weeks of completing Induction Treatment Phase	**Control arm: every 2 two-week cycles** **Experimental arm: every 3-week cycle**	**(≤ 30 days after last dose of study treatment)**	**Every 3 months *until May 31, 2019 (see Appendix 19)***
LVEF [p]	x	Experimental arm only: Cycle 3, 6, 10, 14, 18, 22, 26 and every 4 cycles thereafter	Experimental arm only	
Tumour assessments [q]		*Up to and including May 31, 2019:* Every 8 weeks regardless of treatment delays *After May 31, 2019: per local practice*		*Up to and including May 31, 2019:* Every 8 weeks until disease progression *After May 31, 2019: per local practice*
Metastatic tumour tissue for exploratory biomarker assessment [r] *Supplemental Biomarker Program closed as of May 2018. Collection of these samples has been discontinued.*	*No sample collection Supplemental Biomarker Program CLOSED*	*No sample collection Supplemental Biomarker Program CLOSED*		
Plasma samples [s]		Cycles 1, 2, 4, 6, 8, 10, 12, 14 and every 2 cycles thereafter And at time of PD		At time of progression (if patient has not yet progressed)
Stool sample *Supplemental Biomarker Program closed as of May 2018. Collection of these samples has been discontinued.*	*No sample collection Supplemental Biomarker Program CLOSED*		*No sample collection Supplemental Biomarker Program CLOSED*	

	Prior to randomization	Maintenance Treatment Phase [a]	Study Treatment Discontinuation Visit [b]	Post-Treatment Follow-Up Phase [c]
	Within 3 weeks of completing Induction Treatment Phase	Control arm: every 2 two-week cycles Experimental arm: every 3-week cycle	(≤ 30 days after last dose of study treatment)	Every 3 months *until May 31, 2019 (see Appendix 19)*
Adverse events (including SAEs) [t]		Every cycle	x	x (as applicable)
Study medication administration [u]		Every cycle		
Subsequent anti-cancer therapies (see [c])				x
Patient survival (see [c])			x	x

a. With the exception of Cycle 1, all other study visits and assessments should be performed within ± 7 days of the scheduled date. If a control arm patient receives capecitabine administered according to a 3- week cycle, timing of all study procedures and assessments scheduled according to 2-week control arm treatment cycles (e.g. ECOG performance status) will be defined by the treatment cycles of concurrently administered bevacizumab.

b. Patients who experience PD at any time during the Maintenance Treatment Phase, or who need to permanently discontinue study medication for any reason, will undergo a Study Treatment Discontinuation Visit within 30 days after the last dose of study medication. These patients will then enter the Post-Treatment Follow-up.

c. After discontinuation of study treatment and the Study Treatment Discontinuation Visit, patients will enter the Post-Treatment Follow-up Phase. Beginning after the Study Treatment Discontinuation Visit, patients will be followed up every 3 months. *Up to and including May 31, 2019, follow-up will include recording* subsequent anti-cancer therapies*, disease status (until progression as applicable), survival and safety evaluations. Patients who have completed the adverse event reporting period and, if applicable, 7 month post-treatment pregnancy test will be discontinued from the study at the post-treatment follow-up visit within the 3 months prior to and including May 31, 2019 (i.e. at the visit on/after March 1, 2019). After May 31, 2019, patients who have not yet completed the adverse event reporting period (and 7 month pregnancy test as applicable) will be discontinued from the study after completion of the adverse event reporting period (and 7 month pregnancy test as applicable). Refer to Appendix 19 for the management of patients based on their study status as of May 31, 2019.* Treatment during the Post-Treatment Follow-up Phase is at the Investigator's discretion- Patients who discontinue study treatment prior to disease progression will be followed for PFS, with disease status followed every 8 weeks until progression *or May 31, 2019* whichever comes first.

d. Patients completing the Induction Treatment Phase, and who have not experienced PD can then proceed to the Maintenance Treatment Phase. Depending on the patient's biomarker status (based on the archival sample from initial diagnosis), these patients will be assigned to a

maintenance treatment cohort. Cohorts 2 and 4 are closed to further accrual. Patients with an adequate tumour sample but with unknown biomarker status due to lack of determinant result (e.g. due to technical issues) may still be included in the study depending on the addition of future cohorts.

e. The cohort-specific exclusion criteria must be assessed prior to randomization to study maintenance treatment but assessment of cohort-specific eligibility can only be completed after the biomarker analysis results from the patient's archival tumour tissue from initial diagnosis are known. Patients found ineligible for any cohort will undergo a Study Treatment Discontinuation Visit and enter the Post-Treatment Follow-up Phase.

f. Each cohort will consist of an experimental treatment arm and a control arm. Randomised on a 2:1 (experimental:control) basis to either the experimental treatment arm or the control arm of that cohort. See Section 4.2.

g. Vital signs include measurements of systolic and diastolic blood pressure while the patient is in a seated position, and temperature. For the control arm only, vitals conducted every second treatment cycle only will be recorded in the eCRF.

h. Physical examinations will be symptom-directed, and will include changes from Baseline (pre-Induction) with new or worsened clinically significant abnormalities being reported as AEs if appropriate.

i. See Appendix 8.

j. Concomitant medication includes any prescription medications or over-the-counter preparations used by a patient between the 7 days prior to the date of informed consent up until the Study Treatment Discontinuation visit. Only concomitant medications used for supportive care, to alleviate symptoms of mCRC, or to treat adverse drug reactions should be recorded on the Concomitant Medications eCRF. At subsequent visits, only changes to current medications or medications used since the last documentation of medications will be recorded. Concomitant medications for treatment of AEs related to study medication will continue to be recorded while the AE is being followed. For permitted and prohibited concomitant medications, see Section 4.4.

k. Haematology includes haemoglobin, haematocrit, platelet count, red blood cell count, white blood cell count, and differential. Blood chemistry includes ALT, AST, alkaline phosphatase, total bilirubin, total protein, albumin, blood urea nitrogen or urea, LDH, creatinine, glucose, calcium, phosphorus, sodium, potassium, chloride, and bicarbonate. Haematology and blood chemistry tests must be conducted prior to each treatment cycle, with the results available for review prior to start of treatment according to local standards for treatment management. For the control arm only, tests conducted every second treatment cycle only will be recorded in the eCRF. Clinical laboratory results constituting a clinically significant AE should be recorded as such.

l. INR and aPTT only for patients receiving anticoagulants while on protocol-specified treatment.

m. Urinalysis must be performed by dipstick within 48 hours prior to every cycle. A 24-hour urine collection is needed in the event of proteinuria ≥ ± 2 by dipstick test. For the control arm only, tests conducted every second treatment cycle only will be recorded in the eCRF.

n. Urine or blood pregnancy test, only for women of childbearing potential (i.e. not post-menopausal as indicated by < 12 months of non-therapy-induced amenorrhea, nor surgically sterile [absence of ovaries and/or uterus]), including those who have had a tubal ligation. If a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test. In the experimental arm, a serum pregnancy test must be done ≤ 7 days from maintenance treatment start. Urine pregnancy tests must also be done every 3 cycles during treatment (with result available prior to Day 1 dose of the next cycle), and every 3 months until 7 months after the last doses of trastuzumab and pertuzumab.

o. HIV testing performed in accordance with national and/or institutional guidelines. HBV serology includes HBsAg and anti-HBc. HCV serology includes anti-HCV. Results required to determine eligibility for Cohort 3.

p. LVEF must be assessed in all Cohort 3 patients prior to randomization. Only experimental arm patients require subsequent LVEF monitoring. Subsequent LVEF measurements (using the same method as at baseline) will be conducted every third cycle until Cycle 6 and then every fourth cycle until termination of study treatment (i.e., during Cycles 3, 6, 10, 14, etc.), with the results made available prior to administration of the subsequent treatment cycle (i.e., prior to Cycles 4, 7, 11, 15, etc.). For patients who stop study drug(s) because of a decrease in LVEF, LVEF should be assessed at least every 6 weeks to determine recovery/stabilization (until LVEF recovers to ≥ 50% or 2 years, whichever occurs first). In patients who required a repeat LVEF assessment to ensure an acceptable LVEF before continuing trastuzumab/pertuzumab treatment, an additional LVEF assessment is to be performed at the next treatment cycle. Note: approval of the Medical Monitor must be obtained before continuation of study treatment after delays > 21 days.

q. *Up to and including May 31, 2019, t*~~T~~Tumour assessments *will be conducted* according to RECIST1.1 *and* will include radiology, chest and abdominal CT or MRI, and other scans to document all sites of disease. A CT or MRI scan of the brain is required if there is a clinical suspicion of CNS metastases. Disease status during maintenance treatment will be determined based on comparison with the ~~tumor~~*tumour* assessment done at the end of induction treatment. *Up to and including May 31, 2019,* ~~T~~*t*umour assessments will be conducted every 8 weeks from the start of maintenance treatment regardless of treatment delays. *After May 31, 2019, disease status will not be collected for the study and tumour assessments may be conducting per local practice.* Patients who discontinue study treatment during the Maintenance Treatment Phase prior to disease progression will also continue to be followed for progressive disease, with disease assessments *per RECIST 1.1* conducted every 8 weeks until progression *or May 31, 2019*, whichever comes first.

r. *Supplemental Biomarker Program closed as of May 2018. Collection of these samples has been discontinued* (see Appendix 18).

s. Plasma samples will be collected from all patients for exploratory biomarker analyses. These samples will be sent to a designated laboratory. Samples during treatment should be taken within 48 hours prior to study treatment Day 1 of each cycle indicated, unless otherwise specified (see Appendix 17 and the Laboratory Manual).

t. Adverse events will be documented at every cycle during treatment. Patients in the experimental arm of Cohort 3 will be followed for new AEs for 90 days following the discontinuation of study treatment. Patients in the control arm will be followed for new AEs for 28 days following the discontinuation of study treatment. At the time of treatment discontinuation, any ongoing AE/SAE will be followed until the event resolves, the Investigator assesses the event as stable, the patient is lost to follow-up, dies or withdraws consent. Death related to disease progression is not considered to be an SAE. The Sponsor should be notified if the Investigator becomes aware of any SAE or AEs of special interest occurring after the end of the adverse event reporting period if the event is believed to be related to prior study treatment.

u. Patients in the experimental arm will receive capecitabine 1000 mg/m^2 b.i.d. Days 1-14 followed by a one-week treatment break for every 3-week treatment cycle. Capecitabine dose calculations by body surface area with corresponding tablet counts are provided in Appendix 7. Trastuzumab will be administered by IV infusion on Day 1 of every 3-week treatment cycle at an initial loading dose of 8 mg/kg followed by 6 mg/kg for subsequent doses. Pertuzumab will be administered by IV infusion on Day 1 of each 3-week treatment cycle at an initial fixed loading dose of 840 mg followed by 420 mg for subsequent doses. Patients in the control arm will receive: 5-FU or capecitabine, dose and schedule will be according to local label, where applicable, or otherwise will be determined per the Investigator's discretion, with bevacizumab 5 mg/kg via 15 – 30 minute IV infusion on Day 1 of every 2-week cycle. If a control arm patient receives capecitabine administered according to a 3- week

cycle, timing of all study procedures and assessments scheduled according to 2-week control arm treatment cycles (e.g. ECOG performance status) will be defined by the treatment cycles of concurrently administered bevacizumab.

Appendix 4 : List of Outputs

List of Outputs: Listings

Listing Number	Listing Title	Phase	Population	Primary analysis	Final Analysis
16.2.1.1	Patient Disposition and Study Termination Information	ITP	ITP	X	X
16.2.4.1	Demographics and Baseline Characteristics	ITP/MTP	ITP	X	
16.2.5.5	Drug Exposure during ITP	ITP	ITP	X	
16.2.5.8	Drug Exposure during MTP	MTP	SAF	X	
16.2.6.1	Progression Free-Survival – Primary Analysis (Surgery Censored)	MTP	MTP	X	
16.2.7.1	Adverse Events	ITP/MTP/ Post-treatment	ITP	X	X
16.2.7.5	Deaths	ITP/MTP/ Post-treatment	ITP	X	X

STATISTICAL ANALYSIS PLAN

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

COHORT 4

PROTOCOL NUMBER: MO29112

COHORT 4 STUDY DRUGS: atezolizumab (MPDL3280A, RO5541267),
bevacizumab (RO4876646)
cobimetibib (RO5514041)

VERSION NUMBER: 1.0

IND NUMBER: N/A

EUDRACT NUMBER: 2014-001017-61

SPONSOR: F. Hoffmann-La Roche Ltd

PLAN PREPARED BY: [redacted], Cytel, Inc

DATE FINAL: 9th May 2019

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LIST OF APPENDICES

HISTORY CHANGE

Version	Date	Changes
Final 1.0		N/A

LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	adverse event
AESI	adverse events of special interest
BMI	body mass index
$BRAF^{mut}$	BRAF mutation
BSA	body surface area
CI	confidence interval
CR	complete response
CSR	clinical study report
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic Case Report Form
EU	European Union
HER2	human epidermal growth factor receptor 2
HER2+	human epidermal growth factor receptor 2 positive
HR	hazard ratio
IC	informed consent
ICH	International Conference on Harmonization
iDMC	Independent Data Monitoring Committee
IHC	immunohistochemistry
ITP	Induction Treatment Phase
IxRS	interactive voice or web-based response system
KM	Kaplan Meier
mCRC	metastatic Colorectal Cancer
MedDRA	Medical Dictionary for Regulatory Activities
MSI-H	high microsatellite instability
MSS	microsatellite stable
MTP	Maintenance Treatment Phase
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NE	not evaluable
NGS	next generation sequencing
ORR	objective response rate
OS	overall survival
PD	progressive disease
PDMS	protocol deviation management system
PFS	progression free survival
PK	pharmacokinetic

Abbreviation	Definition
PP	Per protocol
PR	partial response
PS	performance status
PT	preferred term
RDI	relative dose intensity
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	serious adverse event
SAF	safety population
SAP	statistical analysis plan
SC	Steering Committee
SD	stable disease
SI	Système International
SOC	System Organ Class
TEAE	treatment emergent adverse event

1. BACKGROUND

The study is a randomized, multi-center, active-controlled, open-label, parallel-group clinical study of biomarker-driven maintenance treatment for first-line metastatic colorectal cancer (mCRC) patients. All patients will receive induction treatment with FOLFOX and bevacizumab. Induction treatment will be followed by maintenance treatment with chemotherapy combined with targeted therapy within one of several maintenance treatment cohorts. Only those patients who experience disease response or disease control during induction and who are not assessed as resectable at completion of induction will proceed to further treatment in the Maintenance Treatment Phase (MTP) of the study. Patients will be assigned to a maintenance treatment cohort based on their primary tumour biomarker results. The primary study objective within each cohort is to evaluate progression-free survival (PFS).

Maintenance treatment cohorts may be added or modified over the course of the study. This SAP describes planned analyses of patients who were assigned, or would have been assigned, to maintenance treatment Cohort 4 based on their primary tumour biomarker profile. Analyses of patients assigned to all other MODUL cohorts will be described in SAPs applicable to each specific cohort.

A Steering Committee (SC) is responsible for overseeing the general conduct of the study.

In addition, an independent Data Monitoring Committee (iDMC) is responsible for evaluating the safety of the patients participating in the trial at regular intervals throughout the study. The iDMC makes recommendations as to whether cohort recruitment should continue based on benefit-risk evaluations that include efficacy as well as safety data. To minimize the impact of such reviews on efficacy endpoint analyses, efficacy data included in these reviews has to be specified by the iDMC at a preceding iDMC meeting and has to be documented in the iDMC meeting minutes.

2. STUDY DESIGN

Patients continuing from the Induction Treatment Phase (ITP) to the Maintenance Treatment Phase are assigned to a maintenance treatment cohort based on their primary tumour biomarker status. Following eligibility assessment for their assigned cohort, eligible patients are randomized to the experimental or control arm within their cohort.

The study was initiated with 2 maintenance treatment cohorts, Cohorts 1 and 2. Two additional cohorts, Cohorts 3 and 4, were added with protocol amendment 5 (protocol version 6).

In this open-label study, all patients will receive 8 cycles induction treatment that is considered standard in many countries and that has been shown to improve outcomes in the first-line setting. Treatment during the ITP, 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

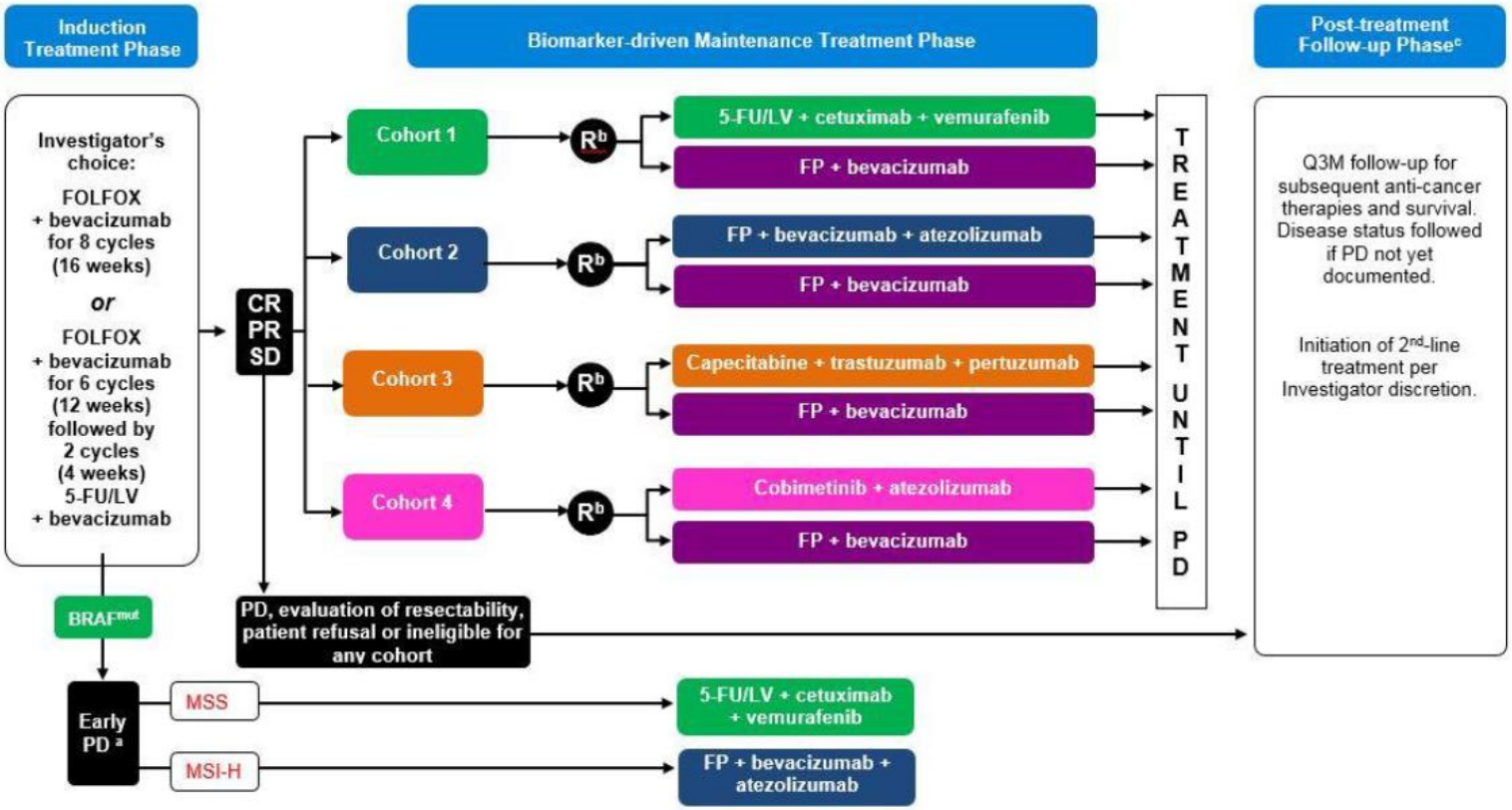
- Six 2-week cycles of FOLFOX in combination with bevacizumab, followed by two 2-week cycles of 5-FU/LV with bevacizumab

Patients who prematurely discontinue study treatment for any reason during the ITP, who experience progressive disease (PD) at any time during or at the end of the ITP, who are evaluated as resectable at the end of ITP, who refuse to proceed to the MTP, or who are not eligible for any maintenance cohort will undergo a study treatment discontinuation visit and enter post-treatment follow-up. Patients who experience disease control or tumor response to induction treatment will continue to the randomized MTP of the study wherein the effects of experimental and control groups will be compared. Patients in screening after Cohort 4 was introduced (i.e. after June 28, 2016), were assigned to Cohort 4 if their primary tumour was HER2-/MSI-H, HER2-/MSS/BRAF^{wt}, or HER2-/MSS/BRAF^{mut}/RAS^{mut} (see Table 1). Treatment in each cohort is shown in Figure 1.

Table 1: Biomarker Profile by Cohort

	Biomarker profile	
	Patients in Screening Prior June 28, 2016	Patients in Screening After June 28, 2016
Cohort 1	BRAF^{mut}	HER2-/MSS/BRAF^{mut}/RAS^{wt}
Cohort 2	BRAF^{wt} or biomarker status unknown	Closed to patients screened after June 28, 2016
Cohort 3	Not applicable	HER2+
Cohort 4	Not applicable	HER2-/MSI-H; HER2-/MSS/BRAF^{wt}; HER2-/MSS/BRAF^{mut}/RAS^{mut}

Figure 1: Study Design as of protocol version 6



FP = fluoropyrimidine (5-FU/LV or capecitabine); 5-FU/LV = 5-fluorouracil/leucovorin; MSI -H= high microsatellite instability; MSS = microsatellite stable

a. Patients who progress early and who are not $BRAF^{mut}$ will enter the Post-treatment Follow-up Phase with initiation of 2nd-line treatment per Investigator discretion

b. Randomization stratified by: Cohorts 1 and 2- region (EU, Americas, Africa or Asia), induction treatment response (CR/PR vs. SD); Cohort 3- induction treatment response (CR/PR vs. SD), HER2 IHC (IHC0/ IHC1+/IHC2+ vs. IHC3+); Cohort 4- region (EU vs. rest of world), induction treatment response (CR/PR vs. SD), microsatellite stability (MSI-H vs. MSS), RAS status (wild-type KRAS and NRAS vs. mutant KRAS and/or NRAS)

c. Patients discontinuing study treatment for any reason during the Induction or Maintenance Treatment Phases will enter the Post-treatment Follow-up Phase.

Primary objective of this study:

The primary study objective within each cohort is to evaluate PFS.

An iDMC is responsible for regularly reviewing safety data.

2.1 PROTOCOL SYNOPSIS

The Protocol version 8 synopsis is provided in Appendix 1. For additional details, see the Schedule of Assessments in Appendix 2.

2.2 OUTCOME MEASURES

As mentioned in the protocol, each cohort will be analysed separately and therefore this SAP focuses on the description of the analysis required for cohort 4 data only, i.e. applicable to enrolled patients eligible for cohort 4 based on primary tumour biomarker status.

2.2.1 Primary Efficacy Outcome Measures

PFS is defined as the time from randomization into the MTP until documented disease progression as per investigator assessment using Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 or death from any cause, whichever occurs first. If no progression / death is observed at the time of clinical cut-off or by the date of any on-study colorectal anti-cancer surgery with palliative or curative intent, patients will be censored at the date of the last evaluable tumor assessment or date of randomization, whichever comes last.

(Of note: (i) Progressive disease are identified by the Overalll Response='PD', even if solely based on symptomatic deterioration, (ii) Only surgery occurring between baseline tumor assessment for MTP and PFS events are considered for censoring PFS)

2.2.2 Secondary Efficacy Outcome Measures

2.2.2.1 Overall Survival (OS)

OS is defined as the time from randomization into the MTP to time of death from any cause. Patients still alive at time of clinical cut-off will be censored at their last date known to be alive as defined in section 4.3. For imputation of "Partial Death Date", please refer to section 4.14.

No other secondary efficacy outcome measures (eg. Overall response rate, disease control rate, time to treatment response, duration of response etc…) will be analysed for Cohort 4.

2.2.3 Safety Outcome Measures

The safety outcome measures for this study are as follows

- Incidence, nature and severity of all adverse events (graded according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) v4.0)
- Incidence and nature of all Grade 3- 5 AEs
- Grade 5 AEs or AEs leading to death on study treatment
- All serious adverse events (SAEs)
- Adverse events of special interest (AESI)
- Clinically significant changes in laboratory values
- Vital signs

2.2.4 Pharmacokinetic (PK) Outcome Measures

There are no PK outcome measures for this study.

2.2.5 Exploratory Biomarker Outcome Measures

The exploratory biomarker outcome measures of the study include molecular markers/marker profiles and efficacy and/or safety outcomes. Efficacy outcomes considered for this analysis may include, but are not limited to, ORR, PFS and OS, as appropriate. Biomarkers, biomarker profiles and microbiomes may be assessed using various methodologies including, but not limited to, IHC (single and multiplex), RNA and DNA analysis (e.g. polymerase chain reaction, next generation sequencing [NGS], mutation expression and microsatellite instability [MSI] analyses) of tumour and/or blood samples collected from all study patients as well as additional tumour samples and stool samples collected from patients participating in the Supplemental Biomarker Program.

Statistical analysis will be covered in a separate SAP (if applicable).

2.3 DETERMINATION OF SAMPLE SIZE

Before study enrolment was closed prematurely, approximately 1820 patients were planned for enrolment in the Induction Treatment Phase of the study in order to randomise 405 patients in Cohort 4, with around 84% of patients assumed to be eligible for Cohort 4 based on biomarker status. Cohort 4 was closed to accrual with 99 patients randomized (ie, prior to reaching the target sample size).

The estimated proportion of patients enrolled into the study that are eligible for cohort 4 is based on published reports (*di Nicolantonio et al. 2008).* Approximately 25% of all patients enrolled are expected to have disease progression prior to randomisation into the Maintenance Treatment Phase (Roche, data on file). Inputs used in cohort-specific sample size calculations are provided in Table 2.

Table 2: Sample Size Determination per Cohort

	Cohort 4
Percent of study population eligible for cohort based on biomarker status	84%

	Cohort 4
Percent of patients eligible for cohort based on biomarker status expected to have disease progression prior to randomization	25%
Average randomization rate (pts/month) [a]	31.5
Estimated median PFS [b] (months) - Experimental group	11.5
Estimated median PFS [b] (months) - Control group	7.5
Hazard ratio (HR)	0.65
Number of expected PFS events	259
Statistical test	2-sided
Alpha level	5%
Power	90%
Randomized patients	405
Randomization ratio (experimental vs control)	2:1
Recruitment period (months)	11
Time to primary analysis of PFS (months) [c]	22
a. Based on 1,820 patients screened over the entire recruitment period b. Per RECIST 1.1 c. Time from first patient randomised in cohort	

2.4 ANALYSIS TIMING

Cohort 4 will not reach its target sample size. As originally planned for cohorts reaching their target number of PFS events (applies to Cohort 2 only), an update analysis of efficacy and safety parameters will be conducted based on 24 months survival follow-up after the clinical cut-off date for the primary analysis. The cut-off date for the Cohort 2 primary analysis was May 31, 2017 so the Cohort 2 update analysis will be conducted based on a cut-off date of May 31, 2019. The primary analysis for cohort 4 will be conducted at the same time as the Cohort 2 update analysis (i.e. based on the same cut-off date of May 31, 2019).

The final analysis of cohort 4, which will consist of updating overall survival analysis and adverse events analysis, will take place after the end of the study. End of study is defined as the date when all study patients have discontinued study treatment and completed the adverse event reporting period. Results of primary and final cohort 4 analyses will be reported in a separate clinical study report (CSR).The outputs to be provided for the analyses (primary or final) are listed in Appendix 5.

Analysis for cohorts other than cohort 4 is not covered in this SAP and will be documented in separate SAPs.

3. STUDY CONDUCT

3.1 RANDOMIZATION ISSUES

Patients will be assigned to a cohort based on the results of biomarker assessments conducted on archival primary tumour tissue obtained during their initial CRC diagnosis. Once assigned to a cohort, patients will be randomized on a 2:1 basis to either the experimental

treatment group or the control group of that cohort. Randomization in Cohort 4 will be stratified by geographical region (EU vs rest of the world), patient response after the Induction Treatment Phase (CR/PR vs. SD), microsatellite stability (MSI-H vs MSS), and RAS status (wild-type KRAS and NRAS vs mutant KRAS and/or NRAS).

3.2 INDEPENDENT REVIEW FACILITY

Not applicable.

3.3 DATA MONITORING

An iDMC is responsible for:

- evaluating the safety of the patients participating in the trial at regular intervals throughout the study,
- making recommendations as to whether cohort recruitment should continue based on benefit-risk evaluations that include efficacy as well as safety data. To minimize the impact of such reviews on efficacy endpoint analyses, efficacy data included in these reviews has to be specified by the iDMC at a preceding iDMC meeting and has to be documented in the iDMC meeting minutes,

4. STATISTICAL METHODS

4.1 GENERAL DESCRIPTIVE METHODS

Categorical variables

For categorical variables, summary tabulations of the number and missing observations as well as the number and percentage within each category of the parameter will be presented. Missing will not be considered as a separate category and thus missing observations will not be part of the denominator to compute the percentages. Percentages will be rounded to one decimal place. Therefore, there may be cases where for instance the total of the percentages does not exactly equal 100%. If number of patients is '0' then 0 will be reported instead of '0 (0.0%)'

Continuous variables

For continuous variables, N, the mean, median, standard deviation, 25th and 75th percentile, minimum and maximum values will be presented.

Time-to-event efficacy variables

Time-to-event efficacy variables (e.g. PFS and OS) summaries will include number of patients in the population (N), number of patients with the event of interest, number of patients censored, median and two-sided 95% confidence interval (CI) computed according to Brookmeyer and Crowley (1982) method. Kaplan-Meier (KM) estimates and median survival times are calculated with the PROC LIFETEST procedure in SAS. KM curves (product-limit method) will be presented as well as the event rates at certain time points with the relevant CIs calculated via log-log transformation method (default option CONFTYPE=LOGLOG in SAS) based on standard errors computed using the Greenwood's formula.

Cox proportional hazards models

Cox proportional hazards model will be implemented using PHREG procedure with option TIES=EXACT. It assumes that there is a true but unknown ordering for the tied event times as contrasted to option TIES=DISCRETE which assumes that the events occurred at exactly the same time.

Missing values

For categorical variables, summary tabulations of the number and missing observations as well as the number and percentage within each category of the parameter will be presented. For continuous variable, number of missing is displayed between brackets next to 'n', unless otherwise specified.

Decimals

Mean, standard deviation, and median (Q1 and Q3 if applicable) will be presented with one more decimal place compared to the raw data, minimum and maximum will be presented with same number of decimal places as the raw data. Hazard ratio, odds ratio will be provided with two decimals. P-value will be provided with three decimals. If <0.001, then '<0.001' will be displayed.

4.2 DEFINITION OF TREATMENT PHASE

In this study, there are 3 treatment phases:

1. Patients are treated first in the Induction Treatment Phase (ITP) for a planned duration of 8 cycles, i.e. 16 weeks.

2. If they do not experience any progressive disease before or at the end of the ITP, are not considered resectable at the end of the ITP and do not withdraw from the study and are still eligible for any cohort, they are randomized and treated in the Maintenance Treatment Phase (MTP).

3. If they discontinue study treatment for any reason during the Induction or Maintenance Treatment Phases, do not withdraw from the study and are still alive, they enter the Post-Treatment Follow-up Phase.

4.2.1 Induction Treatment Phase (ITP)

ITP is defined as the time from first study drug administration until

- the day before the randomization for patients continuing treatment in the MTP
- the last assessment date otherwise

The first day of treatment in the ITP is defined as the earliest day of a non-null administration of any induction phase treatment.

The last day of treatment in the ITP is defined as the last day of the last initiated cycle of the induction phase, or as the death day if the patient died in between. A two-week cycle duration is assumed.

Baseline evaluations for the ITP will be those performed not earlier than 28 days prior to the first day of treatment in the induction phase, unless otherwise stated. The latest available assessment up to start of the first day of treatment in the induction phase will be considered as baseline. For laboratory examinations, weight, vital signs and ECOG PS, assessments

performed on the first day of treatment of the ITP will be assumed to have been performed before drug was given and, thus, will be considered as baseline evaluations.

On-treatment evaluations for the ITP will be post baseline evaluations performed until

- the day before the randomization for patients continuing treatment in the MTP
- (including) the study treatment discontinuation visit within 30 days after last day of treatment of the ITP (as defined above), for patients not randomized in the MTP.

4.2.2 Maintenance Treatment Phase (MTP)

MTP is defined as the time from randomization into MTP until (including) the study treatment discontinuation visit in the MTP.

The first day of treatment in the MTP is defined as the earliest day of a non-null administration of any maintenance phase treatments.

The last day of treatment in the MTP is defined as the last day of the last initiated cycle of the maintenance phase, or as the death day if the patient died in between. A two-week cycle duration is assumed.

Baseline evaluations for the MTP will be those performed prior to the first day of treatment in the maintenance, unless otherwise stated. The latest available assessment prior to the first day of treatment in the maintenance phase will be considered as baseline for safety assessments. For laboratory examinations, weight and vital signs, assessments performed on the first day of treatment of the MTP will be assumed to have been performed before drug was given and, thus, will be considered as baseline evaluations. For subjects randomized but not treated in the MTP, the latest available assessment before or on randomization date (including assessments from ITP) will be considered as baseline for the MTP.

For efficacy assessments, the latest available assessment prior or on the randomization date will be considered as baseline.

On-Treatment evaluations for the MTP will be evaluations performed on or after the first day of treatment in the MTP within 30 days from last day of treatment in the maintenance phase. On-treatment laboratory will be all values collected after the first day of treatment in the maintenance phase and within 30 days from last day of treatment in the maintenance phase (as defined above). For adverse events, treatment emergent adverse events (TEAEs) will be events occurring on or after the first day of treatment in the MTP within 30 days (for patients in control group, i.e. not treated with atezolizumab) and 90 days (for patients in experimental group, i.e. treated with atezolizumab) from last day of treatment in the maintenance phase (as defined above).

4.2.3 Post-Treatment Follow-up Phase

Post treatment Follow-up Phase is defined as the time from (excluding) the study treatment discontinuation visit until the last available assessment date before clinical cut-off date. For patients who discontinue study treatment but without any study treatment discontinuation visit date, please refer to 4.14 for imputation of this missing visit date.

Post-Treatment Follow-up evaluations will be evaluations performed according to the protocol after the study treatment discontinuation visit.

4.3 DATA CONVENTION

All data will be listed (e.g. pre-treatment serious adverse events), whereas only baseline and on-treatment assessments will be considered for summary tables.

Baseline and on-treatment data will be flagged in the data listings as well as the different phases of the study.

The overall column will not be displayed in any summary tables.

The following conversion factors will be used to convert days to months or years, where applicable:

- 1 week= 7 days
- 1 month = 30.4375 days
- 1 year = 365.25 days

Age at informed consent (IC) {in years} = (date of informed consent – date of birth) / 365.25

To calculate **duration / time between** two dates the following convention will be used:

[later date] – [earlier date] + 1 day

Durations and times between two dates will be calculated only when both start and end dates are available (imputed dates cannot be used for computation), apart for overall survival when date of death has only day as missing).

Body surface area (BSA) will be recalculated based on the height and weight of the patient using the following formula:

BSA (m^2) = ([Height {cm} x Weight {kg}] / 3600)^{½}

Body mass index (BMI) will be calculated using the following formula:

BMI (kg/m^2) = Weight {kg} / Height^2 {m}

The last known date to be alive will be the latest date among all dates specified in the eCRF except the following:

- Survival Follow-up date when status is either dead (in this case the date of death is specified on the Adverse events or Study Completion/Early Discontinuation or SAE reporting summary form) or lost to follow-up (in this case last date known to be alive is specified on the Survival follow-up form)
- Study Completion/Early Discontinuation date when reason is either death or lost to follow-up.
- A sample / record with test ‘Not Done’.

4.4 COMPUTING ENVIRONMENT

All statistical analyses will be performed using SAS statistical software (Version 9.2 or newer version), unless otherwise noted.

4.5 GRADING AND CODING OF ADVERSE EVENTS, LABORATORY PARAMETERS AND MEDICATIONS

Laboratory results, adverse events, and other symptoms will be graded using the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Event (CTCAE), version 4.0, except where CTC grades are not available.

Adverse events and relevant Medical History data fields (i.e. prior symptoms / AEs) will be coded using the most recent version of Medical Dictionary for Regulatory Activities (MedDRA) dictionary available at the time of analysis.

Prior and concomitant anti-cancer therapy / other medications will be coded using the most up-to-date version of the in house Genentech Drug Thesaurus Dictionary.

Dictionary versions used will be displayed in analysis outputs.

4.6 ADUSTMENTS FOR COVARIATES

When indicated, efficacy analysis will be adjusted i.e. the covariates will be incorporated in the model used to assess the treatment effect upon the efficacy endpoints. The covariate below will be considered:

- Patient response after induction treatment as per eCRF data: CR/PR vs. SD. For inferential analysis, “SD” will be used as reference, unless otherwise specified.

  (Of note: no adjustment will be made for region since most of patients are in Europe.)

4.7 SUBGROUP ANALYSIS

No subgroup analysis will be performed for Cohort 4.

4.8 ANALYSIS POPULATIONS

The following patient populations will be evaluated and used for presentation and analysis of the data.

4.8.1 All Population

ALL Population: The ALL population consists of all screened patients with HER2-/MSI-H; HER2-/MSS/BRAF^{wt}; HER2-/MSS/BRAF^{mut}/RAS^{mut} biomarker profile who entered study screening after June 28, 2016.

Induction Treatment Phase (ITP) Population: all patients included in the ALL Population and who are treated in the ITP, i.e. who received at least one non-null dose of any study medications during the ITP. The ITP population is the main population to be used to summarize ITP data and Post Induction Treatment data. The 2 following groups will be considered when tabulating ITP data: patients randomized into MTP versus patients not randomized into MTP. Post Induction Treatment data will be summarized using one single group, i.e. patients not randomized into MTP. ITP population will be the main population for the data listings, unless otherwise specified; the 3 following groups will be displayed in listings: patients randomized in the experimental group of MTP, patients randomized in the control group of MTP, patients not randomized into MTP.

4.8.2 Randomized Population

Maintenance Treatment Phase (MTP) Population is defined as all patients randomized into the Cohort 4 MTP of the study, irrespective of whether or not they received study medication. Patients will be allocated to the treatment group into which they were randomized (as per interactive voice or web-based response system [IxRS]). The MTP population is the primary population for the analysis of efficacy parameters and baseline characteristics for the MTP. The MTP population will be used as well to report the Post Maintenance Treatment data.

4.8.3 Safety Population

Safety (SAF) Population: all patients randomized in Cohort 4 who have been treated, i.e. who received at least one non-null dose of any study medications during the MTP.

Patients will be allocated to the treatment group they actually received using the following rule:

- Patients receiving at least one dose (non-null) of cobimetinib or atezolizumab, while on treatment will be allocated to the experimental group cobimetinib+atezolizumab. Even if a patient was allocated to the control group and received by mistake a dose of cobimetinib or atezolizumab, then this patient will be reallocated to the experimental group.
- Patients who did not receive any dose of cobimetinib or atezolizumab will be allocated to the control group FP+bevacizumab.

The SAF population is the primary population for the analysis of MTP safety parameters.

4.8.4 Per Protocol (PP) Population

As stated in the protocol, the PP Population will not be defined for this study but major protocol violations will be listed.

4.8.5 Pharmacokinetic-Evaluable Population

Not applicable.

4.8.6 Biomarker-Evaluable Population

Not applicable.

4.9 ANALYSIS OF STUDY CONDUCT

This SAP focuses only on the description of the analysis required for cohort 4 data. All MTP data will be reported. ITP data for patients with HER2-/MSI-H; HER2-/MSS/$BRAF^{wt}$; HER2-/MSS/$BRAF^{mut}$/RAS^{mut} biomarker profile randomized and not randomized into the MTP will be tabulated in 2 separate columns. Post-treatment data will be reported separately for induction and maintenance treatments. This Post-treatment data includes adverse events, deaths, subsequent anti-cancer therapies and tumor assessments (until PD if PD not experienced before study treatment discontinuation visit), but this last one applies only for Post Maintenance treatment.

4.9.1 Patient Disposition

The patient disposition table for ITP will be based on the ALL population and will include the following information:

- Number of patients enrolled (ALL)
- Number of patients not treated in ITP who discontinued trial without being treated and associated reason
- Number of patients treated with induction treatment (ITP population)
- Number of patients who completed the ITP
- Number of patients treated in induction who discontinued early ITP and reason for early discontinuation
- Number of patients treated in induction and not randomized who went to post-treatment follow-up phase post induction
- Number of patients being treated in induction who discontinued study prior to MTP and associated reason

The patient disposition table for MTP will include the following information:

- Number of randomized patients (MTP population) (percentage based on MTP)
- Number of randomized patients without being treated in MTP still on-trial
- Number of randomized patients who discontinued trial without being treated in MTP and the corresponding reason for trial discontinuation (percentages based on MTP)
- Number of treated patients with maintenance treatment (SAF) (percentages based on MTP)
- Number of patients treated who discontinued all treatments received in MTP and the reason for discontinuation from each maintenance treatment (percentage based on MTP). All reasons for treatment discontinuation will be displayed and will be taken from the individual treatment completion/Early discontinuation eCRF pages.
- Number of patients treated in MTP who discontinued trial during MTP and the corresponding reason for trial discontinuation (percentages based on MTP)
- Number of patients who entered in the follow-up post-MTP
- Number of patients being treated in MTP who discontinued trial during follow-up and the corresponding reason for trial discontinuation (percentages based on MTP)

A consort flow diagram will be provided to show progress of screened patients and especially for patients with HER2-/MSI-H; HER2-/MSS/BRAF^{wt}; HER2-/MSS/BRAF^{mut}/RAS^{mut} biomarker profile. Another diagram for patients randomized in Cohort 4 will be provided.

The following supportive listings will be provided:

- Patient disposition (including the tumor response status at the end of ITP) and study termination information based on ITP
- Patients who discontinue treatment due to AE (based on ITP)

4.9.2 Protocol Deviations

All major protocol deviations from Protocol Deviation Management System (PDMS) will be reported for each phase separately and will be summarized by group. The ITP population will be used for ITP data and the MTP population for the MTP data.

The following will be displayed

- Number of patients having at least one major protocol deviation
- Number of patients by major protocol deviations category

Listings for protocol deviations will be provided based on ITP population. Listing for analysis population will be provided on ALL population.

4.10 ANALYSIS OF TREATMENT GROUP COMPARABILITY

4.10.1 Demographics and Baseline Disease Characteristics

Baseline and demographic characteristics will be summarized using descriptive statistics. No formal statistical comparisons will be performed.

Summaries of Patient Demographics will be provided based on the ITP and MTP population and will present the following information:

- Age at informed consent (yrs)
- Age categories (yrs): < 18, 18-64, 65-84, 85 and over
- Sex
- Ethnicity: Hispanic or Latino, Not Hispanic or Latino, Not reported, Unknown
- Race
- Region: Europe, Americas, Africa, Asia (derived based on country information from the clinical database)
- Smoking status: Never, Current, Previous
- Alcohol use history: Never, Current, Previous
- Drug Use: Never, Current, Previous
- ECOG Performance Status at baseline: 0,1,> 1,
- Baseline Weight (kg)
- BMI (see definition in section 4.3)
- BSA (see definition in section 4.3)
- Baseline Height (cm)
- Female reproductive status (for female participants only. Percentage will be based on the total number of female patients)

The summary of patient's characteristics based on MTP will include in addition the serology results (positive, negative, not done) for the following parameters HIV, Hepatitis B surface antigen (HBsAg), Hepatitis B core antibody (HBcAb), HCV Antibody, HCV RNA (only if HCV Antibody positive). For the summary based on MTP only, ECOG and weight collected just prior to or on the first day of MTP will be used as baseline. Please refer to sections 4.2.1 and 4.2.2 for further details related to definition of baseline evaluations.

All the biomarker outcomes will be summarized using descriptive statistics by treatment group on MTP population:

Given that the end of the induction phase is the same timepoint as the baseline tumor response for the MTP, two summary tables presenting the information as mentioned below will be produced. One for the tumor response status at the end of the induction phase based on ITP population and as per data collected on the eCRF and will present the following information.

- Number of patients with CR or PR at end of ITP
- Number of patients with SD at end of ITP
- Number of patients with PD at end of ITP
- Number of patients with NE at end of ITP
- Number of patients with NA at end of ITP (i.e. no tumor response during ITP)

The number of patients in MTP population will be summarized by country and study center (as per clinical database) and by treatment group based on the MTP population.

In addition, the number of patients will be summarized by the following stratification factors as per IxRS, by treatment group on the MTP:

- Region
  - European Union
  - Rest of the world
- Tumor response at the end of ITP
  - CR/PR
  - SD
- Microsatellite stability
  - MSI-H
  - MSS
- RAS status
  - Wild-type KRAS and NRAS
  - mutant KRAS and/or NRAS

A table will show the concordance between the tumor response status at the end of ITP as per IxRS and the tumor response status at the end of ITP as per data collected on the eCRF. This table will be based on the MTP population and will display the following categories:

- CR/PR, SD, Total for the IxRS tumor response
- CR, PR, CR/PR, SD for eCRF tumor response

eCRF Tumor response status (CR, PR, SD, PD, NE) at the end of ITP is defined as the last tumor response observed during the ITP. Patients without tumor assessment after first day of induction treatment will be assigned a tumor response of NA (Not available). Patients with only non-target lesions classified as having an eCRF tumor response status at the end of the ITP of "Non-CR/Non-PD" are classified as SD for the 2 summary tables mentioned above.

Summary of colorectal cancer history will be provided based on the ITP and MTP population and will present the following information:

- Histological grade at diagnosis
- Location of primary tumor
- Colon Location: left, right
- Cancer type: colon, rectal
- Initial AJCC/UICC stage
- Initial diagnosis: synchronous, metachronous
- Locally recurrent disease: yes, no
- Metastatic disease: yes, no

- Sites of metastatic disease at time of study enrolment (adrenal gland, ascites, bone, liver, lung, mediastinum, skin, other)
- Liver as metastatic site: yes, no
- Extent of disease by number of sites at time of study enrolment: 0, 1, > 1
- Time from initial diagnosis to first dose of ITP (in years)
- Time from first diagnosis of locally recurrent disease to first dose of ITP (in years)
- Time from first diagnosis of metastatic disease to first dose of ITP (in years)
- Number of target lesions at baseline

Of note, if start and/or end dates are incomplete or missing the corresponding time between the start and the end date cannot be derived. In this case, time from initial diagnosis to first dose of ITP or time for first diagnosis of locally recurrent disease to first dose of ITP or time from first diagnosis of metastatic disease to first dose of ITP cannot be derived and will be missing.

The following listings will be provided:

- Patient Demographics based on ITP population
- Biomarker status based on MTP population
- Patients by randomization stratification factors as per IxRS and eCRF (based on MTP)
- Colorectal cancer history based on ITP population

4.10.2 Medical History

Medical history, as collected on the “General Medical History and Baseline Conditions” eCRF page will be summarized using the ITP population. The summary table will include the number and percentage of patients with at least one medical history by Primary System Organ Class (SOC) sorted in a descending order of the total frequency count and by preferred term [PT] (sorted in a descending order of the total frequency count within each SOC).

A patient with more than one occurrence of the same medical history in a particular SOC/PT will be counted only once in the total of those experiencing events in that particular system organ class/preferred term.

4.10.3 Prior and Concomitant Medications

4.10.3.1 Prior Anti-Cancer Treatment/Procedure

Prior anti-cancer treatments/procedures summaries based on the ITP population will present the following information:

- Number of patients with prior colorectal cancer surgery: Yes, No
- Number of patients by site of prior colorectal cancer surgery: Colon, Rectum, Colon and Rectum, Other.
- Number of patients with prior radiotherapy: yes, no
- Number of patients with prior anti-cancer therapies: yes, no
- Number of patients by setting of prior systemic therapy
- Number of patients with prior systemic adjuvant therapy: yes, no
- Number of regimens for prior systemic therapy: 0, 1, 2, >=3.

The following listings will be provided based on the ITP population:

- Prior anti-cancer therapy

- Prior and on-study cancer radiotherapy
- Prior and on-study cancer colorectal surgery

4.10.3.2 Non Anti-Cancer Treatment/Procedure

A prior medication/therapy is defined as any medication/therapy with an end date prior to the start of the induction treatment.

Concomitant medication for ITP

Concomitant medication includes both medication concomitant at baseline and concomitant medication initiated post-baseline. It is defined as any medication/therapy with

- start date before or on:
  - the randomization date for patients randomized in the MTP
  - last dosing date of ITP+30 days for patients not randomized in the MTP
- and end-date on or after first dosing date of the ITP or with a missing (ongoing) end-date

Concomitant medication for MTP

It is defined as any medication/therapy with

- start date before or on last dosing date in the MTP+30 days
- and end-date on or after first dosing date of the MTP or with a missing (ongoing) end-date.

Post-treatment Medication

It is defined as any medication/therapy with a start date more than 30 days after the last dosing date.

In case a medication has an incomplete or missing start date/end date, please refer to section 4.14 for the rules to be applied in order to identify prior, concomitant or post-treatment medications.

Prior Medications/therapies will be summarized. Summary tables will present number and percentage of patients with any medication overall and by Drug Thesaurus Class and Generic Name. At each level of summation (overall, Drug Thesaurus Class, Generic Name), patients reporting more than one medication are counted only once. Drug Thesaurus Class will be sorted in a descending order of the total frequency count and the generic names with the highest frequency will be displayed first within each Drug Thesaurus class, unless otherwise indicated. The analysis population will be the ITP population and the MTP population for ITP data and MTP data, respectively.

The following tables will be provided:

- Concomitant medications during MTP based on MTP population

4.10.4 Subsequent Anti-Cancer Therapy

Post Induction Treatment and Post Maintenance Treatment anti-cancer therapies will be listed using the ITP population patients who have a study treatment discontinuation visit date.

4.11 EFFICACY ANALYSIS

Efficacy analysis will be conducted on the data collected during the MTP/Post maintenance treatment (when applicable) and using the MTP population. Analysis will be performed by randomized treatment group. Tumor assessments collected during the ITP will not be part of the efficacy analysis.

As Cohort 4 will not reach its target sample size, the analysis is not event driven as described in the study protocol, but is time driven instead. As a consequence, all p-values will be reported descriptively only, due to low power. All formal statistical tests will be two-sided and performed at an alpha of 5%, therefore 95% two sided CI will be presented. No adjustment will be made for multiplicity of testing secondary endpoints.

4.11.1 Primary Efficacy Endpoint

The primary efficacy objective of this study is to evaluate PFS.

To answer the primary objective, the following null and alternative hypotheses will be tested

- H0: the distribution of the PFS time is the same in the two treatment groups, i.e. PFS (Experimental group) = PFS (Control group)
- H1: the distribution of the PFS time is different in the two treatment groups, i.e. PFS (Experimental group) ≠ PFS (Control group)

The primary analysis of PFS will be a comparison between the experimental and the control group using an unstratified log-rank test. Please refer to Appendix 4 for the SAS code to be used.

PFS for each treatment group will be estimated using KM product-limit method estimates. PFS will be summarized by treatment group and will display the following information:

- Number of patients in the population (N)
- Number of patients with PFS event
- Number of patients censored
- Median and two-sided 95% CI computed according to Brookmeyer and Crowley method,
- 25th and 75th quantile, and the corresponding two-sided 95% CI computed according to Brookmeyer and Crowley method,
- Minimum and maximum
- The PFS rates (with the two-sided 95% CI) at 3, 6, 9, 12, 15 and 18 months
- Unstratified log-rank test p-value

KM plot of PFS by treatment group will be generated.

PFS time will be listed on MTP population in a dedicated time to event listing.

4.11.2 Secondary Efficacy Endpoints

4.11.2.1 Overall Survival

This study is not powered for OS, so adequately powered statistical testing for this endpoint will not be possible. However, the results of an unstratified log-rank test will be provided in an exploratory manner to assess the difference between treatment groups for OS.

The same analysis as those described for the primary endpoint will be repeated for OS on MTP population The survival rate will be displayed at the following time points: 6, 9, 12 and higher (every 3 months) if appropriate.

OS time will be listed on MTP population in a dedicated time to event listing.

4.11.3 Exploratory Efficacy Endpoints

Not Applicable.

4.11.4 Sensitivity Analyses

In addition, the following sensitivity analyses will be performed on PFS, the primary efficacy endpoint:

- The PFS hazard ratio, and its 95% two-sided confidence interval, of experimental group versus control group, will be estimated using a Cox proportional hazards model with treatment as the single covariate. Please refer to Appendix 4 for the SAS code to be used.
- The PFS hazard ratio, and its 95% two-sided confidence interval, of experimental group versus control group, will be estimated using different adjusted Cox proportional hazards models, using as covariates the treatment and one of the stratification factors, i.e. response at the end of induction treatment as mentioned below
    - cov1 (SD vs CR/PR as per eCRF)
    - cov1 (SD vs CR/PR as per IxRS)

  Note: No adjustment on the region will be performed as almost all the patients are in Europe.

The OS hazard ratio, and its 95% two-sided confidence interval, of experimental group versus control group, will be estimated using a Cox proportional hazards model with treatment as the single covariate. Please refer to Appendix 4 for the SAS code to be used.

4.11.5 Subgroup Analyses

No subgroup analysis will be performed for Cohort 4.

4.12 PHARMACOKINETIC AND PHARMACODYNAMIC ANALYSES

Not applicable

4.13 SAFETY ANALYSES

Separate safety summaries will be produced for ITP and MTP.

For ITP data, outputs will be generated on the ITP displaying randomized vs. non randomized patients in MTP. MTP outputs will be based on the SAF population and will be presented by treatment group.

No inferential statistical analyses are planned.

4.13.1 Exposure of Study Medication

A patient will be considered as having initiated a cycle in the ITP if at least one (non-null) dose of any study drugs of the ITP has been administered in the corresponding cycle.

The overall number of cycles initiated during the ITP is defined as the sum of all initiated cycles (as defined above) in the ITP.

For the MTP, the overall number of cycles initiated (i.e. for drug combination) will be computed as the sum of all initiated cycles as defined below:

- Day 1 of a cycle is defined as the first day in the considered cycle when treatment is administered.
- The cycle length is assumed to be 2 weeks
- For experimental group:
    - a cycle will be assumed to be initiated if cobimetinib and atezolizumab are administered at any time during the same cycle
- For control group:
    - If capecitabine is administered: a cycle will be assumed to be initiated if capecitabine and bevacizumab are administered at any time during the same cycle
    - If 5-FU/LV or LV substitute is administered: a cycle will be assumed to be initiated if bevacizumab and 5-FU and LV or any LV substitute are administered at any time during the same cycle

The overall duration (in weeks) for all components of maintenance treatment is defined as follows:

- Experimental group:

[MAX(min(last dosing date of cobimetinib+6, death date), min(last dosing date of atezolizumab+13, death date)) – MIN (first dosing date of cobimetinib, first dosing date of atezolizumab) + 1]/7

- Control group:
    - If capecitabine is administered in the last cycle:

[MAX(min(last dosing date of capecitabine+6, min(last doing date of bevacizumab+13, death date)) – MIN (first dosing date FP, first dosing date of bevacizumab) + 1]/7.

    - If 5-FU/LV is administered in the last cycle:

[MAX(min(last dosing date of 5-FU/LV+13, death), min(last dosing date of bevacizumab+13, death date)) – MIN (first dosing date of FP, first dosing date of bevacizumab) + 1]/7

with first dosing date of FP = min(fist dosing date of 5-FU, first dosing date of LV or any LV substitute, first dosing date of capecitabine) and last dosing date of 5-FU/LV = max(first dosing date of last administration of 5-FU, first dosing date of last administration of LV or any LV substitute)

The number of cycles administered, duration of dosing, cumulative dose, dose intensity and relative dose intensity (RDI) definitions are provided for each drug individually in Table 2 and Table 3 for induction and maintenance, respectively.

According to protocol, the cycle length is 2 weeks, excepted for capecitabine in the control arm for which each cycle length is as per local practise. A 2-week cycle schedule will be considered for drugs other than capecitabine and for the drug combinations. For capecitabine, a cycle is defined as any continuous administration separated by a rest period, regardless of the duration of the continuous administration and the duration of the rest period. A patient will be considered as having initiated a cycle in the MTP for a specific drug if at least one (non-null) dose of this study drug has been administered in the corresponding cycle.

Table 3: Exposure Definitions for Induction Treatments

	FOLFOX	5-FU/LV	bevacizumab
Number of cycles	sum of all cycles in which at least one non-null dose of FOLFOX has been administered	sum of all cycles in which at least one non-null dose of 5-FU and LV has been administered. Of note, consider only cycles where oxaliplatin is not administered concomitantly with 5-FU/LV.	sum of all cycles in which at least one non-null dose of bevacizumab has been administered
Duration of dosing (weeks) (1)	[min (last date of FOLFOX+13, death date) – first FOLFOX dosing date+1] / 7 or If FOLFOX-4 or FOLFOX-7 or modified FOLFOX-7 is administered in the last cycle initiated [min (last date of FOLFOX +12, death date) – first FOLFOX dosing date+1] / 7	max (min(last date of 5-FU+13, death date), min(last date of LV+13, death date)) – min (first date of 5-FU, first date of LV) +1] / 7 Of note, consider only records/cycles where oxaliplatin is not administered concomitantly with 5-FU/LV.	[min (last date of bevacizumab +13, death date)) – (first bevacizumab dosing date in the induction) +1] / 7

(1) According to the proposed formula, the duration of dosing may be overestimated in case patients discontinued treatment prior to the end of the last cycle.

Table 4: Exposure Definitions for Maintenance

	Capecitabine	5-FU or LV	bevacizumab	atezolizumab	cobimetinib
Number of cycle	The sum of all cycles in which at least one non-null dose of <*treatment*> has been administered				
Duration of dosing (weeks) [(1)]	[min (last dosing date of <treatment> + x, death date)) – (first <treatment> dosing date in the maintenance) +1] / 7 Where x=6 for capecitabine, cobimetinib x=13 for 5FU, LV, bevacizumab, atezolizumab For 5-FU and LV, last dosing date of treatment will be replaced by the first dosing date of the last administration				
Actual dose	<treatment> dose administered (in mg) as collected on the dosing eCRF page Unit: mg				
Planned dose	<treatment> planned dose (in mg) as collected on the dosing eCRF page Unit: mg				
Normalized dose	dose / recalculated BSA[(2)] Unit: mg/m^2		dose / weight[(3)] Unit: mg/kg	NA	NA

	Capecitabine	5-FU or LV	bevacizumab	atezolizumab	cobimetinib
Cumulative dose	The cumulative dose will be derived for each records as below: (end date of administration - start date of administration +1) * normalized actual dose for the record * 2 Cumulative dose= sum of cumulative dose across all records Unit: mg/m2	sum of the all <treatment > normalized actual doses (in mg/m^2) administered in all cycles	sum of the all bevacizumab normalized actual doses (in mg/kg) administered in all cycles	sum of the all of atezolizumab actual doses (in mg) administered in all cycles	The cumulative dose will be derived for each records as below: (end date of administration - start date of administration +1) * actual dose for the record Cumulative dose= sum of cumulative dose across all records Unit: mg
Dose intensity	Cumulative dose / (duration of dosing *7) Unit: mg/m^2/day	Cumulative dose / duration of dosing Unit: mg/m^2/week	Cumulative dose / duration of dosing Unit: mg/kg/week	Cumulative dose / duration of dosing Unit: mg/week	Cumulative dose / (duration of dosing * 7) Unit: mg/day
Cumulative planned dose (CPD)	Sum of all normalized planned dose (in mg/m^2) in all cycles	Sum of all normalized planned dose (in mg/m^2) in all cycles	Sum of all normalized planned dose (in mg/kg) in all cycles	Sum of the all planned doses (in mg) reported in all cycles	Sum of all planned doses (in mg) in all cycles where 'Planned treatment break as per protocol' is not ticked
Planned dose intensity	CPD/(duration of dosing *7) Unit: mg/m^2/day	CPD/duration of dosing Unit: mg/m^2/week	CPD/duration of dosing Unit: mg/kg/week	CPD/duration of dosing Unit: mg/ week	CPD/(Duration of dosing *7) Unit: mg/day

Relative dose intensity (RDI) (%)	100 * (dose intensity) / (planned dose intensity)

(1) According to the proposed formula, the duration of dosing may be overestimated in case patients discontinued treatment prior to the end of the last cycle.
(2) The BSA will be recalculated based on the height and weight (see point 3 for identification of weight) of the patient using the formula as mentioned in section 4.3.
(3) The baseline weight will be used as reference. If the last available weight of the patient prior to or on the cycle start has changed by 10% or greater (i.e. patient has gained or lost more than 10% of their body weight since baseline) the patient new weight will be set as the baseline weight and will be used at the patient current and subsequent cycles. If a patient weight has changed by 10% or greater at a later cycle, then this new weight will be set as the base weight as aforementioned.

The following information will be tabulated for the ITP using the ITP population:

- Summary of total number of cycles initiated per patient
  - Total number of cycles initiated (1,2,3,4,5,6,7,8)
  - Summary statistics of total number of cycles initiated

The following information will be tabulated for the MTP using the SAF population:

- Summary of overall duration of treatment and overall number of cycles initiated
  - Overall duration of maintenance treatment (in weeks)
  - Overall number of cycles initiated: 1,2,3,4,5,6,7,8,9,10, 10-15, >=15
  - Summary statistics of overall number of cycles initiated per patient
- Summary of drug exposure
  - Total number of cycles administered (tabulated separately for each drug)
  - Duration of dosing (in weeks) (tabulated separately for each drug)
  - Cumulative dose (tabulated separately for each drug according to definition provided in table 3)
  - Dose intensity (tabulated separately for each drug according to definition provided in table 3)
  - Relative dose intensity: ≤90%, >90%-≤100%, >100% (tabulated separately for each drug according to definition provided in table 3) Note: Number and percentage will be based on the patients who received the corresponding drug.

Supportive listings presenting the study drug administration as well as the exposure information will be provided separately based on ITP population and SAF population for the induction and for the maintenance, respectively.

4.13.1.1 Cycle Delay

Cycle delay is applicable to the following treatments: FP (5-FU, LV or capecitabine), and bevacizumab.

Cycle delay is defined as follow:

- For 5-FU, LV, bevazicumab, atezolizumab which have planned cycle of 2 weeks:

A cycle delay for <treatment> will be defined as the number of days in excess of the expected days between two consecutive doses of <treatment> (14 days) and will be calculated as D1Cn+1 - D1Cn where D1Cn+1 and D1Cn correspond to date of administration of <treatment> in cycle n+1 and cycle n, respectively. An excess of more than 3 days will qualified cycle Cn+1 as delayed for <treatment>. Of note, the first cycle (C1) cannot be identified as cycle delay.

- For capecitabine:

Cycle delay will be defined as the number of days in excess of the expected days between two non-zero administrations (21 days, i.e. 14 days of administration and a rest period of 7 days) and will be calculated as D1Cn+1 - D1Cn where D1Cn+1 and D1Cn correspond to the start date of the first administration of capecitabine in cycle n+1 and cycle n, respectively. An excess of more than 3 days will qualify cycle Cn+1 as delayed for capecitabine. Of note, the first cycle (C1) cannot be identified as cycle delay.

- For cobimetinib, which has planned cycle of 4 weeks (3 weeks on, 1 week off):

Cycle delay will be defined as the number of days in excess of the expected days between two non-zero administrations (28 days, i.e. 21 days of administration and a rest period of 7 days) and will be calculated as D1Cn+1 - D1Cn where D1Cn+1 and D1Cn correspond to the start date of the first administration of cobimetinib in cycle n+1 and cycle n, respectively. An excess of more than 3 days will qualify cycle Cn+1 as delayed for cobimetinib. Of note, the first cycle (C1) cannot be identified as cycle delay.

Cycle delay will be displayed in listing.

4.13.2 Adverse Events

Adverse events variables are defined in Table 5.

Table 5: Adverse Events Definitions

Variable	Definition
Treatment Emergent Adverse Events (TEAEs) for the induction treatment phase (1)	Any adverse events (serious and non-serious) with an onset date on (only if the "Event occurred prior to first study drug administration" from the AE eCRF page is not checked) or after the first day of treatment of the ITP and up to the: • first day of treatment of the MTP (excluding) if it occurs within the 30 days from last day of treatment of induction treatment for patients treated with maintenance treatment • within 30 days from last day of treatment of induction treatment (as defined in section 4.2.1), for patients not treated with maintenance treatment or for patients treated with maintenance treatment but with first day of treatment of MTP being more than 30 days after last day of treatment of ITP.
TEAEs for the maintenance treatment phase(1)	Any adverse events (serious and non-serious) with an onset date on (only if the "Event occurred prior to first study drug administration" from the AE eCRF page is not checked) or after the first day of treatment of the MTP and up to 30 days (for patients in control group, i.e. not treated with atezolizumab) and 90 days (for patients in experimental group, i.e. treated with atezolizumab) from the last day of treatment of MTP (as defined in section 4.2.2)
Post induction treatment Adverse Events	Any adverse events (serious and non-serious): • with an onset date more than 30 days after the last day of treatment of the ITP (as defined in section 4.2.1) for patients not treated with maintenance treatment. • with an onset date more than 30 days after the last day of treatment of the ITP and prior the first day of treatment of the MTP, for patients treated with maintenance treatment with first day of treatment of MTP being more than 30 days after last day of treatment of ITP..

Post maintenance treatment Adverse events	Any adverse events (serious and non-serious) with an onset date more than 30 days (for patients in control group, i.e. not treated with atezolizumab) and more than 90 days (for patients in experimental group, i.e. treated with atezolizumab) after the last day of treatment of the MTP (as defined in section 4.2.2) (as defined in section 4.2.2).
Adverse Events NCI CTCAE grade	The adverse events grade will be the one with tick box checked for "AE most extreme NCI CTCAE grade"
Serious Adverse Events (SAEs)	Any adverse events qualified as “serious” by the investigator.
Adverse Events with fatal outcome	Any adverse events with outcome of “Fatal”.
Adverse events related to <FOLFOX, bevacizumab, FP, atezolizumab, cobimetinib>	Any adverse events with an “AE suspected to be caused by study drug <FOLFOX, bevacizumab, FP, atezolizumab, cobimetinib> as ‘Yes’. For AE suspected to be caused by FOLFOX while starting in the maintenance phase, the unique text ‘“AE considered related to Folfox”‘ has been reported in the comment field ‘
Adverse events leading to <FOLFOX, bevacizumab, FP, atezolizumab, cobimetinib> discontinuation	Any adverse events with an “Action taken with <FOLFOX, bevacizumab, FP, atezolizumab, cobimetinib> due to SAE/AE” of “drug withdrawn”
Adverse events of Special Interest (AESI) as reported on eCRF	AESIs will be selected based on the tick box from the eCRF.
<Bevacizumab, atezolizumab> AESIs based on pre-defined terms	AESIs will be selected from AEs based on the <bevacizumab, atezolizumab> list of pre-defined terms.

(1) Of note, in case an event has an incomplete or missing start date, which consequently prevents its allocation to only one treatment phase of the study, the event will be allocated to both the induction and maintenance phase. Refer to section 4.14 for further details.

Safety summaries will be produced for the ITP on the ITP population and for the MTP on the SAF population, unless otherwise specified. ITP summaries will display patients randomized vs. patients not randomized in MTP. MTP summaries will be done by actual maintenance treatment group as defined for the SAF. Descriptive statistics will be generated as appropriate. No inferential statistical analyses are planned.

Summaries of adverse events for ITP and MTP will be generated for those events that are considered treatment emergent. The AE tables will include the number and percentage of patients with at least one AE, by MedDRA primary System Organ Classes (SOC) (sorted in a descending order of the total frequency count) and MedDRA Preferred Terms (PT) (sorted by descending order of the overall frequency count within each SOC) unless otherwise indicated. A patient with more than one occurrence of the same adverse event in a particular system organ class/preferred term will be counted only once in the total of those experiencing adverse events in that particular system organ class/preferred term. For the overall summary tables, information presented by grade will not be restricted to the worst grade per patient i.e. all events will be presented. Any AEs with a missing CTC grade will be reported in the "missing" category grade.

An overview table will be produced for the ITP based on the ITP population and will present:

- Number of TEAEs
- Number of patients with at least one TEAE
- Number of patients with at least one TEAE by CTC grade: 1, 2, 3, 4, 5, ≥3, missing
- Number of patients with at least one related TEAE
    - Any study drug
    - FOLFOX
    - 5-FU/LV
    - bevacizumab
- Number of patients with at least one serious TEAE
- Number of patients with at least one related serious TEAE
    - Any study drug
    - FOLFOX
    - 5-FU/LV
    - bevacizumab
- Number of patients with at least one TEAE with fatal outcome
- Number of patients with at least one TEAEs leading to treatment discontinuation of:
    - Any study drug
    - FOLFOX
    - 5-FU/LV
    - bevacizumab

An overview table will be produced for the maintenance phase based on the SAF and will present:

- Number of TEAEs
- Number of patients with at least one TEAE
- Number of patients with at least one TEAE by CTC grade: 1, 2, 3, 4, 5, ≥3, missing
- Number of patients with at least one related TEAE
    - Any study drug
    - Fluoropyrimidines
    - bevacizumab

    - atezolizumab
    - cobimetinib
    - FOLFOX
- Number of patients with at least one serious TEAE
- Number of patients with at least one related serious TEAE
    - Any study drug
    - Fluoropyrimidines
    - bevacizumab
    - atezolizumab
    - cobimetinib
    - FOLFOX
- Number of patients with at least one TEAE with fatal outcome
- Number of patients with at least one TEAEs leading to treatment discontinuation of:
    - Any study drug
    - bevacizumab
    - atezolizumab
    - cobimetinib
- Number of patients with at least one treatment emegent AESI (as reported on eCRF)
- Number of patients with at least one treatment emegent AESI (based on list of pre-defined terms)
    - bevacizumab,
    - atezolizumab
- Number of patients with at least one serious treatment emergent AESI (as reported on eCRF)

In addition, the following tables (number and percentage of patients) will be presented for the ITP based on the ITP population and will display the number of patients (and corresponding number of TEAEs) and percentage with any:

- TEAEs by SOC and PT
- TEAEs by SOC and PT and by Worst Intensity
- Related TEAEs by SOC and PT: any study drugs, bevacizumab,
- TEAEs leading to treatment discontinuation by SOC and PT: any study drugs
- TEAEs leading to dose reduction or interruption by SOC and PT: bevacizumab
- Serious TEAEs by SOC and PT
- Related serious TEAEs by SOC and PT: to any study drugs, bevacizumab
- Treatment emergent AESI by AESI eCRF categories, SOC and PT
- Bevacizumab treatment emergent AESI based on pre-defined categories

The following tables will be presented for the MTP only and will display the number and percentage of patients (and corresponding number of TEAEs) with any:

- TEAEs by SOC and PT
- TEAEs by SOC and PT and by Worst Intensity
- Related TEAEs by SOC and PT: any study drugs, atezolizumab, bevacizumab, cobimetinib
- Serious TEAEs by SOC and PT
- Grade 5 TEAEs or TEAEs with fatal outcome by SOC and PT
- TEAEs leading to treatment discontinuation by SOC and PT: any study drugs,

- TEAEs leading to dose reduction or interruption by SOC and PT: atezolizumab, cobimetinib
- Related serious TEAEs by SOC and PT: to any study drugs, atezolizumab, bevacizumab, cobimetinib
- Treatment emergent AESI by AESI eCRF categories, SOC and PT
- Bevacizumab treatment emergent AESI based on pre-defined categories during MTP
- Atezolizumab treatment emergent AESI based on pre-defined categories during MTP

By-patient listings will be provided for AEs; they will include Post-treatment adverse events. Appropriate flagging of study phase (ITP/MTP) as well as TEAEs/Post-treatment AEs will be done. The following listings will be provided based on ITP population

- All adverse events
- All Grade 5 adverse events or any adverse events with fatal outcome
- All adverse events leading to treatment discontinuation
- All AESI (as reported on eCRF)

4.13.3 Death

The following summary tables will be provided and will present:

- The number of patients who died within 30 days from last day of treatment of MTP (as defined in section 4.2.1) with the corresponding death reason using the SAF population
- The number of patients who died more than 30 days from last day of treatment of maintenance treatment and the corresponding reason of death based on patients from the MTP population who has a study treatment discontinuation visit date

One listing will be generated for deaths based on the ITP population and including appropriate flagging of study phase (ITP and MTP) and on-treatment/post-treatment deaths (i.e. within 30 days from last day of treatment/more than 30 days from last day of treatment).

All deaths information (including reason and date) will be retrieved from the Study Completion/Early Discontinuation eCRF page.

4.13.4 Laboratory Data

The following laboratory parameters will be considered as CTC gradable parameters.

Haematology

- Absolute Neutrophils Count (ANC)
- Hemoglobin (Hb)
- Leukocytes/White Blood Cells counts (WBC)
- Platelet Count

Blood chemistry

- Albumin
- Alkaline Phosphatase (ALP)
- Calcium
- Creatinine

- Creatine phosphakinase
- Glucose
- Potassium
- SGPT or alanine aminotransferase (ALT)
- SGOT or aspartate aminotransferase (AST)
- Sodium
- Total Bilirubin
- Magnesium
- Amylase
- Lipase

Coagulation
- international normalized ratio (INR)
- activated partial thromboplastin time (aPTT)

The following parameters will be considered as non CTC gradable parameters.

Hematology
- Red blood Cell (RBC)
- Hematocrit
- Lymphocytes
- Neutrophils
- Eosinophils
- Basophils
- Monocytes

Blood Chemistry
- Blood Urea Nitrogen
- Bicarbonate
- Chloride Lactate dehydrogenase (LDH)
- Phosphorus
- Total Protein

Urinalysis
- Urine Protein Dipstick
- 24-hour urine protein

Thyroid
- Thyroid-Stimulating Hormone (TSH)
- Free T3
- Free T4

All laboratory parameter information will be summarized for MTP only. Laboratory information reported in tables will be restricted to the baseline and on-treatment measurements. The analysis population will be the SAF population for the MTP.

Clinical laboratory values will be expressed using Système International (SI) units.

When applicable, laboratory tables will display their High (hyper)/Low (hypo) values of a specific parameter (e.g. calcium (high) and calcium (low) in separate tables.

In case of missing normal ranges for parameters that are not differential and have only grade 1 defined from normal ranges (e.g. Neutrophils, WBC, Albumin…) the worst case scenario will be applied, i.e. grade 1.

A "Missing" category will be reported for patients with missing grades or missing reference range indicators at baseline and/or on-treatment and patients with no laboratory assessments.

For hematology, blood chemistry and coagulation parameters which can be graded per CTCAE, the information will be summarized by means of a shift table summarizing the baseline grade versus the worst CTC grade per patient defined as the highest CTC grade among the on-treatment evaluations. If there is no on-treatment evaluation, then the worst grade will be set to 'Missing'.

Hematology and blood chemistry parameters which cannot be graded per CTCAE, the information will be summarized by means of a shift table from baseline category to worst on-treatment category. The following categories will be used:

- Baseline: Low/Normal/High/Missing/Overall
- Worst on-treatment: Low/Normal/High/Missing/Overall

Patient with "High" and "Low" for the same laboratory test (at different visits) is counted for each direction in summary tables.

For urinalysis protein dipstick, all non-missing assessments excepted "0-absent" assessment will be considered "Present". A shift table presenting baseline category versus worst on-treatment category will be produced with the following categories:

- Baseline: Absent/Present/Missing/Overall
- Worst on-treatment: Absent/Present/Missing/Overall

For urinalysis, 24-hour urine protein values will not be tabulated but listed only.

4.13.5 Vital Signs

Vital signs parameters include:

- Temperature (°C)
- Systolic blood pressure (SBP seated position) (mmHg)
- Diastolic blood pressure (DBP seated position) (mmHg)
- Weight (kg)
- BSA (m^2)
- Heart rate (beats/min)
- Respiratory rate (breaths/min)

Vital signs information will be summarized for each phase separately and by treatment group when applicable. Vital signs information reported in tables will be restricted to non-missing baseline and non-missing on-treatment measurements. The analysis population will be the SAF population for the MTP.

Actual value and change from baseline for heart rate and systolic and diastolic blood pressure will be summarized by treatment group for each visit using descriptive statistics. For the experimental arm, vital signs are collected within 60 minutes before the infusion and at other

timepoints when clinically indicated and at the first infusion. Only the timepoint 'Within 60 minutes before the infusion' will be included in the summary table.

4.13.6 Other Safety Assessment

Blood oxygen saturation is measured only in patients randomized to the experimental treatment group. Blood oxygen saturation will be measured by pulse oximetry.

Non-missing pulse oximetry values will be summarized by visit through descriptive statistics.

4.14 MISSING DATA

Imputation of partial/missing death date will be done as follows:

- If the date is completely missing, then the day of "Last known to be alive" +1 will be used
- If only day is missing and year and month are same as "Last known to be alive", then the day of "Last known to be alive"+1 will be used otherwise the 1st day of the month will be used
- If day and month are missing and year is same as "Last known to be alive", then the "Last known to be alive"+1 will be used, otherwise 1st of January will be used

Partially missing dates for adverse events (AEs) will be imputed as follows. Of note, imputation of missing/partial AE date will be done only to identify treatment emergent AEs.

AE onset dates

- Partially missing onset dates will be imputed as follows
  - When only Day is missing:
    - If Month & Year of the onset date are the same as Month & Year of the first day of treatment of the induction/maintenance treatment phase, the imputed onset date will be imputed as the minimum of the first day of treatment of the induction/maintenance treatment phase and the AE resolution date (imputed if needed).
    - Otherwise, the missing day will be replaced by "1".
  - When Day & Month are missing:
    - If Year of the onset date is the same as Year of the induction/maintenance treatment phase, the imputed onset date will be imputed as the minimum of the first day of treatment of the induction/maintenance treatment phase and the AE resolution date (imputed if needed).
    - Otherwise, the missing Day & Month will be replaced by "01JAN".

- Complete missing onset dates for AEs will be imputed by first day of treatment of the induction/maintenance treatment phase and the AE will be considered as treatment emergent, unless the end date of the AE (imputed if needed) or the end year of the AE (if day and month are missing) is entered and is before the year of the first treatment administration of the induction/maintenance treatment phase.

AE resolution dates

- Incomplete resolution dates will be replaced by the last day of the month (if day is missing only), if not resulting in a date later than the date of patient's death. In the latter case the date of death will be used to impute the incomplete resolution date
- In all other cases the incomplete resolution date will not be imputed

Of note, the above rules may allow allocation of an event to both the ITP and MTP treatment phase.

Partially missing dates for medications/therapies will be imputed as follows. Of note, imputation of missing/partial medicationstherapies date will be done only to identify concomitant medications/therapies.

Partial dates will be imputed as follow:

- Start dates
  - When only Day is missing: the missing day will be replaced by “1”
  - When Day & Month are missing: the missing Day & Month will be replaced by “01JAN”.
- End dates
  - When only Day is missing: the missing day will be replaced by the last day of the month
  - When Day & Month are missing: the missing Day & Month will be replaced by “31DEC”.

And rules described in section 4.10.3.2 and below will be applied using imputed dates.

In case of complete missing dates, the following will be applied:

- If the start date of the medication/therapy is unknown (i.e. complete missing date) and there is no end date, medication/therapy is flagged as taken prior to study but not as ongoing then the medication/therapy will be considered as a prior medication.
- If both the start date and end date of the medication/therapy is unknown (i.e. complete missing date), then the medication/therapy will be considered as a concomitant medication/therapy for both the induction and maintenance phase if the patient is treated in the phase of interest.
- If the start date of the medicationtherapy is unknown (i.e. complete missing date), but the end date is known and is prior to the first dosing date of the considered phase, then the medicationtherapy will not be considered as concomitant for the corresponding phase.
- If the start date of the medication/therapy is available and the end date is unknown, then the medication/therapy will not be considered as prior. Concomitance to ITP/MTP will be assessed using the available start date.

Partially missing dates for surgery will be imputed as follows. Of note, imputation of missing/partial surgeries date will be done only to identify concomitant surgeries.

Partial dates will be compared as follow:

- When only Day is missing: Month & Year of the surgery will be compared to Month & Year of the first dosing date of interest (either ITP or MTP). If on or after, the surgery will be considered as concomitant to the period of interest. If on or before the first doing date of ITP, the surgery will be considered as prior.
- When Day & Month are missing: Year of the surgery will be compared to Year of the dosing date of interest (either ITP or MTP). If on or after, the surgery will be considered as concomitant to the period of interest. If on or before the first doing date of ITP, the surgery will be considered as prior.

Of note, the above rules may allow a medication/procedure to be concomitant to both the ITP and MTP treatment phase.

For patients who discontinued study treatment but without any study treatment discontinuation visit date, this visit will be imputed as follows:

- If patient was treated in the MTP, the last dose will be retrieved from the treatment drug completion/early discontinuation page from the eCRF in the maintenance phase. The maximum date among the date mentioned for each treatment during MTP + 30 days will be considered.
- If patient was treated in the ITP, the last dose will be retrieved from the treatment drug completion/early discontinuation page from the eCRF in the induction phase. The maximum date among the date mentioned for each treatment during ITP + 30 days will be considered

with the following exception:

  - If a patient died within 30 days from last dose, the follow up phase does not exist for this patient

Partially missing dates for date of initial histological diagnosis or date of first diagnosis of metastatic disease or date of first diagnosis of locally recurrent disease will be imputed as follows:

Imputation of these partial dates will be done only to determine if the initial diagnosis is synchronous or metachronous and only in case the date day is missing. The imputation will consist in replacing the missing day by “1”. In case month and/or year are missing, no imputation will be done.

No other dates will be imputed, unless otherwise specified. The original incomplete, missing or partial dates will be presented in the listings, not the imputed dates.

4.15 INTERIM ANALYSES

No formal interim analyses on PFS or OS are planned.

5. REFERENCES

Di Nicolantonio F, Martini M, Molinari F, et al. Wild-type BRAF is required for response to panitumumab or cetuximab in metastatic colorectal cancer. J Clin Oncol. 2008 Dec 10;26(35):5705-12. doi: 10.1200/JCO.2008.18.0786. Epub 2008 Nov 10.

Ron Brookmeyer and John Crowley, A Confidence Interval for the Median Survival Time. Biometrics Vol. 38, No. 1 (Mar., 1982), 29-41

Appendix 1: Protocol Synopsis

Objectives

Efficacy Objectives

The primary efficacy objective of the study is to evaluate progression-free survival (PFS) within each maintenance treatment cohort.

Secondary efficacy objectives include the evaluation of efficacy through other endpoints:

- Overall survival (OS)
- Overall response rate (ORR)
- Disease control rate (DCR)
- Time to treatment response (TTR)
- Duration of response (DoR)
- Change in Eastern Cooperative Oncology Group (ECOG) performance status

Safety Objectives

Additional objectives for this study are to assess the safety of each treatment including:

- the 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

Adverse events (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 modified RECIST (mRECIST) in patients treated with atezolizumab

The exploratory biomarker objectives for 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)
- Explore and correlate microbiome with other biomarkers, baseline characteristics and clinical outcome

Study Design

Description of Study

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). The primary study endpoint is PFS according to RECIST 1.1 within each cohort. Secondary endpoints include other efficacy measurements and safety. In addition, exploratory outcomes will focus on the correlations between biomarkers and study outcomes.

Patients with mCRC who have not received any prior chemotherapy in the metastatic setting are eligible for entry. The study will enrol patients in Europe, Asia, Africa, and South America.

For an individual patient, the study will consist of a Screening Phase (≤ 28 days), a 4-month Induction Treatment Phase, a Maintenance Treatment Phase, and finally follow-up during the Post-Treatment Follow-up Phase.

Potential patients will undergo screening assessments to determine study eligibility within 28 days prior to starting study induction treatment. Results from routine assessments conducted prior to informed consent signature may be used as screening assessments as long as they were done within

7 days prior to informed consent signature. The primary tumour tissue block prepared at the time of the initial diagnosis will be used for biomarker assessment for maintenance treatment cohort assignment (see Appendix 17). If the tumour block is not available, ≥ 20 slides cut from the primary tumour sample will be accepted as an alternative. The sample (block or slides) must be shipped to the designated laboratory and confirmation of sample receipt by the laboratory must be obtained before the patient may be enrolled in the study.

All patients enrolled in the study will be asked to give written informed consent to provide blood samples for exploratory biomarker analyses and to allow all available residual samples of tumour, blood and plasma samples collected in the study be used for additional exploratory biomarker research using the Roche Clinical Sample Repository (RCR). No additional sampling is required for RCR samples. Prior to May 2018, an optional metastatic tumour sample was collected from all study patients. In addition, patients at selected centres were able to participate in an optional Supplemental Biomarker Program (described in Appendix 18). As of May 2018, collection of the optional baseline metastatic tumour sample has been discontinued and the Supplemental Biomarker Program has been closed. Baseline metastatic tumour samples and Supplemental Biomarker Program samples collected up to this time point may still be used for exploratory biomarker analyses.

Eligible patients will enter a 4-month Induction Treatment Phase. Treatment during this phase, based on Investigator's choice (see Appendix 6), 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

During the Induction Treatment Phase, patients will be assessed for AEs at every cycle. Clinical laboratory assessments will be conducted at each cycle, however results from tests conducted every second treatment cycle only will be collected in the case report form (CRF). Physical examinations and documentation of concomitant medications will be done every two treatment cycles. 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 prematurely discontinue study treatment for any reason during the Induction Treatment Phase, or who experience PD at any time during or at the end of the Induction Treatment Phase, or who refuse to proceed to the Maintenance Treatment Phase or who are not eligible for any study cohort will undergo a Study Treatment Discontinuation Visit within 30 days after the last dose of study treatment and will then enter the Post-Treatment Follow-up Phase. All patients need to be evaluated for potential resection of metastasis at completion of the induction period. This is of particular importance for patients with liver metastases. If the patient is found to be resectable they will undergo a Study Treatment Discontinuation Visit within 30 days after the last dose of study treatment and will then enter the Post-Treatment Follow-up Phase. Patients completing induction treatment who do not have progressive disease and whose disease has not become resectable can proceed to the Maintenance Treatment Phase. Informed consent based on the information specific to the assigned maintenance cohort will be obtained prior to the conduct of any cohort-specific screening assessments (unless the study site has chosen to conduct informed consent including information for induction regimens and all potential maintenance regimens prior to study entry).

Each maintenance treatment cohort will consist of a cohort-specific experimental treatment arm and a standard control arm of fluoropyrimidine (5-FU/LV or capecitabine) and bevacizumab. At completion of the Induction Treatment Phase of the study, patients continuing to the biomarker-driven Maintenance Treatment Phase will be assigned to a maintenance treatment cohort based on the biomarker profile determined from their primary tumour tissue. Biomarkers considered in maintenance

treatment assignment include presence or absence of HER2 overexpression (HER2+ or HER2- respectively), microsatellite stability status (microsatellite stable [MSS] or high microsatellite instability [MSI-H]), wild-type or mutated BRAF gene ($BRAF^{wt}$ or $BRAF^{mut}$ respectively), and presence or absence of RAS pathway mutation (RAS^{wt} or RAS^{mut} respectively; see Appendix 17 for the biomarker-based cohort assignment decision tree). Patients will be randomised within their assigned cohort on a 2:1 (experimental:control) basis to either the experimental treatment arm or the control arm of that cohort and will begin treatment within 3 weeks of completing induction treatment. Randomisation will be stratified according to specific biomarkers identified for each cohort, by geographical region, and/or by patient response after the Induction Treatment Phase (CR/PR vs. SD). Stratification variables applicable to each cohort are described in Section 4.2 of the protocol.

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 (see Figure 1).

Cohort 1

Biomarker profile (all patients screened prior to June 3, 2016): $BRAF^{mut}$

Biomarker profile (all patients screened after June 3, 2016): HER2-/MSS/$BRAF^{mut}$/RAS^{wt}

5-FU/LV with cetuximab and vemurafenib

vs.

Fluoropyrimidine (5-FU/LV or capecitabine) and bevacizumab

Cohort 2 - CLOSED TO ENROLMENT

(No patients screened after June 3, 2016 will be assigned to this cohort)

Biomarker profile: $BRAF^{wt}$

Fluoropyrimidine (5-FU/LV or capecitabine) with bevacizumab and atezolizumab

vs.

Fluoropyrimidine (5-FU/LV or capecitabine) and bevacizumab

Cohort 3

Biomarker profile: HER2+

Capecitabine with trastuzumab and pertuzumab

vs.

Fluoropyrimidine (5-FU/LV or capecitabine) and bevacizumab

Cohort 4 - CLOSED TO ENROLMENT

(As of February 12, 2018, no further patients are assigned to this cohort. See protocol Section 3.1.2.4.)

Biomarker profiles: HER2-/MSI-H; HER2-/MSS/$BRAF^{wt}$; HER2-/MSS/$BRAF^{mut}$/RAS^{mut}

Cobimetinib and atezolizumab

vs.

Fluoropyrimidine (5-FU/LV or capecitabine) and bevacizumab

See Appendix 17 for additional information on biomarker testing and biomarker-based cohort assignment.

Study Enrolment and Cohort Status Update:

- Accrual to Cohort 2 was completed in November 2016.

- Study enrolment and accrual into Cohort 4 were suspended in February 2018 as a result of an unfavourable benefit-risk evaluation of Cohort 4 by the independent Data Monitoring Committee (iDMC). Accrual to Cohort 4 was not re-opened after February 2018 due to iDMC recommendations. See protocol Section 3.1.2.4.
- Cohort assignment and randomization of any patients who were already enrolled and eligible for Cohorts 1 and 3 were continued following the February 2018 suspension of study enrolment.
- No new or modified cohorts have been identified for addition to the study. In the absence of a cohort with broad biomarker eligibility criteria (i.e. to replace Cohort 4), the majority of patients would not be eligible for maintenance cohort assignment. For this reason, study enrolment will not be re-opened following the February 2018 suspension.

All Cohorts

No other anti-cancer therapy is permitted during the study with the following exceptions:

- local ablation for liver metastases during Induction Treatment Phase only and only if there are other non-ablated sites of measurable disease that have been followed from baseline tumour assessment (i.e. prior to start of induction treatment)
- radiotherapy for pain control during the either Induction or Maintenance Treatment Phases

For all patients who are not receiving atezolizumab, study maintenance treatment will continue until disease progression (based on Investigator's assessment), unacceptable toxicity, initiation of another anti-cancer therapy, patient or physician decision to discontinue, or patient death, whichever occurs first.

For all patients who are receiving atezolizumab, study maintenance treatment may continue after the first tumour assessment showing progression per RECIST 1.1 as long as patients meet the following criteria as assessed by the Investigator:

- Evidence of clinical benefit
- Absence of symptoms and signs (including worsening of laboratory values, e.g. new or worsening hypercalcaemia) indicating unequivocal progression of disease
- No decline in ECOG performance status that can be attributed to disease progression
- Absence of tumour progression at critical anatomical sites (e.g. leptomeningeal disease) that cannot be managed by protocol-allowed medical interventions

Treatment should be discontinued if the next follow-up tumour assessment continues to demonstrate progression per RECIST 1.1 (as compared to the assessment at the end of induction treatment). If the next tumour assessment does not show progression per RECIST 1.1, the patient may continue maintenance treatment until such time as the treatment continuation criteria above are no longer met and/or two sequential tumour assessments show progression per RECIST 1.1.

Atezolizumab treated patients may be discontinued from study treatment for the following reasons other than loss of clinical benefit or persistent progression: unacceptable toxicity, initiation of another anti-cancer therapy, patient or physician decision to discontinue, or patient death, whichever occurs first.

Efficacy, safety and tolerability will be assessed during the entire Maintenance Treatment Phase. While receiving study treatment during the Maintenance Treatment Phase, patients will be assessed for AEs and concomitant medications at every treatment cycle. Clinical laboratory assessments will be conducted at every cycle. For regimens with two week treatment cycles, clinical laboratory results from every second treatment cycle only will be collected in the CRF. For regimens with three week treatment cycles (such as Cohort 3 experimental regimen), clinical laboratory results from every cycle will be collected in the CRF. Physical examinations will be done every treatment cycle (regimens with three week cycles) or every two treatment cycles (regimens with two week cycles). Additional safety

reviews (safety run-ins) will be conducted by the iDMC, when necessary, for a prespecified number of initial patients receiving experimental combinations with inadequate prior safety experience to assure appropriate dosing (e.g., as required for the initial patients treated with the experimental combination of '5-FU/LV + cetuximab + vemurafenib'). Up to and including May 31, 2019, disease status will be evaluated during the Maintenance Treatment Phase as compared to the tumour assessment at the end of induction treatment and in accordance with RECIST 1.1 (see Appendix 10) for all patients, and additionally according to mRECIST (see Appendix 11) for patients treated with atezolizumab. Tumour assessments will be conducted every eight weeks. After May 31, 2019, disease status will no longer be collected for study analyses and should be evaluated according to local practice. Schedules of Assessments for each cohort are provided in Appendices 2 to 5.

Patients who discontinue study treatment for any reason during the Maintenance Treatment Phase will undergo a Study Treatment Discontinuation Visit within 30 days after the last dose of study treatment and will then enter the Post-Treatment Follow-up Phase.

Patients who prematurely discontinue treatment during the Induction Treatment Phase, who did not proceed to the Maintenance Treatment Phase or who discontinue treatment during the Maintenance Treatment Phase, will be followed for new AEs for 28 days (patients discontinuing before maintenance treatment and patients treated in all maintenance cohort control arms and Cohort 1 experimental arm) or 90 days (patients treated in experimental arms of Cohorts 2, 3 and 4 only) following the discontinuation of study treatment. At the time of treatment discontinuation, any ongoing AE/SAE will be followed until the event resolves, the Investigator assesses the event as stable, or the patient is lost to follow-up, dies or withdraws consent. The Sponsor should be notified if the Investigator becomes aware of any SAE or AEs of special interest occurring after the end of the adverse event reporting period if the event is believed to be related to prior study treatment.

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. Before May 31, 2019, patients will be followed every 3 months during the Post-Treatment Follow-up Phase for subsequent anti-cancer therapies, survival, and AEs (as applicable) including therapy-specific safety assessments (e.g., investigations for squamous cell carcinoma in patients who received vemurafenib) (see Appendices 1 to 5). After May 31, 2019, patients in Cohorts 2 and 3 who have completed the adverse event reporting period and, if applicable, cohort-specific post-treatment follow-up safety assessments will be discontinued from the study. Cohorts 2 and 3 patients who have completed the adverse event reporting period (and cohort-specific post-treatment follow-up safety assessments if applicable) prior to May 31, 2019 will be discontinued at their Post-Treatment Follow-up visit within the 3 months prior to and including May 31, 2019. See protocol Section 5.3.1 for adverse event reporting periods and post-treatment follow-up safety assessments. All patients in Cohorts 1 and 4 will continue in the Post-Treatment Follow-up Phase until the end of the study. Refer to Appendix 19 for management of patients in each cohort based on their study status on May 31, 2019.

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 (patients discontinuing during the Induction Treatment Phase) or every eight weeks (patients discontinuing during the Maintenance Treatment Phase) until progression or May 31, 2019, whichever comes first. After May 31, 2019, disease status will no longer be collected for any study patient. Disease assessments in any patient who has not yet progressed as of May 31, 2019 should thereafter be conducted according to local practice.

Second-line treatment during the Post-Treatment Follow-up Phase is at the Investigator's discretion. However, patients who received atezolizumab should not receive other immunomodulatory agents for 10 weeks after maintenance treatment discontinuation.

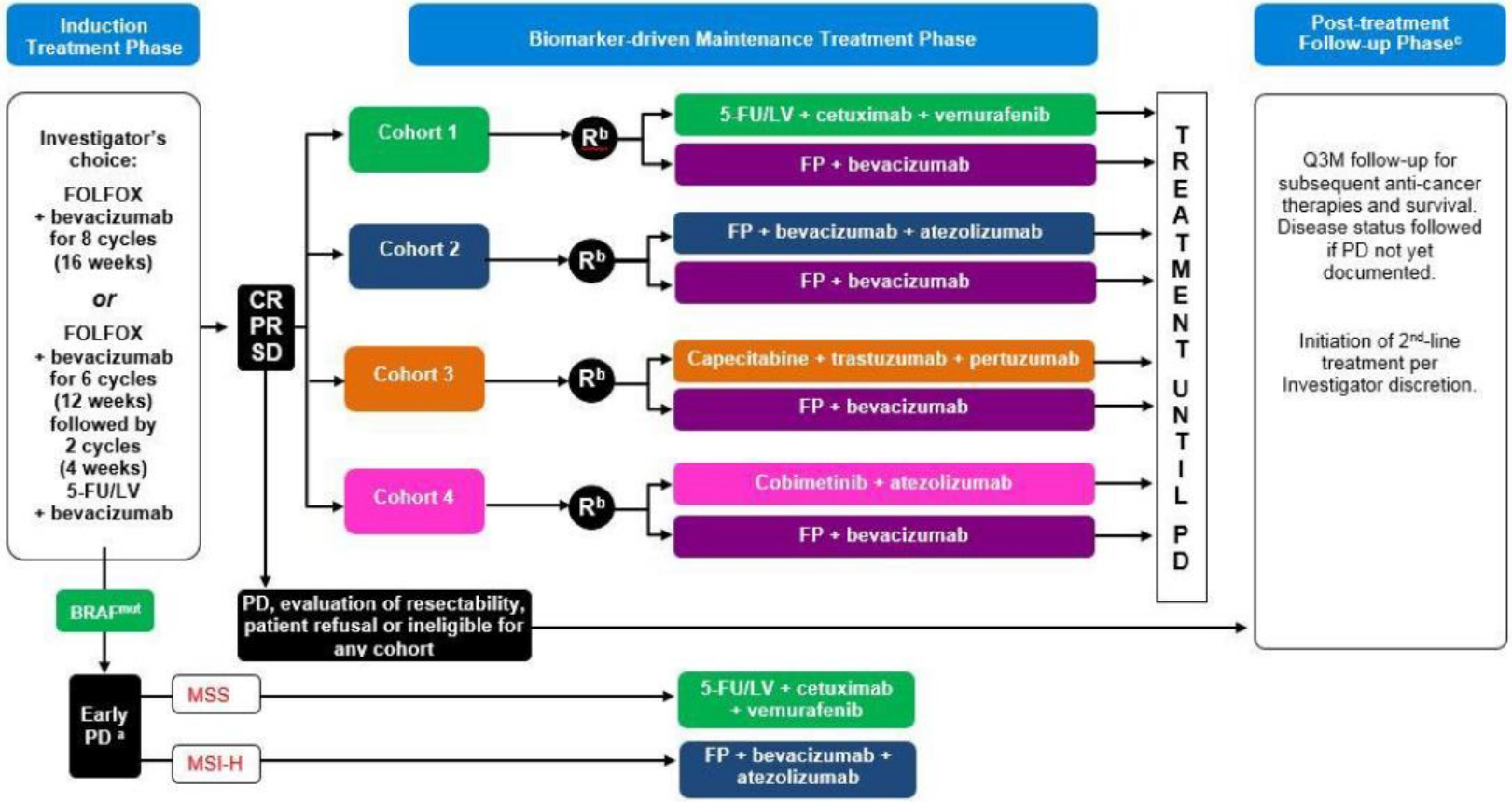
BRAF^{mut} Patients and Early Disease Progression

BRAF^{mut} patients experiencing early disease progression during induction treatment will have the option of proceeding immediately to receive second-line treatment with 5-FU/LV, cetuximab and vemurafenib if their primary tumour is MSS, or with a fluoropyrimidine (5-FU/LV or capecitabine), bevacizumab, and atezolizumab if their primary tumour is MSI-H.

If a patient previously indicated to have a BRAF^{mut} primary tumour (e.g. according to local testing) progresses prior to the availability of results from the study primary tumour biomarker testing, the Investigator may request an expedited biomarker report from the sponsor's Medical Monitor to confirm BRAF^{mut} status and to obtain MS status. Such patients will be allocated to the appropriate second-line treatment and may begin treatment following approval from the Medical Monitor.

Early progressing BRAF^{mut} patients receiving 5-FU/LV, cetuximab and vemurafenib as second-line treatment will be followed for safety and efficacy in accordance with the Maintenance Treatment Phase Schedule of Assessments (including eligibility, biomarker sampling and post-treatment follow-up) for Cohort 1 (see Appendix 2) and will be managed according to protocol recommendations and requirements for the experimental arm of Cohort 1. Early progressing BRAF^{mut} patients receiving a fluoropyrimidine (5-FU/LV or capecitabine), bevacizumab, and atezolizumab as second-line treatment will be followed for safety and efficacy in accordance with the Maintenance Treatment Phase Schedule of Assessments (including eligibility, biomarker sampling and post-treatment follow-up) for Cohort 2 (see Appendix 3) and will be managed according to protocol recommendations and requirements for the experimental arm of Cohort 2. This includes continuation of therapy beyond progression per RECIST 1.1 as described for Maintenance Treatment Phase patients receiving atezolizumab.

Figure 1: Study Design



FP = fluoropyrimidine (5-FU/LV or capecitabine); 5-FU/LV = 5-fluorouracil/leucovorin; MSI -H= high microsatellite instability; MSS = microsatellite stable

a. Patients who progress early and who are not $BRAF^{mut}$ will enter the Post-treatment Follow-up Phase with initiation of 2nd-line treatment per Investigator discretion

b. Randomization stratified by: Cohorts 1 and 2- region (EU, Americas, Africa or Asia), induction treatment response (CR/PR vs. SD); Cohort 3- induction treatment response (CR/PR vs. SD), HER2 IHC (IHC0/ IHC1+/IHC2+ vs. IHC3+); Cohort 4- region (EU vs. rest of world), induction treatment response (CR/PR vs. SD), microsatellite stability (MSI-H vs. MSS), RAS status (wild-type KRAS and NRAS vs. mutant KRAS and/or NRAS)

c. Patients discontinuing study treatment for any reason during the Induction or Maintenance Treatment Phases will enter the Post-treatment Follow-up Phase.

Study Conduct

A Steering Committee (SC) will be responsible for overseeing the general conduct of the study. An iDMC will be responsible for evaluating the safety of the patients participating in the trial at regular intervals throughout the study. This includes ongoing evaluation of benefit-risk balance based on accumulating safety and, as warranted, efficacy data. The iDMC will make recommendations as to whether cohort recruitment should continue based on each interim evaluation. In addition, when necessary due to the nature of prior experience with a particular experimental regimen, the iDMC will conduct a safety run-in review of a pre-specified number of initial patients (e.g. as conducted for the initial patients treated with '5-FU/LV + cetuximab + vemurafenib'). Safety run-ins deemed necessary for additional cohorts will be specified in the protocol. The schedule of iDMC reviews will be determined by the iDMC and described in the iDMC Charter. Additional data are provided in the respective SC and iDMC Charters.

Number of Patients

Before study enrolment was closed prematurely, approximately 1,820 patients were expected to be screened and approximately 1,400 patients were expected to be enrolled in the Induction Treatment Phase of the study in order to randomise the target sample size in each maintenance cohort. This included 405 patients in Cohort 2. Accrual into Cohort 4 was terminated prior to reaching the target sample size. Due to early closure of study enrolment, target sample sizes will not be reached for Cohorts 1 and 3.

Screening procedures

For comparability reasons, only the archival primary tumour sample from the original diagnosis will be used for the biomarker assessment which determines treatment assignment during the Maintenance Treatment Phase, as this material will be available for all patients. To be eligible for the study, patients must have an archival primary tumour sample for biomarker assessment for cohort assignment. If the tumour block is not available, ≥ 20 slides cut from the primary tumour sample will be accepted as an alternative. The sample (block or slides) must be shipped to the designated lab with confirmation of sample receipt provided by the laboratory prior to study enrolment. Biomarker analyses for cohort assignment will be conducted during the Induction Treatment Phase and these results will only be available during the Induction Treatment Phase and not during Screening. Patients with an adequate tumour sample but with unknown biomarker status due to lack of determinant result (e.g. due to technical issues) may still be included in the study depending on the addition of future cohorts.

For enrolment into the study, patients who do not meet the study eligibility criteria (screen failures) may be re-screened within 7 days of the date they are determined to be screen failures. Re-screening of a patient > 7 days after screen failure is allowed only with prior approval from the Medical Monitor. Patients cannot be re-screened for the study more than once.

Target Population

The target study population consists of patients with mCRC who have not received any prior chemotherapy in the metastatic setting. Cohort-specific target populations are further defined by specific biomarker profiles.

The "All Cohort" eligibility criteria are evaluated prior to initiating the first cycle of study treatment during the Induction Treatment Phase. Cohort-specific exclusion criteria must be assessed within 3 weeks of completing Induction Treatment Phase. Biomarker assessments will be completed prior to randomisation, as the results of the biomarker assessments are required to identify the intended cohort in order to complete the appropriate cohort-specific eligibility assessments.

Inclusion Criteria

Patients must meet the following criteria for study entry:

All Cohorts

Patient Status

1. Have provided written informed consent prior to any study specific procedures
2. Willing and able to comply with the protocol
3. ≥ 18 years of age
4. ECOG status of ≤ 2 (see Appendix 8)
5. At least 16 weeks of life expectancy at time of entry into the study

Disease-related

6. Histologically confirmed CRC with mCRC confirmed radiologically
7. Measurable, unresectable disease according to RECIST 1.1
8. No prior chemotherapy for CRC in the metastatic setting
9. Archival tumour formalin-fixed paraffin-embedded tissue (FFPET) block from the primary tumour obtained at the time of the initial diagnosis must be shipped to the Sponsor's designated laboratory with sample receipt confirmed by the laboratory. If the tumour block is not available, ≥ 20 slides cut from the primary tumour sample will be accepted as an alternative (see Appendix 17). The slides must be shipped with receipt confirmed by the Sponsor's designated laboratory prior to study enrolment.

Exclusion Criteria

Patients who meet any of the following criteria will be excluded from study entry:

All Cohorts

Other Prior or Current Treatments

1. Less than 6 months from completion of any prior neoadjuvant or adjuvant chemotherapy or radiotherapy
2. Prior or current treatment with bevacizumab or any other anti-angiogenic drug (i.e. anti-VEGF or vascular endothelial growth factor receptor [VEGFR] therapies or tyrosine kinase inhibitors)
3. Current or recent (within 10 days of start of study induction treatment) use of aspirin (> 325 mg/day), clopidogrel (> 75 mg/day), therapeutic oral or parenteral anticoagulants, or thrombolytic agents for therapeutic purposes.

   Note: The use of full-dose oral or parenteral anticoagulants is permitted as long as the international normalised ratio (INR) or activated partial thromboplastin time (aPTT) is within therapeutic limits (according to the medical standard of the institution) and the patient has been on a stable dose of anticoagulants for at least two weeks prior to the start of study induction treatment. Prophylactic use of anticoagulants is allowed.
4. Requirement for treatment with any medicinal product that contraindicates the use of any of the study medications, may interfere with the planned treatment, affects patient compliance or puts the patient at high risk for treatment-related complications
5. Treatment with any other investigational agent within 28 days or 5 investigational agent half-lives (whichever is longer) prior to the start of study induction treatment

Haematological, Biochemical and Organ Function

6. Inadequate haematological function indicated by one or more of the following:
   - Absolute neutrophil count (ANC) < 1.5 x 10^9/L
   - Platelet count < 100 x 10^9/L
   - Haemoglobin < 9 g/dL (patients may have transfusions and/or growth factors to attain adequate haemoglobin)
7. Inadequate liver function indicated by one or more of the following:
   - Total bilirubin ≥ 1.5 x upper limit of normal (ULN)
   - Aspartate transaminase (AST) or alanine aminotransferase (ALT) ≥ 2.5 x ULN (≥ 5 x ULN in patients with known liver metastases)
   - Alkaline phosphatase (ALP) ≥ 2 x ULN (≥ 5 x ULN in patients with known liver metastases)
8. Inadequate renal function indicated by one or more of the following:
   - Serum creatinine > 1.25 x ULN or calculated creatinine clearance < 50 ml/min
   - Urine dipstick for proteinuria ≥ 2+ unless a 24-hour urine protein < 1 g of protein is demonstrated
9. INR > 1.5 or aPTT > 1.5 x ULN within 7 days prior to the start of study induction treatment for patients not receiving anti-coagulation. For patients, receiving anticoagulants INR and aPTT must be within the medical standard of enrolling institution.

   The use of full-dose oral or parenteral anticoagulants is permitted as long as the INR or aPTT is within therapeutic limits (according to the medical standard of the enrolling institution) and the patient has been on a stable dose of anticoagulants for at least two weeks prior to the start of study induction treatment.

General Criteria

10. Active infection requiring intravenous antibiotics at the start of study induction treatment
11. Previous or concurrent malignancy, except for adequately treated basal or squamous cell skin cancer, *in situ* cervical cancer, or other cancer for which the patient has been disease-free for five years prior to study entry
12. Evidence of any other disease, neurologic or metabolic dysfunction, physical examination finding or laboratory finding giving reasonable suspicion of a disease or condition that contraindicates the use of any of the study medications, puts the patient at higher risk for treatment-related complications or may affect the interpretation of study results
13. Inadequately controlled hypertension (defined as systolic blood pressure > 150 mmHg and/or diastolic blood pressure > 100 mmHg)
14. Prior history of hypertensive crisis or hypertensive encephalopathy
15. Clinically significant (i.e. active) cardiovascular disease, for example cerebrovascular accidents ≤ 6 months prior to start of study induction treatment, myocardial infarction ≤ 6 months prior to study enrolment, unstable angina, New York Heart Association (NYHA) Functional Classification Grade 2 or greater congestive heart failure, or serious cardiac arrhythmia uncontrolled by medication or potentially interfering with protocol treatment
16. History or evidence upon physical or neurological examination of central nervous system (CNS) disease (e.g. seizures) unrelated to cancer unless adequately treated with standard medical therapy
17. Significant vascular disease (e.g. aortic aneurysm requiring surgical repair or recent arterial thrombosis) within 6 months of start of study induction treatment
18. Any previous venous thromboembolism > National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) Grade 3 within 12 months prior to start of study induction treatment

19. Active, symptomatic or untreated CNS metastases; CNS disease other than supratentorial or cerebellar metastases (i.e. patients with metastases to midbrain, pons, medulla or spinal cord are excluded); history of or known carcinomatous meningitis.

    Note: Treatment of brain metastases, either by surgical or radiation techniques, must have been completed > 4 weeks prior to start of study induction treatment. Patients requiring anticonvulsants or corticosteroids for symptom control and patients with evidence of interim progression between the completion of CNS-directed therapy and study baseline disease assessments are excluded from the study.

    Note: Patients without measurable disease outside the CNS are excluded from the study.

20. History of haemoptysis ≥ Grade 2 (defined as ≥ 2.5 mL bright red blood per episode) within 1 month of start of study induction treatment
21. History or evidence of inherited bleeding diathesis or significant coagulopathy at risk of bleeding (i.e. in the absence of therapeutic anticoagulation)
22. Surgical procedure (including open biopsy, surgical resection, wound revision, or any other major surgery involving entry into a body cavity) or significant traumatic injury within 28 days prior to start of study induction treatment, or anticipation of need for major surgical procedure during the course of the study
23. Minor surgical procedure including placement of a vascular access device, within 2 days of start of study induction treatment
24. History of abdominal fistula, gastrointestinal (GI) perforation, intra-abdominal abscess or active GI bleeding within 6 months prior to start of study induction treatment
25. Serious, non-healing wound, active ulcer, or untreated bone fracture
26. Known hypersensitivity to any component of any of the study induction or maintenance treatment medications
27. History of severe allergic, anaphylactic, or other hypersensitivity reactions to chimeric or humanised antibodies or fusion proteins
28. Known dihydropyrimidine dehydrogenase (DPD) deficiency
29. Pregnancy or lactation. A serum pregnancy test is required within 7 days prior to start of study induction treatment, or within 14 days with a confirmatory urine pregnancy test within 7 days prior start of study induction treatment
30. For women who are not post-menopausal (< 12 months of non-therapy-induced amenorrhea) or surgically sterile (absence of ovaries and/or uterus): refusal to use a highly effective contraceptive method (i.e. with a failure rate of < 1% per year such as sexual abstinence, hormonal implants, combined oral contraceptives, vasectomised partner), during both the Induction and Maintenance Treatment Phases and for at least 7 months after the last dose of study medication. Periodic abstinence [e.g., calendar, ovulation, symptothermal, postovulation methods] and withdrawal are not acceptable methods of contraception. A combination of male condom with cap, diaphragm or sponge with spermicide (double barrier methods) is not considered highly effective, birth control methods. Acceptable methods of contraception may include total abstinence in cases where the lifestyle of the patient ensures compliance. A vasectomised partner is a highly effective birth control method provided that partner is the sole sexual partner of the MODUL trial participant and that the vasectomised partner has received medical assessment of the surgical success. Some of the study-related medication, such as vemurafenib may decrease the plasma exposure of those hormonal contraceptives predominantly metabolised by CYP3A4. In these cases, the use of an alternate highly effective method of contraception must be considered.
31. For men: refusal to use a highly effective contraceptive method (i.e. with a failure rate of < 1% per year such as vasectomy, sexual abstinence or female partner use of hormonal implants or combined oral contraceptives) during both the Induction and Maintenance Treatment Phases and for a period of at least 6 months after the last dose of study medication. Periodic abstinence [e.g., calendar, ovulation, symptothermal, postovulation methods] and withdrawal are not acceptable

methods of contraception. A combination of male condom with either cap, diaphragm or sponge with spermicide (double barrier methods) is not considered highly effective, birth control methods. Acceptable methods of contraception may include total abstinence in cases where the lifestyle of the patient ensures compliance. A vasectomised MODUL trial participant is a highly effective birth control method provided that the MODUL trial participant has received medical assessment of the surgical success. Men must also agree not to donate sperm for at least 6 months after their last dose of study drug.

Cohort-Specific Exclusion Criteria

The following criteria will be assessed following biomarker-based cohort assignment:

Additional criteria for Cohort 1

1. Have not provided informed consent to participate in Cohort 1.

   Note: At study centers where a single informed consent form is used, informed consent to participate in any maintenance cohort will have already been provided at study entry. Patients enrolled at centers using two informed consent forms must provide maintenance cohort-specific consent after cohort assignment and prior to cohort-specific eligibility assessments other than eligibility assessments already conducted as part of routine care.

2. Inability to swallow pills.
3. Refractory nausea and vomiting, malabsorption, external biliary shunt or significant bowel resection that would preclude adequate absorption.
4. History or presence of clinically significant ventricular or atrial dysrhythmias ≥ NCI CTCAE Grade 2
5. Corrected QT (QTc) interval ≥ 450 msec as assessed within 3 weeks prior to randomization, long QT syndrome, uncorrectable electrolyte abnormalities (including magnesium) or requirement for medicinal products known to prolong the QT interval
6. For women who are not post-menopausal (< 12 months of non-therapy-induced amenorrhea) or surgically sterile (absence of ovaries and/or uterus): refusal to use an alternate highly effective contraceptive method (i.e. with a failure rate of < 1% per year such as sexual abstinence, vasectomised partner) other than hormonal contraceptives, during both the Induction and Maintenance Treatment Phases and for at least 7 months after the last dose of study medication. Vemurafenib may decrease the plasma exposure of those hormonal contraceptives predominantly metabolised by CYP3A4.
7. ECOG PS > 2.

   Note: Due to the potential risks associated with treatment in the experimental arm of Cohort 1, patients with ECOG PS = 2 and a low body mass index (BMI) must be judged by the Investigator as adequately physically fit to receive treatment with 5-FU/LV + cetuximab + vemurafenib to be considered eligible. See protocol Section 4.3.2.2.2.

Additional criteria for Cohort 2

1. Have not provided informed consent to participate in Cohort 2

   Note: At study centers where a single informed consent form is used, informed consent to participate in any maintenance cohort will have already been provided at study entry. Patients enrolled at centers using two informed consent forms must provide maintenance cohort-specific consent after cohort assignment and prior to cohort-specific eligibility assessments other than eligibility assessments already conducted as part of routine care.

2. Known hypersensitivity or allergy to Chinese hamster ovary cell products
3. History of autoimmune disease including but not limited to myasthenia gravis, myositis, autoimmune hepatitis, systemic lupus erythematosus, rheumatoid arthritis, inflammatory bowel

disease, vascular thrombosis associated with antiphospholipid syndrome, Wegener's granulomatosis, Sjögren's syndrome, Guillain-Barré syndrome, multiple sclerosis, vasculitis, or glomerulonephritis (see Appendix 9 for a more comprehensive list of autoimmune diseases)

Patients with the following are eligible:

- a history of autoimmune-related hypothyroidism on a stable dose of thyroid replacement hormone
- controlled Type 1 diabetes mellitus on a stable insulin regimen
- eczema, psoriasis, lichen simplex chronicus, or vitiligo with dermatologic manifestations only (e.g. patients with psoriatic arthritis would be excluded) are permitted provided that they meet the following conditions:
  - rash must cover less than 10% of body surface area (BSA)
  - disease is well controlled prior to randomization and only requires low potency topical steroids
  - no acute exacerbations of underlying condition within the previous 12 months (not requiring PUVA [psoralen plus ultraviolet A radiation], methotrexate, retinoids, biologic agents, oral calcineurin inhibitors, high potency or oral steroids)

4. Prior allogeneic bone marrow transplantation or prior solid organ transplantation
5. History of idiopathic pulmonary fibrosis (including pneumonitis), drug-induced pneumonitis, organizing pneumonia (i.e., bronchiolitis obliterans, cryptogenic organizing pneumonia), or evidence of active pneumonitis on most recent chest imaging (CT scan or MRI)

   Note: History of radiation pneumonitis in the radiation field (fibrosis) is permitted.
6. Positive test for human immunodeficiency virus (HIV)
7. Active hepatitis B (defined as having a positive hepatitis B surface antigen [HBsAg] test prior to randomization) or hepatitis C

   Note: Patients with past hepatitis B virus (HBV) infection or resolved HBV infection (defined as having a negative HBsAg test and a positive antibody to hepatitis B core antigen [anti-HBc] antibody test) are eligible.

   Patients positive for hepatitis C virus (HCV) antibody are eligible only if polymerase chain reaction (PCR) is negative for HCV RNA.
8. Active tuberculosis
9. Severe infection within 4 weeks prior to start of maintenance treatment including, but not limited to, hospitalization for complications of infection, bacteremia, or severe pneumonia; has signs or symptoms of significant infection or has received oral or IV antibiotics within 2 weeks prior to start of maintenance treatment.

   Note: Patients receiving prophylactic antibiotics (e.g. for prevention of a urinary tract infection or chronic obstructive pulmonary disease) are eligible.
10. Administration of a live, attenuated vaccine within 4 weeks prior to start of study maintenance treatment or anticipation that such a live attenuated vaccine will be required during the study
11. Prior treatment with CD137 agonists, anti-CTLA4, anti-PD-1, or anti-PD-L1 therapeutic antibody or pathway-targeting agents
12. Treatment with systemic immunostimulatory agents (including but not limited to interferons or interleukin-2) within 4 weeks or five half-lives of the drug, whichever is longer, prior to start of study maintenance treatment
13. Treatment with systemic corticosteroids or other systemic immunosuppressive medications (including but not limited to prednisone, dexamethasone, cyclophosphamide, azathioprine, methotrexate, thalidomide, and anti-tumour necrosis factor [TNF] agents) within 2 weeks prior to

start of study maintenance treatment, or requirement for systemic immunosuppressive medications during the trial.

Note: The use of inhaled corticosteroids for chronic obstructive pulmonary disease (≤ 10 mg oral prednisone or equivalent), mineralocorticoids (e.g., fludrocortisone) for patients with orthostatic hypotension, and low-dose supplemental corticosteroids for adrenocortical insufficiency are allowed.

Patients who have received acute, low-dose (≤ 10 mg oral prednisone or equivalent), systemic immunosuppressant medications may be enrolled in the study after discussion with and approval by the Medical Monitor.

14. If receiving a RANKL inhibitor (e.g. denosumab), unwilling to adopt alternative treatment such as (but not limited to) bisphosphonates, while receiving atezolizumab.

Additional criteria for Cohort 3

1. Have not provided informed consent to participate in Cohort 3

   Note: At study centers where a single informed consent form is used, informed consent to participate in any maintenance cohort will have already been provided at study entry. Patients enrolled at centers using two informed consent forms must provide maintenance cohort-specific consent after cohort assignment and prior to cohort-specific eligibility assessments other than eligibility assessments already conducted as part of routine care.

2. Inability to swallow pills
3. Left ventricular ejection fraction (LVEF) < 50% as assessed after completion of induction treatment by either 2D echocardiogram (ECHO) or multiple-gated acquisition (MUGA) (ECHO is the preferred method).
4. Clinically significant cardiovascular disease, including unstable angina, history of or active congestive heart failure of ≥ NYHA Grade 2, history of or ongoing serious cardiac arrhythmia requiring treatment (except for controlled atrial fibrillation and/or paroxysmal supraventricular tachycardia).
5. Current uncontrolled hypertension (systolic > 150 mmHg and/or diastolic > 100 mmHg) with or without medication
6. Current dyspnoea at rest due to complications of advanced malignancy or other disease requiring continuous oxygen therapy
7. Insulin-dependent diabetes
8. Current known infection with HIV, HBV, or HCV (active infection or carriers)
9. Requirement for concurrent use of the antiviral agent sorivudine (antiviral) or chemically related analogues, such as brivudine
10. Malabsorption syndrome, disease significantly affecting gastrointestinal function, resection of the stomach or small bowel, or ulcerative colitis
11. Known hypersensitivity to murine proteins

Additional Criteria for Cohort 4

1. Have not provided informed consent to participate in Cohort 4

   Note: At study centers where a single informed consent form is used, informed consent to participate in any maintenance cohort will have already been provided at study entry. Patients enrolled at centers using two informed consent forms must provide maintenance cohort-specific consent after cohort assignment and prior to cohort-specific eligibility assessments other than eligibility assessments already conducted as part of routine care.

2. Inability to swallow medications
3. Known hypersensitivity or allergy to Chinese hamster ovary cell products

4. History of autoimmune disease including but not limited to myasthenia gravis, myositis, autoimmune hepatitis, systemic lupus erythematosus, rheumatoid arthritis, inflammatory bowel disease, vascular thrombosis associated with antiphospholipid syndrome, Wegener's granulomatosis, Sjögren's syndrome, Guillain-Barré syndrome, multiple sclerosis, vasculitis, or glomerulonephritis (see Appendix 9 for a more comprehensive list of autoimmune diseases)

   Patients with the following are eligible:

   - a history of autoimmune-related hypothyroidism on a stable dose of thyroid replacement hormone
   - controlled Type 1 diabetes mellitus on a stable insulin regimen
   - eczema, psoriasis, lichen simplex chronicus, or vitiligo with dermatologic manifestations only (e.g. patients with psoriatic arthritis would be excluded) are permitted provided that they meet the following conditions:
     - rash must cover less than 10% of body surface area (BSA)
     - disease is well controlled prior to randomization and only requires low potency topical steroids
     - no acute exacerbations of underlying condition within the previous 12 months (not requiring PUVA [psoralen plus ultraviolet A radiation], methotrexate, retinoids, biologic agents, oral calcineurin inhibitors, high potency or oral steroids)
5. History of idiopathic pulmonary fibrosis (including pneumonitis), drug-induced pneumonitis, organizing pneumonia (i.e., bronchiolitis obliterans, cryptogenic organizing pneumonia), or evidence of active pneumonitis on most recent chest imaging (CT scan or MRI)

   Note: History of radiation pneumonitis in the radiation field (fibrosis) is permitted.
6. Malabsorption condition that would alter the absorption of orally administered medications
7. Amylase or lipase ≥ 1.5 × ULN within 14 days prior to maintenance treatment initiation
8. Serum albumin < 2.5 g/dL
9. LVEF < institutional lower limit of normal or < 50%, whichever is lower.
10. Poorly controlled hypertension, defined as a blood pressure consistently above 150/90 mmHg despite optimal medical management.
11. Uncontrolled pleural effusion, pericardial effusion or ascites requiring repeated drainage more than once every 28 days. Indwelling drainage catheters (e.g. PleurX®) are allowed.
12. Unstable angina, new onset angina within last 3 months, myocardial infarction within last 6 months and current congestive heart failure ≥ NYHA Grade 2
13. History of stroke, reversible ischemic neurological defect, or transient ischemic attack within 6 months prior to initiation of maintenance treatment
14. History or evidence of intracranial hemorrhage or spinal cord hemorrhage
15. Evidence of clinically significant vasogenic edema
16. Any hemorrhage or bleeding event ≥ NCI CTCAE Grade 3 within 28 days prior to initiation of maintenance treatment
17. History or evidence of retinal pathology on ophthalmologic examination that is considered a risk factor for central serous retinopathy, retinal vein occlusion, or neovascular macular degeneration

    Patients will be excluded if they currently have any of the following risk factors for retinal vein occlusion:

    - Uncontrolled glaucoma with intra ocular pressure ≥ 21 mmHg
    - Uncontrolled hypercholesterolemia > 300 mg/dL or 7.75 mmol/L
    - Uncontrolled hypertriglyceridemia > 300 mg/dL or 3.42 mmol/L
    - Fasting hyperglycemia > 160 mg/dL or 8.9 mmol/L

18. Positive HIV test
19. Active hepatitis B (defined as having a positive HBsAg test prior to randomization) or hepatitis C

    Note: Patients with past HBV infection or resolved HBV infection (defined as having a negative HBsAg test and a positive anti-HBc antibody test) are eligible.

    Patients positive for HCV antibody are eligible only if PCR is negative for HCV RNA.
20. Active tuberculosis
21. Severe infection within 4 weeks prior to start of maintenance treatment including, but not limited to, hospitalization for complications of infection, bacteremia, or severe pneumonia; has signs or symptoms of significant infection or has received oral or IV antibiotics within 2 weeks prior to start of maintenance treatment.

    Note: Patients receiving prophylactic antibiotics (e.g. for prevention of a urinary tract infection or chronic obstructive pulmonary disease) are eligible.
22. Prior allogeneic bone marrow transplantation or prior solid organ transplantation
23. Administration of a live, attenuated vaccine within 4 weeks prior to start of study maintenance treatment or anticipation that such a live attenuated vaccine will be required during the study
24. Prior treatment with CD137 agonists, anti-CTLA4, anti-PD-1, or anti-PD-L1 therapeutic antibody or pathway-targeting agents
25. Prior treatment with a MEK or ERK inhibitor
26. Treatment with systemic immunostimulatory agents (including but not limited to interferons or interleukin-2) within 4 weeks or five half-lives of the drug, whichever is longer, prior to start of study maintenance treatment
27. Treatment with systemic corticosteroids or other systemic immunosuppressive medications (including but not limited to prednisone, dexamethasone, cyclophosphamide, azathioprine, methotrexate, thalidomide, and anti-TNF agents) within 2 weeks prior to start of study maintenance treatment, or requirement for systemic immunosuppressive medications during the trial.

    Note: The use of inhaled corticosteroids for chronic obstructive pulmonary disease (≤ 10 mg oral prednisone or equivalent), and mineralocorticoids (e.g., fludrocortisone) for patients with orthostatic hypotension, and low-dose supplemental corticosteroids for adrenocortical insufficiency are allowed.

    Note: Patients who have received acute, low-dose (≤ 10 mg oral prednisone or equivalent), systemic immunosuppressant medications (e.g. a one-time dose of dexamethasone for nausea) may be enrolled in the study after discussion with and approval by the Medical Monitor.
28. If receiving a RANKL inhibitor (e.g. denosumab), unwilling to adopt alternative treatment such as (but not limited to) bisphosphonates, while receiving atezolizumab.
29. Consumption of foods, supplements or drugs that are potent CYP3A4 enzyme inducers or inhibitors ≤ 7 days before initiation of study maintenance treatment or expected concomitant use during maintenance treatment. These include St. John's wort or hyperforin (potent CYP3A4 enzyme inducer) and grapefruit juice (potent cytochrome P450 CYP3A4 enzyme inhibitor).

Length of Study

Study recruitment started in April 2015. Patient screening was temporarily suspended beginning in June 2016 for the addition of maintenance Cohorts 3 and 4. Screening and enrolment were again suspended in February 2018 to accommodate closure of accrual to Cohort 4. Study enrolment will not be re-opened. The entire study duration is estimated to be approximately 5 years.

End of Study

The end of the study is defined as the date when all study patients have discontinued study treatment and completed the adverse event reporting period and, if applicable, cohort-specific post-treatment follow-up safety assessments (see protocol Section 5.3.1 for adverse event reporting periods and post-treatment follow-up safety assessments). After this, the trial will end and no further data will be collected in the clinical database for this study.

Continued access to Roche investigational medicinal products (IMPs) used in the study will be in accordance with the Roche Global Policy on Continued Access to Investigational Medicinal Product.

Efficacy Outcome Measures

All Cohorts

Efficacy outcome measures will be assessed within each cohort (experimental arm vs. control arm) during the Maintenance Treatment Phase.

Primary

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

Secondary

- 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. Response will be determined by the Investigator according to RECIST 1.1 based on comparisons to the tumour assessment done at the end of the Induction Treatment Phase.
- DCR (defined as CR, PR or SD) during the Maintenance Treatment Phase. Response will be determined by the Investigator according to RECIST 1.1 based on comparisons to the tumour assessment done at the end 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

Safety Outcome Measures

All Cohorts

The safety outcome measures for this study are as follows:

- Incidence, nature and severity of all adverse events (graded according to NCI CTCAE v4.0)
- Incidence and nature of all Grade 3 – 5 AEs
- Grade 5 AEs or AEs leading to death on study treatment
- All SAEs
- Incidence and reasons for any premature discontinuation of any component of study treatment

- Incidence and reasons for any dose reductions or interruptions of any component of study treatment
- AEs of special interest
- Clinically significant changes in laboratory values

Adverse events 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 Outcome Measures

Cohorts 2 and 4- Experimental Arms Only

PFS in patients treated with atezolizumab defined as the time from randomisation into the Maintenance Treatment Phase until disease progression per Investigator assessment using mRECIST or death from any cause, whichever occurs first.

All Cohorts

The exploratory biomarker and microbiome outcome measures for this study include molecular markers/marker profiles and efficacy and/or safety outcomes. Efficacy outcomes considered for this analysis may include, but are not limited to, ORR, PFS and OS, as appropriate. Biomarkers, biomarker profiles and microbiomes may be assessed using various methodologies including, but not limited to, immunohistochemistry (single and multiplex), RNA and DNA analysis (e.g polymerase chain reaction; next generation sequencing; and mutation, expression and microsatellite instability analyses) of tumour and blood samples collected from all study patients as well as additional tumour samples and stool samples collected from patients participating in the Supplemental Biomarker Program.

Study Treatment

Induction Treatment Phase

All Cohorts

All patients will receive 4 months of study treatment in the Induction Treatment Phase. Treatment during this phase, based on Investigator's choice, will be either:

- eight 2-week cycles of 5-FU/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

and should be in accordance with locally approved prescribing information including any recommendations for pre-treatment (i.e. antiemetic therapies). The Investigator will select the FOLFOX regimen (e.g. FOLFOX-4, FOLFOX-6, modified FOLFOX-6, FOLFOX-7 or modified FOLFOX-7; see Appendix 6) also in accordance with local standards.

Maintenance Treatment Phase

All Cohorts

Each cohort will contain an experimental treatment arm based specifically on the patient's biomarker status based on the patient's archival tumour sample from the initial diagnosis (see Appendix 17 for additional details on cohort assignment). Patients with an adequate tumour sample but with unknown

biomarker status due to lack of determinant result (e.g. due to technical issues) may still be eligible depending on the addition of future cohorts. Each cohort will also include a control treatment arm containing a fluoropyrimidine and bevacizumab. Maintenance treatment will begin within 3 weeks of completing induction treatment.

For patients in Cohorts 1 and 3, and the control arms of Cohorts 2 and 4, study treatment during the Maintenance Treatment Phase will continue until disease progression (based on Investigator's assessment according to RECIST 1.1), unacceptable toxicity, initiation of another anti-cancer therapy, patient or physician decision to discontinue, or patient death, whichever occurs first.

For patients randomised to the experimental arms of Cohorts 2 and 4 (i.e. patients who are receiving atezolizumab), study treatment during the Maintenance Treatment Phase may continue after the first tumour assessment showing progression per RECIST 1.1 as long as they meet the following criteria as assessed by the Investigator:

- Evidence of clinical benefit
- Absence of symptoms and signs (including worsening of laboratory values, e.g. new or worsening hypercalcaemia) indicating unequivocal progression of disease
- No decline in ECOG performance status that can be attributed to disease progression
- Absence of tumour progression at critical anatomical sites (e.g. leptomeningeal disease) that cannot be managed by protocol-allowed medical interventions

Treatment should be discontinued if the next follow-up tumour assessment continues to demonstrate progression per RECIST 1.1 (as compared to the assessment at the end of induction treatment). If the next tumour assessment does not show progression per RECIST 1.1, the patient may continue maintenance treatment until such time as the treatment continuation criteria above are no longer met and/or two sequential tumour assessments show progression per RECIST 1.1.

Atezolizumab treated patients may be discontinued from study treatment during the Maintenance Phase for the following reasons other than loss of clinical benefit or persistent progression: unacceptable toxicity, initiation of another anti-cancer therapy, patient or physician decision to discontinue, or patient death, whichever occurs first.

Dose reductions or interruptions of IMPs are only allowed as recommended in the applicable Investigator's Brochure. If any drug of any study treatment regimen in either the Induction or Maintenance Treatment Phase is discontinued or held for > 21 days, approval from the Medical Monitor will be required before treatment can be re-initiated. If Medical Monitor approval is not obtained, the patient will come off all study treatment and will enter the Post-Treatment Follow-up Phase.

All Cohorts - Control Arms

The maintenance treatment regimen is the same for the control arms of all cohorts.

Fluoropyrimidine (5-FU/LV or capecitabine): dose and schedule will be according to local label, where applicable, or otherwise will be determined per the Investigator's discretion. Administration should be according to local prescribing information.

Bevacizumab: 5 mg/kg via 15 – 30 minute IV infusion on Day 1 of every 2-week cycle. Bevacizumab should be prepared and administered in accordance with local prescribing information.

Cohort 1 – Experimental Arm

Patients assigned to the experimental arm of Cohort 1 with an ECOG PS = 2 and a low BMI must be carefully assessed by the Investigator for physical fitness adequate for receipt of this regimen prior to initiating treatment. Such patients must be closely monitored through the maintenance treatment period.

5-FU: The first six patients in this cohort received 1,600 mg/m² 5-FU administered via 46-hour IV infusion, in combination with LV 400 mg/m² administered via 2-hour infusion, on Day 1 of every 2-week cycle. Subsequent patients in this cohort will receive 1,600 – 2,400 mg/m² 5-FU administered via 46-hour IV infusion (IV bolus is not permitted), in combination with LV 400 mg/m² administered via 2-hour infusion, on Day 1 of every 2-week cycle.

Cetuximab: The dose and scheduling of cetuximab is 500 mg/m² via IV infusion on Day 1 of every 2-week cycle. Cetuximab must be administered in hospital under the supervision of a physician experienced in the use of antineoplastic medicinal products. Cetuximab must be administered via infusion pump or syringe pump at a rate not exceeding 5 mg/min for the first administration and 10 mg/min for subsequent administrations. Close monitoring is required during the infusion and for at least 1 hour after the end of the infusion. Availability of resuscitation equipment must be ensured. Prior to the first infusion of cetuximab, patients must receive premedication with an antihistamine and a corticosteroid. This premedication is recommended prior to all subsequent infusions. Refer to cetuximab Package Insert (Appendix 14).

Vemurafenib: The dose and scheduling of vemurafenib is 960 mg b.i.d by mouth. Vemurafenib should be taken at approximately the same times each day, the first dose is to be taken in the morning and the second dose is to be taken approximately 12 hours later in the evening. Each dose should always be taken in the same manner i.e. either with or without a meal. Missed doses will not be made up.

Note: A safety run-in review of the first six patients treated with the experimental combination of '5-FU/LV + cetuximab + vemurafenib' was conducted in February 2016. The iDMC recommended that patients allocated to this regimen may now receive 5-FU at doses up to 2,400 mg/m². The iDMC will continue to monitor initial patients in this regimen treated with 5-FU doses ≥ 1,600 mg/m² and have also recommended that patients with ECOG PS = 2 and a low BMI be carefully assessed by the Investigator for physical fitness adequate for receipt of this regimen.

Cohort 2 - Experimental Arm

Fluoropyrimidine (5-FU/LV or capecitabine): 1,600 – 2,400 mg/m² 5-FU administered via 46-hour IV infusion (IV bolus is not permitted) on Day 1 of every 2-week cycle, and LV 400 mg/m² administered via a 2-hour infusion on day 1 every 2 weeks; or 1000 mg/m² twice-daily capecitabine (b.i.d.) by mouth given days 1-14 every 2 weeks followed by a one-week treatment break.

Bevacizumab: The dose and schedule of bevacizumab is 5 mg/kg via 15 – 30 minute IV infusion on Day 1 of every 2-week cycle. Bevacizumab should be prepared and administered in accordance with local prescribing information. Patients may be at risk of developing infusion / hypersensitivity reactions with bevacizumab. Close observation of the patient during and following the administration of bevacizumab is recommended as expected for any infusion of a therapeutic humanised monoclonal antibody. If a reaction occurs, the infusion should be discontinued and appropriate medical therapies should be administered. A systematic premedication is not warranted.

Atezolizumab: Atezolizumab is administered at a fixed dose of 800 mg via 60-minute IV infusion on Day 1 of every 2-week cycle. Atezolizumab must be administered in hospital under the supervision of a physician experienced in the use of antineoplastic medicinal products. For the first infusion, the patient's vital signs (heart rate, respiratory rate, blood pressures, and temperature) should be determined within 60 minutes before the infusion, every 15 ± 5 minutes during the infusion, and 30 ± 10 minutes after the infusion. For subsequent infusions, vital signs will be collected within 60 minutes before the infusion and should be collected during or after the infusion if clinically indicated or if symptoms occurred in the prior infusion. If the initial infusion is well tolerated, subsequent infusions will be done over a 30-minute time period. No premedication is indicated for the first dose of atezolizumab. Patients who experience an infusion-related reaction with Cycle 1 of atezolizumab may receive premedication with antihistamines or

antipyretics/analgesics (e.g. acetaminophen) for subsequent infusions. The rate of atezolizumab infusion should be modified in the event of an infusion-related reaction.

Cohort 3 - Experimental Arm

Capecitabine, trastuzumab and pertuzumab will be administered according to the doses and schedules described below. For the first treatment cycle, pertuzumab should be administered on Day 1, followed by the first dose of trastuzumab and capecitabine on Day 2. If the administration of all three agents is well tolerated in the first treatment cycle, they may be given sequentially on Day 1 (pertuzumab and trastuzumab should not be mixed in the same infusion bag) in subsequent cycles thereafter. If a patient cannot tolerate all three drugs given on the same day, pertuzumab should continue to be delivered on Day 1, with trastuzumab and capecitabine delivered on Day 2 for subsequent treatment cycles.

Capecitabine: 1000 mg/m^2 twice-daily capecitabine (b.i.d.; for a total daily dose of 2000 mg/m^2) by mouth given days 1-14 every 2 weeks followed by a one-week treatment break administered in accordance with local prescribing information. See Appendix 7 for capecitabine dose calculations by body surface area with corresponding tablet counts.

Trastuzumab: Trastuzumab is administered by IV infusion on Day 1 of every 3-week treatment cycle at an initial loading dose of 8 mg/kg followed by 6 mg/kg for subsequent doses. Trastuzumab must be administered in hospital under the supervision of a physician experienced in the use of antineoplastic medicinal products. The first infusion should be delivered over 90 minutes followed by a 60 minute observation period. If the first infusion is well tolerated without infusion-associated AEs, the second and subsequent infusions may be delivered over 30 minutes with an observation period of 30 minutes. Longer infusion and/or observation times can be maintained if there is any doubt about tolerability. No premedication will be allowed for the first dose of trastuzumab. Premedication may be administered for subsequent cycles at the discretion of the treating physician. The rate of trastuzumab infusion should be modified in the event of an infusion-related reaction.

Pertuzumab: Pertuzumab is administered by IV infusion on Day 1 of each 3-week treatment cycle at an initial fixed loading dose of 840 mg followed by 420 mg for subsequent doses. Pertuzumab must be administered in hospital under the supervision of a physician experienced in the use of antineoplastic medicinal products. The first infusion should be delivered over 60 minutes followed by a 60 minute observation period. The observation period for subsequent infusions may be between 30 and 60 minutes if the first infusion is well tolerated without infusion-associated AEs. No premedication will be allowed for the first dose of pertuzumab. Premedication may be administered for subsequent cycles at the discretion of the treating physician. The rate of pertuzumab infusion should be modified in the event of an infusion-related reaction.

Cohort 4 - Experimental Arm

In an Urgent Safety Measure Letter dated July 25, 2018, the Sponsor advised investigators to strongly consider discontinuing treatment in any Cohort 4 patients receiving experimental treatment. Investigators were advised to discuss appropriate next treatment options, including combination treatment with a fluoropyrimidine plus bevacizumab, with patients discontinuing experimental treatment. Please refer to protocol Section 3.1.2.4 for further details of the basis for Sponsor decisions for Cohort 4 and management of ongoing patients randomized to the experimental arm.

Cobimetinib: Cobimetinib is administered orally at a dose of 60 mg for 3 weeks followed by a 1 week treatment break (21/7 schedule). Treatment cycle length in this arm is 2 weeks. Cobimetinib will be administered daily every day of each odd numbered 2-week treatment cycle, and for the first 7 days only of each even numbered 2-week treatment cycle. Cobimetinib should be taken at the same time every day with or without food. If a dose is missed or vomiting occurs when a dose is taken, dosing should be resumed at the next scheduled dose.

Atezolizumab: Atezolizumab is administered at a fixed dose of 840 mg via 60-minute IV infusion on Day 1 of every 2-week cycle. Atezolizumab must be administered in hospital under the supervision of a physician experienced in the use of antineoplastic medicinal products. For anaphylaxis precautions, see Appendix 16. For the first infusion, the patient's vital signs (heart rate, respiratory rate, blood pressures, and temperature) should be determined within 60 minutes before the infusion, every 15 ± 5 minutes during the infusion, and 30 ± 10 minutes after the infusion. For subsequent infusions, vital signs will be collected within 60 minutes before the infusion and should be collected during or after the infusion if clinically indicated or if symptoms occurred in the prior infusion. If the initial infusion is well tolerated, subsequent infusions will be done over a 30-minute time period. No premedication is indicated for the first dose of atezolizumab. Patients who experience an infusion-related reaction with Cycle 1 of atezolizumab may receive premedication with antihistamines or antipyretics/analgesics (e.g. acetaminophen) for subsequent infusions. The rate of atezolizumab infusion should be modified in the event of an infusion-related reaction.

Post-Treatment Follow-up Phase

All Cohorts

Second-line treatment during the Post-Treatment Follow-up Phase is at the Investigator's discretion. However, patients who received atezolizumab should not receive other immunomodulatory agents for 10 weeks after maintenance treatment discontinuation.

$BRAF^{mut}$ Patients and Early Disease Progression

Exceptionally, $BRAF^{mut}$/MSS patients experiencing early disease progression during the induction treatment will have the option of proceeding immediately to receive second-line treatment with 5-FU/LV, cetuximab and vemurafenib. These patients will be followed for safety and efficacy in accordance with the Maintenance Treatment Phase Schedule of Assessments (including eligibility, biomarker sampling and post-treatment follow-up) for Cohort 1 (see Appendix 2) and will be managed according to protocol recommendations and requirements for the experimental arm of Cohort 1.

Similarly, $BRAF^{mut}$/MSI-H patients experiencing early disease progression during induction treatment will have the option of proceeding immediately to receive second-line treatment with a fluoropyrimidine (5-FU/LV or capecitabine), bevacizumab, and atezolizumab. These patients will be followed for safety and efficacy in accordance with the Maintenance Treatment Phase Schedule of Assessments (including eligibility, biomarker sampling and post-treatment follow-up) for Cohort 2 (see Appendix 3) and will be managed according to protocol recommendations and requirements for the experimental arm of Cohort 2.

Investigational Medicinal Products

The IMPs used in this study include:

- all non-fluoropyrimidine agents comprising the experimental arms of each maintenance treatment cohort (i.e. cetuximab and vemurafenib in Cohort 1, bevacizumab and atezolizumab in Cohort 2, trastuzumab and pertuzumab in Cohort 3, cobimetinib and atezolizumab in Cohort 4)
- bevacizumab in the Induction Treatment Phase
- bevacizumab in the control arms of each maintenance treatment cohort
- cetuximab, vemurafenib, bevacizumab and atezolizumab administered as optional second-line treatments to early progressing $BRAF^{mut}$ patients

Non-Investigational Medicinal Products

Non-IMPs used in this study include all fluoropyrimidine agents (i.e. 5-FU and capecitabine) and leucovorin administered during the Induction and Maintenance Treatment Phases and as optional

second-line treatment to early progressing $BRAF^{mut}$ patients. Oxaliplatin administered as part of induction treatment is also considered a non-IMP.

Statistical Methods

All Cohorts

The cohorts will be based on different biomarkers (see Appendix 17), with each cohort consisting of an experimental treatment arm and a control arm. The inclusion of a control group allows discrimination of patient outcomes caused by the experimental treatment from outcomes caused by other factors. Randomisation avoids systematic differences (bias) between the groups with respect to known or unknown baseline variables that could affect outcome. The treatment for patients in the control arms represents standard of care.

The primary objective of the study is to evaluate PFS per RECIST 1.1 within each cohort.

Provided the iDMC does not recommend discontinuation of enrolment to a cohort or enrolment is not otherwise discontinued prior to a cohort reaching its target sample size, the primary analysis will occur for each cohort when the target number of PFS events has been reached. Secondary endpoints will also be summarised at this time. Analyses of any cohort closed to accrual before its target sample size is reached will be described in an SAP and will depend on accrual at the time of closure.

Update on statistical analysis plans and cohort status following premature closure of study enrolment: Accrual to Cohort 2 was completed in November 2016. Accrual to Cohort 4 was closed in February 2018 due to iDMC recommendations as a result of an unfavourable benefit-risk evaluation (see protocol Section 3.1.2.4). Study enrolment was suspended at the time of discontinuation of accrual to Cohort 4 (February 2018) and will remain permanently closed to further enrolment. Cohorts 1, 3 and 4 will not reach their target sample size. As originally planned for cohorts reaching their target number of PFS events (applies to Cohort 2 only), an update analysis of efficacy and safety parameters will be conducted based on 24 months survival follow-up after the clinical cut-off date (CCOD) for the primary analysis. The CCOD for the Cohort 2 primary analysis was May 31, 2017. The Cohort 2 update analysis will be conducted based on a CCOD of May 31, 2019. The primary analysis for cohorts 1, 3 and 4 will be conducted at the same time as the Cohort 2 update analysis (i.e. based on the same CCOD of May 31, 2019).

The final study analysis for all cohorts will be conducted after all patients in the study have discontinued study treatment and completed the adverse event reporting period and any applicable post-treatment follow-up safety assessments (see protocol Section 5.3.1 for adverse event reporting periods and post-treatment follow-up safety assessments). Data will be summarised using appropriate summary statistics: mean, standard deviation, median, quartiles and range (minimum and maximum) for continuous variables, and number and percentage for categorical variables.

Analysis Populations

For each cohort, the Intent-To-Treat (ITT) Population will include patients entered into the Maintenance Treatment Phase of the study, irrespective of whether or not they received study medication. In this population, patients will be allocated to the study maintenance treatment into which they were randomised. The ITT Population will be used for all efficacy analyses.

The Per Protocol Population will not be defined for this study but major protocol violations will be listed.

The Safety Population will include all patients who received at least one dose of study medication during the Induction or Maintenance Treatment Phases. Patients will be allocated to the treatment regimen that they actually received. The Safety Population will be used for all safety analyses.

Statistical Hypotheses

Cohorts 1 and 3

The null and alternative hypotheses when comparing PFS between the two randomised treatments in Cohort 1 (Arm A: 5-FU/LV with cetuximab and vemurafenib vs. Arm B: fluoropyrimidine and bevacizumab) and in Cohort 3 (Arm A: capecitabine with trastuzumab and pertuzumab vs. Arm B: fluoropyrimidine and bevacizumab) are:

H_0: the distribution of the PFS time is the same in the two treatment groups

PFS (Arm A) = PFS (Arm B)

H_1: the distribution of the PFS time is different in the two treatment groups

specifically PFS (Arm A) > PFS (Arm B)

If the hazard ratio (HR) of Arm A compared to Arm B is assumed to be constant over time, then the null and alternative hypotheses are:

H_0: HR = 1 vs. H_1: HR < 1

Due to the relatively low prevalence of mCRC patients with HER2+ or $BRAF^{mut}$ disease, the formal statistical tests for Cohorts 1 and 3 will be one-sided and performed at an alpha level (type I error rate) of 10%.

Cohorts 2 and 4

The null and alternative hypotheses when comparing PFS between the two randomised treatments in Cohort 2 (Arm A: fluoropyrimidine with bevacizumab and atezolizumab vs. Arm B: fluoropyrimidine and bevacizumab) and in Cohort 4 (Arm A: cobimetinib with atezolizumab vs. Arm B: fluoropyrimidine and bevacizumab) are:

H_0: the distribution of the PFS time is the same in the two treatment groups

PFS (Arm A) = PFS (Arm B)

H_1: the distribution of the PFS time is different in the two treatment groups

PFS (Arm A) ≠ PFS (Arm B)

If the HR of Arm A compared to Arm B is assumed to be constant over time, then the null and alternative hypotheses are:

H_0: HR = 1 vs. H_1: HR ≠ 1

The formal statistical tests for Cohorts 2 and 4 will be two-sided and performed at an alpha level (type I error rate) of 5%.

Primary Endpoint

All Cohorts

The primary efficacy endpoint of PFS is defined as the time from randomisation into the Maintenance Treatment Phase until disease progression per Investigator assessment using RECIST 1.1 or death from any cause, whichever occurs first. Tumour size will be calculated using the sum of the longest diameters of all target lesions, and reduction will be based on comparisons to the tumour assessment done at the end of the Induction Treatment Phase.

Patients without an event will be censored at the date of their last evaluable tumour assessment or, if this is not available, at the date of randomisation. For each cohort, the primary analysis of PFS will occur when the target number of PFS events has been reached.

Within each cohort, PFS will be presented graphically for each treatment group using the Kaplan-Meier method. Estimates and the corresponding 95% confidence interval will be reported by treatment group for median survival time, and for the 4-, 6- and 12-month PFS rates.

Within each cohort, the comparison of PFS between the treatment groups will be performed using an unstratified log-rank test. In addition, a Cox regression will be performed with treatment and applicable stratification variables (biomarkers, geographic region and/or response after induction treatment) as terms in the model. The estimated hazard ratio and its corresponding 95% confidence interval will be presented.

The timing and methods of the primary efficacy endpoint analyses for any cohort closed to accrual before its target sample size is reached may differ from above. These will be described in the SAP applicable to the cohort and will depend on accrual at the time of early closure.

Secondary Efficacy Endpoints

All Cohorts

The secondary efficacy endpoints for each cohort are OS, ORR, DCR, TTR, DoR and ECOG performance status.

OS is defined as the time from randomisation until death from any cause. Patients who are still alive at the time of analysis (clinical cut-off) and patients who are lost to follow-up will be censored at their last clinical assessment date.

Best overall response will be assessed for all patients after randomisation until disease progression. ORR will be calculated as the proportion of patients with a best overall response of CR or PR determined according to RECIST 1.1. ORR will be summarised and presented along with the 95% Clopper-Pearson confidence interval.

DCR will be calculated as the proportion of patients with a best overall response of CR, PR or SD as determined according to RECIST 1.1. DCR will be summarised and presented along with the 95% Clopper-Pearson confidence interval.

TTR will be calculated as the time from randomisation to the first occurrence of a documented objective response (CR or PR) determined according to RECIST 1.1.

DoR will be assessed for all patients after randomisation until PD. Only patients with a best overall response of CR or PR per RECIST 1.1 are considered responders. The duration of response is the time from the first assessment of CR or PR until disease progression or death from any cause, whichever occurs first.

The secondary time-to-event endpoints will be analysed by the same methods and at the same time as the primary endpoint.

ECOG performance status will be summarised over time.

Safety Endpoints

All Cohorts

Verbatim adverse event (AE) data will be mapped to Medical Dictionary for Regulatory Activities (MedDRA) thesaurus terms.

All treatment-emergent AEs occurring during or after the first dose of study medication will be summarised by treatment group in frequency tables, as follows:

- By preferred term and system organ class
- By severity of all adverse events (graded according to NCI CTCAE v4.0)
- Grade 3 – 5 AEs
- Grade 5 AEs or AEs leading to death on study treatment

- All SAEs
- AEs leading to premature discontinuation of any component of study treatment
- AEs leading to dose reduction or interruption of any component of study treatment
- AEs of special interest

The above safety data will be summarised separately for the Induction and Maintenance Treatment Phases overall and by individual maintenance treatment cohort.

Deaths reported during the study treatment period and those reported during follow-up after treatment completion/discontinuation will be summarised.

Study medication exposure will be separately summarised by number of cycles, duration, dose and dose intensity.

Vital signs data, clinical laboratory parameters, concomitant medication and subsequent anti-cancer therapy will also be summarised.

Analysis for Exploratory Outcome Measures

Cohorts 2 and 4 - Experimental Arms Only

The exploratory efficacy endpoint of PFS in patients treated with atezolizumab is defined as the time from randomisation into the Maintenance Treatment Phase until disease progression per Investigator assessment using mRECIST or death from any cause, whichever occurs first. Patients without an event will be censored at the date of their last evaluable tumour assessment or, if this is not available, at the date of randomisation. PFS may be presented graphically using the Kaplan-Meier method. Estimates and the corresponding 95% confidence interval may be reported for the 4-, 6- and 12-month PFS rates.

All Cohorts

Biomarker analyses will be of exploratory nature only, utilizing all available data obtained from archival tumour samples from initial diagnoses, all tumour and blood samples collected during the study (including additional tumour samples collected from Supplemental Biomarker Program participants), and stool samples collected during the study from Supplemental Biomarker Program participants. These analyses will be of exploratory nature only, using descriptive methods with no fixed hypotheses testing.

With the ongoing analyses of the study's various biomarker-based cohorts, more information on the concordance of different biomarkers will be collected and summarised. Relevant findings will be discussed with the study's SC in order to conduct further exploratory biomarker analyses accordingly.

Interim Analyses

The iDMC will evaluate accumulating safety and efficacy data within each cohort to assure these data continue to support an early positive benefit-risk ratio and to confirm that continued enrolment into each cohort is appropriate. The amount of efficacy data to be assessed in a given cohort will be determined by the iDMC at a preceding iDMC meeting. Details of this process are described in the iDMC charter. Decisions on what efficacy data have to be evaluated for each cohort will be documented in the iDMC meeting minutes. In addition, the iDMC will review data from any safety run-in patients required for an experimental regimen (e.g. as conducted for the initial patients treated with the experimental combination of '5-FU/LV + cetuximab + vemurafenib'). These safety run-ins will be specified in the protocol.

Determination of Sample Size

Before study enrolment was closed prematurely, approximately 1,820 patients were expected to be screened and approximately 1,400 patients were expected to be enrolled in the Induction Treatment Phase of the study in order to randomise the planned number of patients in each of the maintenance

cohorts (see Table 1). Cohort 2 reached its target sample size and was closed to further accrual. Cohort 4 was closed to accrual with 99 patients randomized (i.e. prior to reaching the target sample size per Table 1). Due to early closure of study enrolment, target sample sizes will not be reached in Cohort 1 (final n=60) or Cohort 3 (final n=5).

Within each cohort, the required sample size is based on the comparison of PFS between the treatment groups and an assumed recruitment period of 11 months for Cohorts 2 and 4. Median PFS assumed for each cohort and treatment arm are shown in Table 1.

Table 1: PFS and Sample Size Estimates per Cohort

Cohort	Median PFS (months)		Target Sample Size
	Experimental treatment group	Control group (FP and bevacizumab)	
Cohort 1	7	4.9	126
Cohort 2	11.5	7.5	405
Cohort 3	11.5	7.5	90
Cohort 4	11.5	7.5	405

Additional details of the sample size calculation inputs are found in the statistical section of the protocol.

Appendix 2: Schedule of Assessments for All Patients (Screening / Baseline and Induction Treatment Phase)

					Patients who have PD during or at end of Induction Treatment Phase or who refuse Maintenance Treatment or who are not eligible for any study cohort	
	Screening / Baseline		Induction Treatment Phase [a]		Study Treatment Discontinuation Visit [b]	Post-Treatment Follow-Up Phase [c]
	≤ 28 days	≤ 7 days	Day 1 Cycle 1	Every 2 cycles (every 4 weeks)	(≤ 30 days after last dose of study treatment)	Every 3 months *until May 31, 2019 (see Appendix 19)*
Informed consent [d]	x					
Confirmation of general eligibility [e]	x	x		As required		
Demographics and medical history [f]	x					
Vital signs and weight [g]	x	x	x	x	x	
Physical examination[h]	x		x	x	x	
ECOG performance status [i]		x	x	x	x	
Concomitant medications [j]	x	x	x	x	x	
Haematology and blood chemistry [k]		x		x	x	
INR, aPTT (select patients) [l]		x		x		
Urinalysis (dipstick) [m]		x		x	x	
Pregnancy test [n]		x		If clinically indicated		
Tumour assessments [o]	x			Mandatory at end of Induction Treatment Phase		According to local standard of care until disease progression

					Patients who have PD during or at end of Induction Treatment Phase or who refuse Maintenance Treatment or who are not eligible for any study cohort	
	Screening / Baseline		Induction Treatment Phase [a]		Study Treatment Discontinuation Visit [b]	Post-Treatment Follow-Up Phase [c]
	≤ 28 days	≤ 7 days	Day 1 Cycle 1	Every 2 cycles (every 4 weeks)	(≤ 30 days after last dose of study treatment)	Every 3 months *until May 31, 2019 (see Appendix 19)*
Archival primary tumour tissue for biomarker assessment [p]	x					
Metastatic tumour tissue for exploratory biomarker assessment [q] Collection of these samples discontinued as of May 2018	No sample collection			No sample collection Supplemental Biomarker Program CLOSED		
Whole blood sample [r]			x			
Plasma samples [r]			x	Cycles 4, 6 and 8		At time of progression (if patient has not yet progressed)
Stool sample Supplemental Biomarker Program closed as of May 2018. Collection of these samples has been discontinued.	No sample collection Supplemental Biomarker Program CLOSED				No sample collection Supplemental Biomarker Program CLOSED	
Adverse events (including SAEs) [s]	x	x	x	Every cycle	x	x (as applicable)
Study medication administration [t]			x Administered every 2 weeks			

					Patients who have PD during or at end of Induction Treatment Phase or who refuse Maintenance Treatment or who are not eligible for any study cohort	
	Screening / Baseline		Induction Treatment Phase [a]		Study Treatment Discontinuation Visit [b]	Post-Treatment Follow-Up Phase [c]
	≤ 28 days	≤ 7 days	Day 1 Cycle 1	Every 2 cycles (every 4 weeks)	(≤ 30 days after last dose of study treatment)	Every 3 months *until May 31, 2019 (see Appendix 19)*
Subsequent anti-cancer therapies (see [c])						x
Patient survival (see [c])					x	x

a. With the exception of Cycle 1, all other study visits and assessments should be performed within ± 7 days of the scheduled date.

b. Patients who experience PD during or at the end of the Induction Treatment Phase, or who refuse to go into the Maintenance Treatment Phase or who are not eligible for any study cohort, will undergo a Study Treatment Discontinuation Visit within 30 days after the last dose of study medication. These patients will then enter the Post-Treatment Follow-up Phase. All patients need to be evaluated for potential resection of metastasis at completion of the induction period. This is of particular importance for patients with liver metastases. If the patient is found to be resectable they will undergo a Study Treatment Discontinuation Visit within 30 days after the last dose of study treatment and will then enter the Post-Treatment Follow-up Phase.

c. Patients in the Post-Treatment Follow-up Phase will be followed up every 3 months after their Study Treatment Discontinuation Visit. During post-treatment follow-up subsequent anti-cancer therapies will be recorded and survival assessed up to May 31, 2019 only. Refer to Appendix 19 for management of patients based on their study status on May 31, 2019. Treatment during the Post-Treatment Follow-up Phase is at the Investigator's discretion; $BRAF^{mut}$/MSS patients experiencing early disease progression during induction treatment will have the option of proceeding immediately to receive second-line treatment with 5-FU/LV, cetuximab and vemurafenib; $BRAF^{mut}$/MSI-H patients experiencing early disease progression during induction treatment will have the option of proceeding immediately to receive second-line treatment with a fluoropyrimidine (5-FU/LV or capecitabine), bevacizumab and atezolizumab. See Section 3.1.1.1 for further details including if disease progression occurs prior to availability of study biomarker test results in a patient with a previous BRAF mutation-positive result (e.g. by local test). Patients who discontinue study treatment during the Induction Treatment Phase prior to disease progression will also continue to be followed for PFS, with disease status followed according to local practice until progression or May 31, 2019, whichever comes first. Disease status will not be collected for the study after May 31, 2019.

d. Written informed consent for participation in the study must be obtained before performing any study-specific screening tests or evaluations and before shipping primary tumour blocks or slides to the Sponsor-designated laboratory. However, results from routine assessments conducted

prior to informed consent signature may be used as screening assessments as long as they were done within 7 days prior to informed consent signature.

e. The “All Cohort” eligibility criteria are evaluated prior to initiating the first cycle of study treatment during the Induction Treatment Phase.

f. Medical history includes clinically significant diseases, surgeries, cancer history (including prior cancer therapies and procedures), reproductive status, smoking history, use of alcohol and drugs of abuse, and all medications (e.g., prescription drugs, over-the-counter drugs, herbal or homeopathic remedies, nutritional supplements) used by the patient within 7 days prior to the Screening visit. Demographic data will include age, sex, and self-reported race/ethnicity (where permitted by federal regulations).

g. Vital signs include measurements of systolic and diastolic blood pressure while the patient is in a seated position, and temperature. During Screening, weight only required ≤ 7 days.

h. Baseline assessment requires a complete physical exam. A complete physical examination should include an evaluation of the head, eyes, ears, nose, and throat, and the cardiovascular, dermatological, musculoskeletal, respiratory, gastrointestinal, genitourinary, and neurological systems. Abnormalities identified at Screening / Baseline will be recorded as baseline conditions. At subsequent visits (or as clinically indicated), limited, symptom-directed physical examinations should be performed. Changes from Baseline, with new or worsened clinically significant abnormalities, should be reported as AEs if appropriate.

i. ECOG status assessed within 7 days prior to Day 1 of Cycle 1 (Induction Treatment Phase) for eligibility determination. See Appendix 8.

j. Concomitant medication includes any prescription medications or over-the-counter preparations used by a patient between the 7 days prior to the date of informed consent up until the date of study discontinuation. Only concomitant medications used for supportive care, to alleviate symptoms of mCRC, or to treat adverse drug reactions should be recorded on the Concomitant Medications eCRF. At subsequent visits, only changes to current medications or medications used since the last documentation of medications will be recorded. Concomitant medications for treatment of AEs related to study medication will continue to be recorded while the AE is being followed. For permitted and prohibited concomitant medications, see Section 4.4.

k. Haematology includes haemoglobin, haematocrit, platelet count, red blood cell count, white blood cell count, and differential. Blood chemistry includes ALT, AST, alkaline phosphatase, total bilirubin, total protein, albumin, blood urea nitrogen or urea, LDH, creatinine, glucose, calcium, phosphorus, sodium, potassium, chloride, and bicarbonate. Hematology and blood chemistry tests must be conducted prior to each treatment cycle, with the results available for review prior to start of treatment according to local standards for treatment management. However, only tests conducted every second treatment cycle will be recorded in the eCRF. Clinical laboratory results constituting a clinically significant AE should be recorded as such.

l. INR and aPTT are required for all patients at screening but only for patients receiving anticoagulants while on protocol-specified treatment.

m. Urinalysis must be performed by dipstick at Baseline and within 48 hours prior to every cycle. A 24-hour urine collection is needed in the event of proteinuria ≥ ± 2 by dipstick test.

n. Urine or blood pregnancy test, only for women of childbearing potential (i.e. not post-menopausal as indicated by < 12 months of non-therapy-induced amenorrhea, nor surgically sterile [absence of ovaries and/or uterus]), including those who have had a tubal ligation. A serum pregnancy test is required within 7 days prior to start of study induction treatment, or within 14 days with a confirmatory urine pregnancy test within 7 days prior start of study induction treatment

o. Will include radiology, chest and abdominal CT or MRI, and other scans to document all sites of disease. Include upper abdomen at Baseline. A CT or MRI scan of the brain is required if there is clinical suspicion of CNS metastases at screening/Baseline or at any time during the Induction Treatment Phase. Subsequent tumour assessments will be done according to standard of care at each study centre, with the exception that all patients must have a tumour assessment at the end of the Induction Treatment Phase. Tumour assessments are not required for study purposes after disease progression has been documented. Patients who discontinue study treatment during the Induction Treatment Phase prior to disease progression will also continue to be followed for progressive disease, with disease status followed according to local practice until progression or May 31, 2019, whichever comes first. After May 31, 2019, disease status will not be collected for the study.

p. Archival tumour tissue (FFPET) block from the primary tumour obtained at the time of the initial diagnosis. If the tumour block is not available, ≥ 20 slides cut from the primary tumour sample will be accepted as an alternative. Before a patient can be enrolled, the sample (block or slides) must be shipped to the designated laboratory with the corresponding pathology report and receipt of the shipment must be confirmed by the laboratory. See Appendix 17.

q. Collection of the optional core biopsy of metastatic tumours was discontinued as of May 2018 (See Appendix 18).

r. Whole blood and plasma samples will be collected from all study patients for exploratory biomarker analyses unless genomic analysis is not allowed per local regulations. In such instances, only plasma samples will be collected. All samples will be sent to a designated laboratory. Samples during treatment should be taken within 48 hours prior to study treatment Day 1 of each cycle indicated, unless otherwise specified (see Appendix 17 and Laboratory Manual).

s. After the signing of the informed consent form, and prior to Day 1 of Cycle 1 (Induction Treatment Phase), any SAEs thought to be related to a protocol-mandated intervention should be reported. Adverse events will be documented at every cycle during treatment. All patients will be followed for new AEs for 28 days following the discontinuation of study treatment. At the time of treatment discontinuation, any ongoing AE/SAE will be followed until the event resolves, the Investigator assesses the event as stable, the patient is lost to follow-up, dies or withdraws consent. Death related to disease progression is not considered to be an SAE. The Sponsor should be notified if the Investigator becomes aware of any SAE or AEs of special interest occurring after the end of the adverse event reporting period if the event is believed to be related to prior study treatment.

t. 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-FU, 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.

Appendix 3: Schedule of Assessments During Maintenance Phase (Cohort 4)

	Prior to randomization	Maintenance Treatment Phase [a]	Study Treatment Discontinuation Visit [b]	Post-Treatment Follow-Up Phase [c]
	Within 3 weeks of completing Induction Treatment Phase	Every 2 cycles (approximately every 4 weeks)	(≤ 30 days after last dose of study treatment)	Every 3 months
Assignment of cohort [d]	x			
Cohort- specific informed consent	x (sites using 2 consent forms only)			
Confirmation of cohort-specific eligibility [e]	x			
Randomisation [f]	x			
Vital signs and weight [g]		x	x	
Physical examination [h]		x	x	
ECOG performance status [i]		x	x	
Concomitant medications [j]		Every cycle	x	
Haematology and blood chemistry [k]		Every cycle	x	
INR, aPTT (select patients) [l]		According to local standard of care		
Urinalysis (dipstick) [m]		Every cycle	x	
Pregnancy test [n]		If clinically indicated		
TSH, free *or total* T3, free *or total* T4 *(Experimental Arm only)*		Prior to Cycles 1, 4, 7, 10, 13, 16, 19, 22 and every 3 cycles thereafter	x	
Pulse oximetry *(Experimental Arm only)*		Prior to Cycles 1, 3, 5, 7, 9, 11, 13, 15 and every 2 cycles thereafter	x	

	Prior to randomization	Maintenance Treatment Phase [a]	Study Treatment Discontinuation Visit [b]	Post-Treatment Follow-Up Phase [c]
	Within 3 weeks of completing Induction Treatment Phase	Every 2 cycles (approximately every 4 weeks)	(≤ 30 days after last dose of study treatment)	Every 3 months
Tuberculosis test [o]	x			
HIV, HBV, HCV serology [p]	x			
LVEF [q]	X	Experimental arm only: Cycles 4, 10, 16, 22, 28, 34, 40 and every 6 cycles thereafter	Experimental arm only	
Ophthalmology exam [r]	X	Experimental arm only: Cycles 4, 10, 16, 22, 30, 38, 46, 58 and every 12 cycles thereafter	Experimental Arm only	
Tumour assessments [s]		*Up to and including May 31, 2019:* Every 8 weeks regardless of treatment delays *After May 31, 2019: per local practice*		*Up to and including May 31, 2019:* Every 8 weeks until disease progression *After May 31, 2019: per local practice*
Metastatic tumour tissue for exploratory biomarker assessment [t] *Supplemental Biomarker Program closed as of May 2018. Collection of these samples has been discontinued.*	*No sample collection Supplemental Biomarker Program CLOSED*	*No sample collection Supplemental Biomarker Program CLOSED*		
Plasma samples [u]		Cycles 1, 2, 4, 6, 8, 10, 12, 14 and every 2 cycles thereafter And at time of PD		At time of progression (if patient has not yet progressed)

	Prior to randomization	Maintenance Treatment Phase [a]	Study Treatment Discontinuation Visit [b]	Post-Treatment Follow-Up Phase [c]
	Within 3 weeks of completing Induction Treatment Phase	Every 2 cycles (approximately every 4 weeks)	(≤ 30 days after last dose of study treatment)	Every 3 months
Stool sample *Supplemental Biomarker Program closed as of May 2018. Collection of these samples has been discontinued.*	*No sample collection Supplemental Biomarker Program CLOSED*		*No sample collection Supplemental Biomarker Program CLOSED*	
Adverse events (including SAEs) [v]		Every cycle	x	x (as applicable)
Study medication administration [w]		Every cycle		
Subsequent anti-cancer therapies (see [c])				x
Patient survival (see [c])			x	x

a. With the exception of Cycle 1, all other study visits and assessments should be performed within ± 7 days of the scheduled date. If a control arm patient receives capecitabine administered according to a 3- week cycle, timing of all study procedures and assessments scheduled according to 2-week treatment cycles (e.g. ECOG performance status) will be defined by the treatment cycles of concurrently administered bevacizumab.

b. Patients who experience PD at any time during the Maintenance Treatment Phase, or who need to permanently discontinue study medication for any reason, will undergo a Study Treatment Discontinuation Visit within 30 days after the last dose of study medication. These patients will then enter the Post-Treatment Follow-up.

c. After discontinuation of study treatment and the Study Treatment Discontinuation Visit, patients will enter the Post-Treatment Follow-up Phase. Beginning after the Study Treatment Discontinuation Visit, patients will be followed up every 3 months. *Up to and including May 31, 2019, follow-up will include disease status (patients discontinuing study treatment prior to disease progression only), in addition to safety evaluations and recording of subsequent anti-cancer therapies and survival. After May 31, 2019, disease status will not be collected for the study.* Treatment during the Post-Treatment Follow-up Phase is at the Investigator's discretion, however, patients treated with atezolizumab should not receive other immunomodulatory agents for 10 weeks after study treatment discontinuation. Patients who discontinue study treatment prior to disease progression will be followed for PFS, with disease status followed every 8 weeks until progression *or May 31, 2019*, whichever comes first.

d. Patients completing the Induction Treatment Phase, and who have not experienced PD can then proceed to the Maintenance Treatment Phase. Depending on the patient's biomarker status (based on the archival sample from initial diagnosis), these patients will be assigned to a maintenance treatment cohort. Cohorts 2 and 4 are closed to further accrual. Patients with an adequate tumour sample but with unknown biomarker status due to lack of determinant result (e.g. due to technical issues) may still be included in the study depending on the addition of future cohorts.

e. The cohort-specific exclusion criteria must be assessed prior to randomization to study maintenance treatment but assessment of cohort-specific eligibility can only be completed after the biomarker analysis results from the patient's archival tumour tissue from initial diagnosis are known. Patients found ineligible for any cohort will undergo a Study Treatment Discontinuation Visit and enter the Post-Treatment Follow-up Phase.

f. Each cohort will consist of an experimental treatment arm and a control arm. Randomised on a 2:1 (experimental:control) basis to either the experimental treatment arm or the control arm of that cohort. See Section 4.2.

g. Vital signs include measurements of systolic and diastolic blood pressure while the patient is in a seated position, and temperature. Experimental arm only: For the first atezolizumab infusion, the patient's vital signs (heart rate, respiratory rate, blood pressures, and temperature) should be determined within 60 minutes before the infusion, every 15 ± 5 minutes during the infusion, and 30 ± 10 minutes after the infusion. For subsequent infusions, vital signs will be collected within 60 minutes before the infusion and should be collected during or after the infusion if clinically indicated or if symptoms occurred in the prior infusion. Vital sign measurements from every second treatment cycle only will be recorded in the eCRF.

h. Physical examinations will be symptom-directed, and will include changes from Baseline (pre-Induction) with new or worsened clinically significant abnormalities being reported as AEs if appropriate.

i. See Appendix 8.

j. Concomitant medication includes any prescription medications or over-the-counter preparations used by a patient between the 7 days prior to the date of informed consent up until the Study Treatment Discontinuation visit. Only concomitant medications used for supportive care, to alleviate symptoms of mCRC, or to treat adverse drug reactions should be recorded on the Concomitant Medications eCRF. At subsequent visits, only changes to current medications or medications used since the last documentation of medications will be recorded. Concomitant medications for treatment of AEs related to study medication will continue to be recorded while the AE is being followed. For permitted and prohibited concomitant medications, see Section 4.4.

k. Haematology includes haemoglobin, haematocrit, platelet count, red blood cell count, white blood cell count, and differential. Blood chemistry includes ALT, AST, alkaline phosphatase, total bilirubin, total protein, albumin, blood urea nitrogen or urea, LDH, creatinine, glucose, calcium, phosphorus, sodium, potassium, chloride, bicarbonate. For experimental arm only patients, blood chemistry will also include magnesium, creatine phosphokinase, lipase and amylase. Haematology and blood chemistry tests must be conducted prior to treatment administration on Day 1 of each treatment cycle with the results available for review prior to start of treatment according to local standards for treatment management. Clinical laboratory results from every second cycle only will be recorded in the CRF. Clinical laboratory results constituting a clinically significant AE should be recorded as such.

Appendix 4: SAS code

The following SAS code will be used to obtain the log-rank p-value from the unstratified log-rank test mentioned in section 4.11.1:

```
PROC LIFETEST data=dataset METHOD=KM CONFTYPE=LOGLOG;
TIME pfstime*censor(1);
STRATA treat / test=logrank;
RUN;
* pfstime represents variable containing event/censor times;
* censor represents censoring variable (1=censored, 0=event);
* treat represents treatment group variable;
Further options to control the output may be added.
```

The following SAS code will be used to obtain the hazard ratio and corresponding confidence interval from the Cox Model with treatment as single covariate mentioned in section 4.11.44.11.1:

```
PROC PHREG data=dataset;
CLASS treat;
MODEL pfstime*censor(1)=treat /RL TIES=EXACT;
RUN;
* pfstime represents variable containing event/censor times;
* censor represents censoring variable (1=censored, 0=event);
* treat represents treatment group variable;
Further options to control the output may be added.
```

The following SAS code will be used to obtain the hazard ratio and corresponding confidence interval from the adjusted Cox Model mentioned in section 4.11.4:

```
PROC PHREG data=dataset;
CLASS treat strate1;
MODEL pfstime*censor(1)=treat stratum1 /RL TIES=EXACT;
RUN;
* pfstime represents variable containing event/censor times;
* censor represents censoring variable (1=censored, 0=event);
* treat represents treatment group variable;
* strate1 represents the categorical covariates related to stratification
factors;
Further options to control the output may be added.
```

Appendix 5: List of Outputs

List of Outputs: Tables

Table Number	Table Title	Phase	Population	Primary analysis	Final Analysis
	Patient Disposition				
14.1.1.1	Patient Disposition For Induction Treatment Phase	ITP	ALL	X	
14.1.1.2	Patient Disposition For Maintenance Treatment Phase	MTP	MTP	X	X
14.1.1.3	Duration of Follow-up	MTP	MTP	X	X
14.1.2.1	Major Protocol Deviations For Induction Treatment Phase	ITP	ITP	X	
14.1.2.2	Major Protocol Deviations For Maintenance Treatment Phase	MTP	MTP	X	X
	Demographics and Baseline Characteristics				
14.1.3.1	Summary of Baseline and Demographic Characteristics	ITP	ITP	X	
14.1.3.2	Summary of Baseline and Demographic Characteristics	MTP	MTP	X	
14.1.3.3	Summary of Baseline Biomarker Status	MTP	MTP	X	
14.1.4.1	Tumor Response Status (RECIST 1.1) at End of Induction (eCRF data)	ITP	ITP	X	
14.1.5	Randomization by Country and Study Center	MTP	MTP	X	
14.1.6	Stratification Factors as per IxRS	MTP	MTP	X	
14.1.7.2	Tumor Response (RECIST 1.1) at End of Induction as per IxRS versus eCRF Data	MTP	MTP	X	
14.1.8.1	Summary of Colorectal Cancer History	ITP	ITP	X	
14.1.8.2	Summary of Colorectal Cancer History	ITP	MTP	X	
14.1.10.1	Medical History	ITP	ITP	X	
14.1.11.1	Summary of Prior Anti-Cancer Treatments/Procedures	ITP	ITP	X	
14.1.13.2	Concomitant Medications during the Maintenance Phase	MTP	SAF	X	
	Exposure				
14.1.16.1	Summary of Total Number of Cycles Initiated during ITP	ITP	ITP	X	
14.1.17.1	Summary of Overall Duration of Treatment and Number of Cycles Initiated during MTP	MTP	SAF	X	X

Table Number	Table Title	Phase	Population	Primary analysis	Final Analysis
14.1.17.2	Summary of Drug Exposure during MTP	MTP	SAF	x	x
	Efficacy				
14.2.1.1	Summary of Progression Free Survival - Primary Analysis (Surgery Censored)	MTP	MTP	X	
14.2.1.2	Progression Free Survival: Hazard Ratio	MTP	MTP	X	
14.2.7.1	Summary of Overall Survival	MTP	MTP	X	X
14.2.7.2	Overall Survival: Hazard Ratio	MTP	MTP	X	X
	Adverse Events				
14.3.1.1.1	Treatment Emergent Adverse Events (TEAEs) during ITP: Overall Summary	ITP	ITP	X	
14.3.1.1.2	Treatment Emergent Adverse Events (TEAEs) during MTP: Overall Summary	MTP	SAF	X	X
14.3.1.2.1	Treatment Emergent Adverse Events by SOC and PT and by Worst Intensity during ITP	ITP	ITP	X	
14.3.1.2.2	Treatment Emergent Adverse Events by SOC and PT and by Worst Intensity during MTP	MTP	SAF	X	x
14.3.1.2.5	Treatment Emergent Adverse Events by SOC and PT during MTP	MTP	SAF	X	X
14.3.1.2.6	Treatment Emergent Adverse Events by SOC and PT during ITP	ITP	SAF	X	
14.3.1.3.1	Treatment Emergent Adverse Events Related to Any Study Drug by SOC and PT during ITP	ITP	ITP	X	
14.3.1.3.4	Treatment Emergent Adverse Events Related to Bevacizumab by SOC and PT during MTP			x	
14.3.1.3.5	Treatment Emergent Adverse Events Related to Any Study Drug by SOC and PT during MTP	MTP	SAF	X	X
14.3.1.3.8	Treatment Emergent Adverse Events Related to Atezolizumab by SOC and PT during MTP	MTP	SAF	X	X
14.3.1.3.9	Treatment Emergent Adverse Events Related to Bevacizumab by SOC and PT during MTP	MTP	SAF	X	X
14.3.1.3.11	Treatment Emergent Adverse Events Related to Cobimetinib by SOC and PT during MTP	MTP	SAF	X	X
14.3.1.4.1	Treatment Emergent Adverse Events Leading to Discontinuation of Any Study Drug by SOC and PT during ITP	ITP	ITP	X	

Table Number	Table Title	Phase	Population	Primary analysis	Final Analysis
14.3.1.4.5	Treatment Emergent Adverse Events Leading to Discontinuation of Any Study Drug by SOC and PT during MTP	MTP	SAF	X	X
14.3.1.5.4	Treatment Emergent Adverse Events Leading to Dose Reduction or Interruption of Bevacizumab by SOC and PT during ITP	ITP	ITP	X	
14.3.1.5.7	Treatment Emergent Adverse Events Leading to Dose Reduction or Interruption of Atezolizumab by SOC and PT during MTP	MTP	SAF	x	X
14.3.1.5.11	Treatment Emergent Adverse Events Leading to Dose Reduction or Interruption of Cobimetinib by SOC and PT during MTP	MTP	SAF	x	x
14.3.1.7.1	Serious Treatment Emergent Adverse Events by SOC and PT during ITP	ITP	ITP	x	
14.3.1.7.2	Serious Treatment Emergent Adverse Events by SOC and PT during MTP	MTP	SAF	X	X
14.3.1.8.1	Serious Treatment Emergent Adverse Events Related to Any Study Drug by SOC and PT during ITP	ITP	ITP	x	
14.3.1.8.4	Serious Treatment Emergent Adverse Events Related to Bevacizumab by SOC and PT during ITP	ITP	ITP	x	
14.3.1.8.5	Serious Treatment Emergent Adverse Events Related to Any Study Drug by SOC and PT during MTP	MTP	SAF	x	x
14.3.1.8.8	Serious Treatment Emergent Adverse Events Related to Atezolizumab by SOC and PT during MTP	MTP	SAF	x	x
14.3.1.8.9	Serious Treatment Emergent Adverse Events Related to Bevacizumab by SOC and PT during MTP	MTP	SAF	x	x
14.3.1.8.12	Serious Treatment Emergent Adverse Events Related to Cobimetinib by SOC and PT during MTP	MTP	SAF	x	x
14.3.1.9.2	Treatment Emergent Adverse Events with Fatal Outcome by SOC and PT during MTP	MTP	SAF	X	X
14.3.1.10.1	Treatment Emergent AESI Based on eCRF Categories during MTP	MTP	SAF	X	X
14.3.1.10.2	Treatment Emergent AESI Based on eCRF Categories during ITP	ITP	ITP	X	
14.3.1.10.3	Bevacizumab Treatment Emergent AESI Based on Pre-Defined Categories during MTP	MTP	SAF	X	X
14.3.1.10.4	Bevacizumab Treatment Emergent AESI Based on Pre-Defined Categories during ITP	ITP	ITP	X	

Table Number	Table Title	Phase	Population	Primary analysis	Final Analysis
14.3.1.10.5	Atezolizumab Treatment Emergent AESI Based on Pre-Defined Categories during MTP	MTP	SAF	X	X
	Deaths				
14.3.1.12.3	Deaths within 30 Days from Last Day of Treatment of MTP and Reason	MTP	SAF	X	X
14.3.1.12.5	Post Maintenance Treatment Deaths and Reason	Post-Treatment	SAF	X	X
	Laboratory Data				
14.3.4.1.2	Shift Table (Baseline versus Worst On-Treatment) during MTP for CTC Gradable Hematology Parameters	MTP	SAF	x	
14.3.4.2.2	Shift Table (Baseline versus Worst On-Treatment) during MTP for CTC Gradable Blood Chemistry Parameters	MTP	SAF	x	
14.3.4.3.2	Shift Table (Baseline versus Worst On-Treatment) during MTP for CTC Gradable Coagulation Parameters	MTP	SAF	x	
14.3.4.4.2	Shift Table (Baseline versus Worst On-Treatment) during MTP for Non CTC Gradable Hematology Parameters	MTP	SAF	x	
14.3.4.5.2	Shift Table (Baseline versus Worst On-Treatment) during MTP for Non CTC Gradable Blood Chemistry Parameters	MTP	SAF	x	
14.3.4.6	Shift Table (Baseline versus Worst On-Treatment) during MTP for Non CTC Gradable Thyroid Parameters	MTP	SAF	x	
14.3.4.7.2	Shift Table (Baseline versus Worst On-Treatment) during MTP for Urinalysis Protein Dipstick	MTP	SAF	x	
	Vital Signs				
14.3.5.2	Summary of Vital Signs Over Time during MTP	MTP	SAF	x	
14.3.6	Summary of Blood Oxygen Saturation Over Time during MTP	MTP	SAF	x	

List of Outputs: Figures

Figure Number	Figure Title	Phase	Population	Primary analysis	Final Analysis
	Disposition				
14.1.1	CONSORT Flow Diagram for All Screened Patients	All	Screened	X	
14.1.2	CONSORT Flow Diagram for Patients Randomized in Cohort 4	All	MTP	X	X
	Efficacy				
14.2.1.1	Kaplan Meier Plot of Progression Free Survival - Primary Analysis	MTP	MTP	X	
14.2.2.1	Kaplan Meier Plot of Overall Survival	MTP	MTP	X	X

List of Outputs: Listings

Listing Number	Listing Title	Phase	Population	Primary analysis	Final Analysis
	Disposition				
16.2.1.1	Patient Disposition and Study Termination Information	ITP	ITP	X	X
16.2.1.2	Patient Who Discontinue Treatment due to Adverse Event	ITP	ITP	X	X
16.2.2	Major Protocol Deviations from PDMS	ITP/MTP	ITP	X	x
16.2.3	Analysis Population	ITP/MTP	ALL	X	
	Demographics and Baseline Characteristics				
16.2.4.1	Demographics and Baseline Characteristics	ITP/MTP	ITP	X	
16.2.4.4	Baseline Biomarker Status	MTP	MTP	X	
16.2.4.5	Randomization Stratification Factors as per IxRS and eCRF	MTP	MTP	X	
16.2.4.6	Colorectal Cancer History	ITP	ITP	X	
16.2.4.8	Prior Anti-Cancer Therapy	ITP	ITP	X	
16.2.4.9	Cancer Radiotherapy: Prior and On-study	ITP/MTP	ITP	X	
16.2.4.10	Colorectal Cancer Surgery : Prior and On-Study	ITP/MTP	ITP	X	

Listing Number	Listing Title	Phase	Population	Primary analysis	Final Analysis
16.2.4.12	Subsequent Anti-cancer Therapies	Post-Treatment	ITP	X	
	Drug Administration				
16.2.5.5	Drug Exposure during ITP	ITP	ITP	X	
16.2.5.8	Drug Exposure during MTP	MTP	SAF	X	X
	Efficacy				
16.2.6.1	Progression Free Survival - Primary Analysis (Surgery Censored)	MTP	MTP	X	
16.2.6.9	Overall Survival	MTP	MTP	X	X
	Safety				
16.2.7.1	Adverse Events	ITP/MTP/ Post-treatment	ITP	X	X
16.2.7.2	Grade 5 Adverse Events or any Adverse Events with Fatal Outcome	ITP/MTP/ Post-treatment	ITP	X	X
16.2.7.3	Adverse Events Leading to Treatment Discontinuation	ITP/MTP/ Post-treatment	ITP	X	X
16.2.7.4	Adverse Events of Special Interest as Reported on eCRF	MTP/ Post-treatment	ITP	X	X
16.2.7.5	Deaths	ITP/MTP/ Post-treatment	ITP	X	X