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

NCT Number: NCT02291289

Document Date: Protocol Version 9: 18-Feb-2020

PROTOCOL

TITLE:	**A MULTI-CENTRE RANDOMISED CLINICAL TRIAL OF BIOMARKER-DRIVEN MAINTENANCE TREATMENT FOR FIRST-LINE METASTATIC COLORECTAL CANCER (MODUL)**
PROTOCOL NUMBER:	MO29112
VERSION NUMBER:	9
EUDRACT NUMBER:	2014-001017-61
IND NUMBER:	N/A
TEST PRODUCT:	Atezolizumab (MPDL3280A, RO5541267) Bevacizumab (RO4876646) Cobimetinib (RO5514041) Pertuzumab (RO4368451) Trastuzumab (RO0452317) Vemurafenib (RO5185426) Cetuximab And combinations thereof
MEDICAL MONITOR:	Dr. [redacted]
SPONSOR:	F. Hoffmann-La Roche Ltd.
DATE FINAL:	See electronic date stamp below

FINAL PROTOCOL APPROVAL

Date and Time (UTC)	Title	Approver's Name
18-Feb-2020 15:44:34	Company Signatory	[redacted]

CONFIDENTIAL

This clinical study is being sponsored globally by F. Hoffmann-La Roche Ltd of Basel, Switzerland. However, it may be implemented in individual countries by Roche's local affiliates, including Genentech, Inc. in the United States. The information contained in this document, especially any unpublished data, is the property of F. Hoffmann-La Roche Ltd (or under its control) and therefore is provided to you in confidence as an investigator, potential investigator, or consultant, for review by you, your staff, and an applicable Ethics Committee or Institutional Review Board. It is understood that this information will not be disclosed to others without written authorization from Roche except to the extent necessary to obtain informed consent from persons to whom the drug may be administered.

DATES AMENDED:	Version 1:	5 August 2014
	Version 2:	29 October 2014
	Version 3:	2 February 2015
	Version 4:	30 November 2015
	Version 5:	11 April 2016
	Version 6:	24 November 2016
	Version 7:	8 August 2018
	Version 8:	19 December 2018

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

PROTOCOL ACCEPTANCE FORM

TITLE:	**A MULTI-CENTRE RANDOMISED CLINICAL TRIAL OF BIOMARKER-DRIVEN MAINTENANCE TREATMENT FOR FIRST-LINE METASTATIC COLORECTAL CANCER (MODUL)**
PROTOCOL NUMBER:	MO29112
VERSION NUMBER:	9
EUDRACT NUMBER:	2014-001017-61
IND NUMBER:	N/A
TEST PRODUCTS:	Atezolizumab (MPDL3280A, RO5541267) Bevacizumab (RO4876646) Cobimetinib (RO5514041) Pertuzumab (RO4368451) Trastuzumab (RO0452317) Vemurafenib (RO5185426) Cetuximab And combinations thereof
MEDICAL MONITOR:	Dr. [redacted]
SPONSOR:	F. Hoffmann-La Roche Ltd.

I agree to conduct the study in accordance with the current protocol.

_____

Principal Investigator's Name (print)

_____ _____

Principal Investigator's Signature Date

Please retain the signed original of this form for your study files. Please return a copy of this form as instructed by your local Roche affiliate.

PROTOCOL SYNOPSIS

TITLE:	**A MULTI-CENTRE RANDOMISED CLINICAL TRIAL OF BIOMARKER-DRIVEN MAINTENANCE TREATMENT FOR FIRST-LINE METASTATIC COLORECTAL CANCER (MODUL)**
PROTOCOL NUMBER:	MO29112
VERSION NUMBER:	9
EUDRACT NUMBER:	2014-001017-61
IND NUMBER:	N/A
TEST PRODUCT:	Atezolizumab (MPDL3280A, RO5541267) Bevacizumab (RO4876646) Cobimetinib (RO5514041) Pertuzumab (RO4368451) Trastuzumab (RO0452317) Vemurafenib (RO5185426) Cetuximab And combinations thereof
PHASE:	2
INDICATION:	Metastatic colorectal cancer
SPONSOR:	F. Hoffmann-La Roche Ltd

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

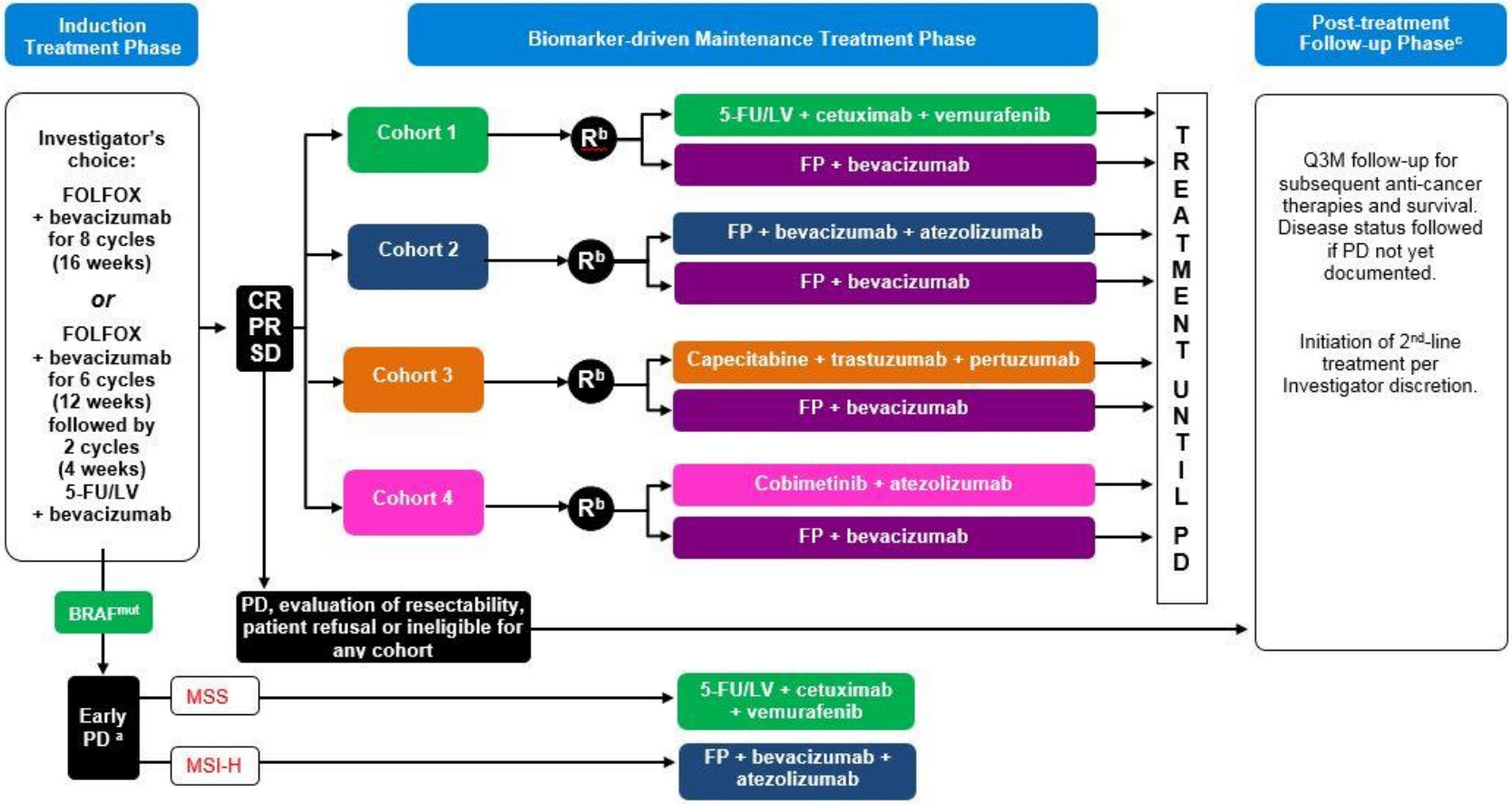
$BRAF^{mut}$ patients experiencing early disease progression during induction treatment will have the option of proceeding immediately to receive second-line treatment with 5-FU/LV, cetuximab and

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/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. Subsequent patients in this cohort will receive 1,600 – 2,400 mg/m^2 5-FU administered via 46-hour IV infusion (IV bolus is not permitted), 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 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/m^2. The iDMC will continue to monitor initial patients in this regimen treated with 5-FU doses ≥ 1,600 mg/m^2 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/m^2 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/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.

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.

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
5-FU	5-fluorouracil
AE	adverse event
AKT	v-akt murine thymoma viral oncogene homolog
ALT	alanine aminotransferase
ALP	alkaline phosphatase
ANC	absolute neutrophil count
aPTT	activated partial thromboplastin time
AST	aspartate transaminase
AUC	area under the curve
b.i.d.	twice daily
BMI	body mass index
BRAF	v-raf murine sarcoma viral oncogene homolog B1
$BRAF^{mut}$	BRAF mutation positive
$BRAF^{V600}$	BRAF mutation at codon 600
$BRAF^{wt}$	wild-type BRAF (mutation negative)
BWFI	bacteriostatic water for injection
CA19-9	carbohydrate antigen 19-9
CAPIRI	capecitabine with irinotecan
CAPOX	capecitabine with oxaliplatin
CAPOX-B	capecitabine with oxaliplatin and bevacizumab
CHF	congestive heart failure
CNS	central nervous system
CPK	creatine phosphokinase
cSCC	cutaneous squamous cell carcinoma
CR	complete response
CRC	colorectal cancer
CRO	contract research organization
CT	computed tomography
CTCAE v4.0	Common Terminology Criteria for Adverse Events version 4.0
DCR	disease control rate
DNA	deoxyribonucleic acid
DOR	duration of response
DPD	dihydropyrimidine dehydrogenase
EC	Ethics Committee
ECG	electrocardiogram
ECHO	echocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic Case Report Form
EDC	electronic data capture
EDTA	ethylenediaminetetraacetic acid
EGFR	epidermal growth factor receptor

Abbreviation	Definition
EMA	European Medicines Agency
EU	European Union
FDA	Food and Drug Administration
FFPET	formalin-fixed paraffin-embedded tissue
FOLFIRI	5-fluorouracil, leucovorin and irinotecan
FOLFOX	5-fluorouracil, leucovorin and oxaliplatin
GI	gastrointestinal
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HER2	human epidermal growth factor receptor 2
HER2+	human epidermal growth factor receptor 2 positive
hERG	human Ether-à-go-go Related Gene
HIV	human immunodeficiency virus
HLH	hemophagocytic lymphohistiocytosis
HPV	human papillomavirus
HR	hazard ratio
ICH	International Conference on Harmonisation
iDMC	independent Data Monitoring Committee
IHC	immunohistochemistry
IMP	investigational medicinal product
IND	Investigational New Drug (application)
INR	international normalised ratio
IRB	Institutional Review Board
ITT	Intent-to-Treat
IV	intravenous(ly)
IxRS	interactive voice or web-based response system
KA	keratoacanthoma
KRAS	V-Ki-ras2 Kirsten rat sarcoma viral oncogene homolog
LDH	lactate dehydrogenase
LFT	liver function test(s)
LPLV	last patient, last visit
LV	leucovorin calcium
LVEF	left ventricular ejection fraction
LVSD	left ventricular systolic dysfunction
mRECIST	modified Response Evaluation Criteria in Solid Tumors
mCRC	metastatic colorectal cancer
MAb	monoclonal antibody
MAPK	mitogen-activated protein kinase
MAS	macrophage activation syndrome
MRI	magnetic resonance imaging
MSI	microsatellite instability
MSI-H	high microsatellite instability

Abbreviation	Definition
MSS	microsatellite stable
MUGA	multiple-gated acquisition
NCI	National Cancer Institute
NGS	next generation sequencing
NRAS	neuroblastoma RAS viral oncogene homolog
NSCLC	non-small cell lung cancer
ORR	overall response rate
OS	overall survival
PD	progressive disease
PD-L1	programmed death-ligand 1
PFS	progression-free survival
PR	partial response
PRES	posterior reversible encephalopathy syndrome
PTEN	phosphatase and tensin homolog
QTc	corrected QT
QTcF	Fridericia-corrected QT
RCR	Roche Clinical Repository
RECIST 1.1	Response Evaluation Criteria in Solid Tumors version 1.1
RNA	ribonucleic acid
RPLS	reversible posterior leukoencephalopathy syndrome
SAE	serious adverse event
SAP	statistical analysis plan
SC	Steering Committee
SCC	squamous cell carcinoma
SD	stable disease
SIA	systemic immune activation
SmPC	summary of product characteristics
SPF	sun protection factor
T3	triiodothyronine
T4	thyroxine
TSH	thyroid-stimulating hormone
TTR	time to response
ULN	upper limit of normal
VEGF	vascular endothelial growth factor
VEGFR	vascular endothelial growth factor receptor
WBC	white blood cell
XELOX	capecitabine (Xeloda) and oxaliplatin

1. BACKGROUND

1.1 BACKGROUND ON METASTATIC COLORECTAL CANCER

1.1.1 Epidemiology

Colorectal cancer (CRC) is the second most common cancer in women and the third most common in men worldwide (Chawla et al. 2013). It is also the fourth leading cause of cancer deaths worldwide, with an estimated 1.36 million cases and 694,000 deaths in the year 2012 (Ferlay et al. 2013). Unfortunately, these numbers are expected to rise with the worldwide incidence reaching 2.44 million by the year 2035. In more developed regions of the world (Europe, North America, Australia, New Zealand and Japan), CRC is the third leading cause of cancer deaths after lung and prostate cancer. In the European Union (EU), CRC is the third leading newly diagnosed cancer after lung cancer and prostate cancer in males, and the second after breast cancer in females, and is the second leading cause of overall cancer deaths (Karim-Kos 2008). The estimated 2012 EU incidence of CRC is 345,000 cases with 152,000 deaths for 2012 (Ferlay et al. 2013).

High CRC mortality rates are fuelled by the large proportion of patients with metastatic disease at initial diagnosis (approximately 25%) and the fact that almost 50% of patients will develop metastatic disease (Van Cutsem et al. 2010). Treatment and support of CRC patients is significant and this, coupled with high disease morbidity and mortality that are expected to increase, has resulted in a substantial socio-economic burden and public health problem that will worsen (Karsa et al. 2010).

1.1.2 Etiology and Risk Factors

Colorectal cancer represents a paradigm for cancer genetics, as almost all the major-gene influences on CRC have been identified. There are several syndromes with Mendelian dominant inheritance in which there is a primary predisposition for benign or malignant tumours of the large bowel, including: familial adenomatous polyposis; hereditary non-polyposis colon cancer (caused by inheritance of defective deoxyribonucleic acid (DNA) mismatch repair genes MLH1, MSH2, PMS2 and MSH6); Peutz–Jeghers syndrome (caused by germline mutations of the LKB1/STK11 gene); juvenile polyposis (with the underlying mutation of SMAD4 or ALK3), and the MYH-associated polyposis (MAP) syndrome. These single gene defects account for up to 2–6% of CRC cases. The great majority of CRCs do not have a recognizable inherited cause, but an extensive analysis of twins has suggested that 35% of CRCs arise through inherited factors. Inherited predisposition to CRC in humans is more likely to be the result of low-penetrance alleles at several or many genetic loci (Kemp et al. 2004). Recent genome-wide association studies have identified single-nucleotide polymorphisms localizing to multiple chromosomal regions that influence CRC risk. While the risk of CRC associated with each of the variants is individually modest, taken together, they may significantly contribute to disease burden by virtue of their high frequencies in the population (Houlston et al. 2012). Germline genetic testing based on a blood sample is recommended to detect potential mutations in those patients whose tumour sample demonstrates altered molecular screening (Schmoll et al. 2012).

Other predisposing factors and common risk factors associated with CRC development include long-standing inflammation and augmented inflammatory response, diet and lifestyle, altered intestinal microbiota and commensals, and chronic inflammatory bowel diseases (Savari et al. 2014).

1.1.3 Current Treatment of mCRC

The management of metastatic CRC (mCRC) remains a significant clinical challenge to oncologists worldwide. Even though appropriate screening programmes (implementation of faecal occult blood test and colonoscopy) and preventive strategies are in place in many countries, a significant number of patients are still diagnosed at late stages of the disease, resulting in high disease burden and mortality (Schmoll et al. 2012; Temraz et al. 2014). Although care for patients with CRC has improved greatly in the last 20 years, considerable variation still exists in cancer management and outcome between European countries, and large variation is also apparent between national guidelines and patterns of cancer care in Europe (van de Velde et al. 2014).

While surgery remains the mainstay of curative treatment (5-year survival rates of 20 – 45% reported after the surgical resection of R0 resectable colorectal liver metastases), the management of mCRC must be a multi-modal approach. Long-term survival, maintained quality of life, and even cure can be achieved in selected patients by a combination of optimal choice chemotherapy and surgery (Schmoll et al. 2012). The choice of first-line treatment for mCRC is influenced by the clinical presentation and patterns of tumour biology (e.g., metastases limited to liver and/or lung, or peritoneum; dynamics of progression; present or imminent symptoms; prognostic molecular or biochemical markers, like BRAF mutation), as well as patient-related factors (e.g. comorbidity and related potential to undergo secondary resection), and drug-related factors (availability of targeted drugs; predictive markers, e.g. RAS mutation) (Schmoll et al. 2012).

Pharmacological treatment options for mCRC have increased substantially in the past decade (Stein and Bokemeyer, 2014). While combinations of fluoropyrimidines with oxaliplatin or irinotecan (such as in 5-FU, leucovorin and oxaliplatin [FOLFOX] / capecitabine and oxaliplatin [XELOX] or 5-FU, leucovorin and irinotecan [FOLFIRI]) constitute the main treatment of choice in this patient population (Temraz et al. 2014), the addition of novel biological therapies targeting cancer-specific molecules to these cytotoxic agents have led to significantly improved outcomes and is the current standard treatment for mCRC (Tejpar et al. 2014b; Temraz et al. 2014). A broad variety of molecular targeting agents are currently available, such as anti-angiogenic agents (bevacizumab) and epidermal growth factor receptor (EGFR) antibodies (cetuximab, panitumumab) for first-line treatment of mCRC (Stein and Bokemeyer, 2014). A recent systematic review of randomised controlled trials concluded that the oral fluoropyrimidine formulation, capecitabine had similar outcomes and better safety than 5-fluorouracil (5-FU) with oxaliplatin but not irinotecan; first-line oxaliplatin and irinotecan appear equivalent; and that antiangiogenics (bevacizumab, ziv-aflibercept, ramucirumab), and EGFR-targeted monoclonal antibodies (MAb) (cetuximab and panitumumab) further improved the efficacy of fluoropyrimidine-based regimens in the treatment of mCRC (Bekaii-Saab et al. 2014). However, while metastatic CRC patients have

many treatment options, the optimal use and sequence of targeted agents remain to be determined (Temraz et al. 2014).

1.1.3.1 *The Role of Maintenance Therapy in mCRC Treatment*

Though effective, the toxicity of first-line chemotherapy regimens renders treatments untenable for prolonged periods without regimen modifications or complete breaks. Oxaliplatin in particular causes debilitating neuropathy which can become irreversible, in addition to unacceptable nausea, diarrhoea and asthenia. The results of several studies conducted to assess the impact of intermittent chemotherapy regimens with or without maintenance treatment with fewer agents as compared to continuous therapy have been largely equivocal often due to poor protocol adherence and drug toxicities (Seymour 2012; Strickler et al. 2012a). Despite the lack of definitive evidence from these trials, current treatment guidelines recommend treatment breaks from combination therapy with continued maintenance therapy composed of fewer cytotoxic agents once cumulative toxicity occurs (VanCutsem et al. 2010; National Comprehensive Cancer Network 2014).

More recently, results of the Phase 3 CAIRO3 study comparing maintenance treatment with capecitabine and bevacizumab versus observation alone following induction with capecitabine and oxaliplatin plus bevacizumab (CAPOX-B) were presented (Koopman et al. 2014). A significant increase in median PFS was observed in the treatment arm (8.5 vs. 4.1 months; stratified HR 0.43, 95% CI [0.36-0.52]; $p < 0.0001$). When patients progressed following their initial induction in this study, they were treated again with CAPOX-B. PFS was again significantly better in patients who had received maintenance treatment prior to their first progression (13.9 vs. 11.1 months; stratified HR 0.68, 95% CI [0.57-0.82]; $p < 0.0001$). A significant difference in OS was not detected in the overall study group but a planned subgroup analyses indicated that patients with synchronous disease who underwent resection of the primary tumour and patients who had a CR or PR to induction treatment experienced a significant survival benefit.

Recent interim results of an additional study (AIO KRK 0207) evaluating the non-inferiority of no therapy or bevacizumab alone as compared to bevacizumab plus fluoropyrimidine as maintenance treatment following fluoropyrimidine/oxaliplatin/bevacizumab induction indicate that active maintenance treatment (either bevacizumab plus fluoropyrimidine or bevacizumab alone) show prolonged first-line progression free survival (Arnold et al. 2014). Completion of data collection for the primary analysis of this study is estimated to occur in 2015.

1.2 BACKGROUND ON BIOMARKER-DRIVEN THERAPY

1.2.1 Biomarkers

Biomarkers are characteristics that indicate a normal or pathogenic process or a response to a specific therapeutic intervention (Alymani et al. 2010). Cancer biomarkers identified to date have a variable range of application for screening, determining diagnosis and prognosis, assessing the response to therapy and monitoring for recurrence. Prognostic biomarkers provide information on the natural course of the patient's disease independent of treatment, whereas predictive biomarkers provide information on the likelihood of response to a

particular treatment (Alymani et al. 2010). Predictive markers for efficacy are highly relevant, in order to avoid unnecessary treatment, toxicity or even detrimental effects, and expenses. However, adequate evidence only exists for RAS mutations excluding patients from treatment with EGFR-antibodies. There is a clear need for evidence-based recommendations regarding predictive molecular markers relevant to decisions regarding first-line treatment in mCRC. The potential use of the BRAF mutation in the treatment decision-making process also needs further validation (Schmoll et al. 2012).

1.2.2 Biomarker-driven Therapy

As the treatment landscape for mCRC is becoming more complex, the need for individualised or personalised therapy based on predictive factors is gaining importance. Personalised medicine aims to tailor treatment according to the characteristics of the individual patient to increase response rates and survival, and at the same time, reduce toxicity (Diamandis et al. 2010). Prognostic and predictive markers have been identified that appear to be directly related to sensitivity to targeted therapies, such as those against EGFR. However, the sensitivities of individual tumours toward different biological agents appear to be more complex, and therefore a more complete molecular signature of the tumour must be taken into account when making individual treatment choices (Tejpar et al. 2014b). Recent advances, such as extended RAS testing is a further step toward a patient-tailored selection of the most beneficial treatment approach (Stein and Bokemeyer, 2014).

RAS gene mutations in mCRC has been identified as a predictor of response to EGFR MAb therapy and to oxaliplatin-based therapy (Lievre et al. 2006; Basso et al. 2013; Lin et al. 2014). In several randomised clinical trials including the CRYSTAL, OPUS and PRIME studies (Van Cutsem et al. 2009; Bokemeyer et al. 2009; Douillard et al. 2010) evaluating first-line chemotherapy plus EGFR MAbs in the treatment of mCRC, patients with KRAS mutations had an approximately 2-month shorter PFS compared to $KRAS^{wt}$ patients. Based on the results of these randomised clinical studies, EGFR MAb treatment is not recommended in patients with $KRAS^{mut}$ mCRC (Roth et al. 2013). More recently, re-analyses of samples deemed KRAS wild-type based on exon 2 testing in the OPUS (Tejpar et al. 2014a) and PRIME (Douillard et al. 2013) studies indicated that other RAS mutations (i.e. in exons 3 or 4 of KRAS and/or exons 2, 3 or 4 of NRAS) are also associated with lack of benefit from EGFR-targeted therapy. These findings have led to the revision of European labelling indications for both cetuximab and panitumumab to patients with RAS^{wt} tumours (Erbitux® Summary of Product Characteristics [SmPC] 2014; Vectibix® SmPC 2014).

BRAF mutation has also been investigated as a biomarker, in particular as a prognostic indicator in patients with mCRC undergoing anti-EGFR MAb treatment, but current results are still inconclusive. A recently published meta-analysis of 21 clinical trials including 5,229 patients found that BRAF mutation is a predictive biomarker for poor prognosis in mCRC patients undergoing anti-EGFR MAb therapy, especially in $KRAS^{wt}$ patients (Yuan et al. 2013).

Unlike the anti-EGFR MAbs, there is a paucity of biomarkers for bevacizumab as predictors of outcome in mCRC patients. A retrospective analysis of the AVF2107 trial investigating the influence of the KRAS mutation on the efficacy of bevacizumab in combination with chemotherapy showed no differences in terms of treatment efficacy (Hurwitz et al. 2009).

Similarly, in the AIO KRK-0604 trial, patients with KRAS-mutated tumours showed comparable efficacy when treated with bevacizumab plus capecitabine and oxaliplatin (CAPOX) or bevacizumab plus capecitabine and irinotecan (CAPIRI), but had a trend towards lower overall response rates and shorter survival (Reinacher-Schick et al. 2010).

A recent study investigating the predictive value of the presence of KRAS and BRAF mutations on PFS and OS in 172 patients with mCRC treated with the combination of FOLFIRI and bevacizumab did not confirm the predictive value of KRAS and BRAF mutations as potential biomarkers for bevacizumab therapy in mCRC (Selcukbiricik et al. 2013).

There is clearly a need to further identify and evaluate biomarkers related to treatment response in mCRC. Typically, potential biomarkers are identified in studies evaluating response in patients that have already undergone treatment or in studies of populations enriched for a biomarker that has already been clinically validated. There are many new therapies reaching clinical testing that have been developed based on a putative biomarker that requires clinical validation. Study designs that incorporate prospective evaluation of new therapies with their corresponding biomarkers in confirmatory (Phase 2/3) trial settings are important to the integration and application of these new agents in the most effective setting as quickly as possible. New trial designs, such as this proposed MODUL study and the FOCUS4 study already underway (Kaplan et al. 2013), employ multiple study arms, biomarker based- stratification and randomization, and placebo control to achieve these goals.

1.2.3 Clinical Experience with Bevacizumab as First-line Treatment of mCRC

Bevacizumab (Avastin®) is a vascular endothelial growth factor (VEGF)-specific angiogenesis inhibitor approved for use in many countries for the treatment of mCRC, with intravenous (IV) 5-FU–based chemotherapy for first- or second-line treatment, and with fluoropyrimidine-irinotecan- or fluoropyrimidine-oxaliplatin-based chemotherapy for second-line treatment in patients who have progressed on a first-line bevacizumab-containing regimen (Avastin® Prescribing Information, December 2013).

Bevacizumab has been shown to improve clinical outcomes when combined with any of the fluoropyrimidine and oxaliplatin or irinotecan combinations (FOLFOX/XELOX, FOLFIRI) as well as with single-agent 5-FU or capecitabine (Strickler et al. 2012b). The results of large Phase 3 clinical trials of bevacizumab combined with a fluoropyrimidine and oxaliplatin or irinotecan as first-line treatment for mCRC are provided in Table 2. Studies of bevacizumab combined with a fluoropyrimidine alone include a randomised Phase 2 study of 5-FU with or without bevacizumab as first-line treatment for mCRC patients deemed inappropriate for irinotecan-based therapy (Kabbinavar et al. 2005b). In this study median PFS was significantly improved with the addition of bevacizumab (9.2 months versus 5.5 months; HR 0.50; p = 0.0002). Though the difference in OS between treatment groups was not statistically significant, a follow-up pooled analysis of three randomised studies comparing 5-FU with and without bevacizumab found a longer median OS time for patients receiving 5-FU with bevacizumab than for those receiving 5-FU alone (p = 0.008) (Kabbinavar et al. 2005a). Similarly, significantly improved PFS has been shown with the addition of

bevacizumab to capecitabine in a randomised Phase 3 trial (the MAX study) conducted in mCRC patients unsuitable for combination chemotherapy.

Table 2: Efficacy Outcomes from Phase 3 Clinical Trials of Bevacizumab plus Chemotherapy Regimens in First-Line Treatment of mCRC

Study Reference	Treatment	ORR [BEV arms]	PFS (months)	OS (months)
AVF2107g Study Hurwitz et al. 2004	IFL+BEV vs IFL	44.8%	10.6 vs 6.2 HR 0.54; p<0.001	20.3 vs 15.6 HR 0.66; p<0.01
BICC-C Study Fuchs et al. 2007 Fuchs et al. 2008	FOLFIRI+BEV vs mIFL+BEV	57.9% 53.3%	11.2 vs 8.3	28.0 vs 19.2
ARTIST Study Guan et al. 2011	mIFL+BEV vs mIFL	35% 17%, p=0.013	8.3 vs 4.2 p<0.001	18.7 vs 13.4 p=0.014
NO16966 Study Saltz et al. 2008	FOLFOX4/CAPOX+ BEV vs FOLFOX4/CAPOX	47%	9.4 vs 8.0 HR 0.83; p=0.002	21.3 vs 19.9 HR 0.89; p=0.077
MAX Study Tebbutt et al. 2010	CAP+BEV vs CAP	56%	8.5 vs 5.7 HR 0.63, p< 0.001	-
CAIRO-2 Study Tol et al. 2009	CAPOX-B vs CAPOX-B+CTX	50.0% 52.7%	10.7 vs 9.4 p=0.01	20.3 19.4
CAIRO3 Study Maintenance treatment Koopman et al. 2014	CAPOX-B Induction followed by CAP + BEV vs Observation only	NA	8.5 vs 4.1 (not including 3-4 mth induction treatment period) p< 0.0001	NS
PACCE Study Hecht et al. 2009	Oxaliplatin-based+BEV Irinotecan-based+BEV	48% 40%	11.4 11.7	24.5 20.5

BEV: bevacizumab, CAP: capecitabine; CAPOX: oxaliplatin and capecitabine; CAPOX-B: oxaliplatin, capecitabine and bevacizumab; CTX: cetuximab; FOLFIRI: fluorouracil, leucovorin, and irinotecan; FOLFOX4: oxaliplatin, fluorouracil, and leucovorin; IFL: 5-FU, leucovorin and irinotecan; IRI: irinotecan; ORR: overall response rate; OS: overall survival; OX: oxaliplatin; PFS: progression-free survival

The most serious AEs identified in clinical trials with bevacizumab were GI perforations, haemorrhage (including tumour associated haemorrhage and pulmonary haemorrhage / haemoptysis, which is more common in non-small cell lung cancer patients [NSCLC]), and arterial thromboembolic events. Other AEs observed in patients treated with bevacizumab were fistulae, wound healing complications, hypertension, venous thromboembolism, and proteinuria. In addition, congestive heart failure (CHF) was observed rarely and predominantly in patients with metastatic breast cancer who had received prior anthracycline-based therapy and prior chest wall radiation. Analyses of the clinical safety data suggest that the occurrence of hypertension and proteinuria with bevacizumab therapy are likely to be dose dependent. The most frequently observed AEs across clinical trials in patients receiving bevacizumab were hypertension, fatigue or asthenia, diarrhoea and abdominal pain. Increased rates of severe neutropenia, febrile neutropenia, or infection with

severe neutropenia (including some fatalities) have been observed in patients treated with some myelotoxic chemotherapy regimens plus bevacizumab in comparison to chemotherapy alone.

There have been rare reports of bevacizumab treated patients developing signs and symptoms that are consistent with posterior reversible encephalopathy syndrome (PRES). Very rare cases of hypertensive encephalopathy have also been reported, some of which were fatal.

Additional information regarding the safety profile of bevacizumab and details of preclinical and clinical studies with bevacizumab are provided in the current Bevacizumab Investigator's Brochure or local labelling where applicable.

1.2.4 Clinical Experience with Cetuximab in CRC

Cetuximab (Erbitux®) is an EGFR antagonist indicated for treatment of RAS^{wt}, EGFR-expressing, mCRC: (i) in combination with FOLFIRI for first-line treatment; (ii) in combination with irinotecan in patients who are refractory to irinotecan-based chemotherapy; and (iii) as a single agent in patients who have failed oxaliplatin- and irinotecan-based chemotherapy or who are intolerant to irinotecan (Erbitux SmPC 2014).

Cetuximab in combination with either FOLFIRI (the CRYSTAL study, Van Cutsem et al. 2009; Van Cutsem et al. 2011) or FOLFOX (the OPUS Study, Bokemeyer et al. 2011) increased response rates particularly in liver-limited disease, progression-free survival (PFS) and overall survival (OS). Biomarker analyses from these studies have shown cetuximab activity is limited to patients with RAS^{wt} tumours and that BRAF mutation does not appear to be a predictive biomarker in this setting, but is a marker of poor prognosis (Bokemeyer et al. 2012, Tejpar et al. 2014a).

The main AEs associated with cetuximab are skin reactions occurring in more than 80% of patients treated, hypomagnesaemia occurring in more than 10% of patients treated and infusion-related reactions occurring with mild to moderate symptoms in more than 10% of patients treated and with severe symptoms in more than 1% of patients.

In studies where cetuximab was used in combination with fluoropyrimidines to treat NSCLC, head and neck cancer and CRC, an increased frequency of cardiac ischaemia including myocardial infarction and congestive heart failure as well as the frequency of hand-foot syndrome (palmar-plantar erythrodysaesthesia) were increased compared to with fluoropyrimidines alone.

Cetuximab may also increase the frequency of severe diarrhoea when used in combination with capecitabine and oxaliplatin.

Immunogenicity including the development of human anti-chimeric antibodies (HACAs) may occur with any monoclonal chimeric antibody. Limited data regarding the development of HACAs with cetuximab treatment are available to date. Overall, measurable HACA titres were noted in 3.4% of the patients studied, with incidences ranging from 0% to 9.6% in the studies of mCRC and head and neck cancer. No conclusive data on the neutralising effect of HACAs on cetuximab is available to date. The appearance of HACA did not correlate with the occurrence of hypersensitivity reactions or any other adverse effects of cetuximab.

For additional details regarding preclinical and clinical studies with cetuximab and for further information on the risks associated with cetuximab, please refer to the current Erbitux SmPC.

1.2.5 Clinical Experience with Vemurafenib

The protein kinase BRAF is a key component of the RAS-RAF signalling pathway, which plays an important role in regulating cell proliferation, differentiation, and survival. Mutations in BRAF at codon 600 promote catalytic activity and are associated with 8% of all human solid tumours, including 8 – 10% of CRC (Yang et al. 2012). These BRAF mutations are usually mutually exclusive with oncogenic KRAS mutations, but imply a similar treatment-refractory prognosis (Van Cutsem et al. 2011, Connolly et al. 2014).

Vemurafenib (RG7204; PLX4032; RO5185426), is a first-in-class, specific small molecule inhibitor of BRAF (V600E). Vemurafenib is currently authorised for the treatment of $BRAF^{mut}$ metastatic melanoma in more than 40 countries worldwide. As a single agent, vemurafenib shows dose-dependent inhibition of ERK and MEK phosphorylation, thereby arresting cell proliferation in BRAF (V600)-expressing cell lines and inhibiting tumour growth in BRAF (V600E) bearing xenograft models. Vemurafenib has shown limited single-agent clinical activity in BRAF (V600E)-mutant metastatic CRC cell lines. However, the addition of vemurafenib to capecitabine and/or bevacizumab, cetuximab and/or irinotecan, or erlotinib resulted in increased anti-tumour activity and improved survival in xenograft models, indicating that vemurafenib in combination with standard-of-care or novel targeted therapies may lead to enhanced and sustained clinical anti-tumour efficacy in CRCs harbouring the BRAF (V600E) mutation (Yang et al. 2012). In clinical studies, vemurafenib has been shown to induce dramatic responses in melanomas containing missense V600E BRAF mutations (Chapman et al. 2011).

Recent laboratory studies have confirmed that *de novo* resistance to BRAF inhibitors in BRAF (V600E)-mutated CRC is caused by EGFR signalling (Corcoran et al. 2012; Prahallad et al. 2012), suggesting that dual blockade of the BRAF and EGFR pathways might be therapeutically useful (Yang et al. 2012). Lastly, a previous randomised trial of cetuximab combined with the non-specific RAF inhibitor sorafenib indicated a doubling of the response rate in patients with mCRC (Galal et al. 2011). Taken together, it is hypothesised that patients with mCRC may benefit from combination non-cytotoxic drug therapy simultaneously targeting the EGFR and BRAF signalling pathways.

In addition to post-market experience, multiple clinical trials with vemurafenib, either alone or in combination with other agents, have been completed or are underway. The majority of these studies have been conducted in melanoma patients with BRAF mutations, where results have shown consistent efficacy and significant benefit in terms of OS, PFS and overall survival compared to chemotherapy. Preliminary results from Phase 1 and 2 completed studies of vemurafenib BRAF mutation-positive papillary thyroid cancer indicate disease response and favourable PFS. Clinical efficacy data in mCRC are currently limited to results of Phase 1 dose escalation study (Study PLX06-02) extension cohorts wherein 1 out of 20 evaluable patients achieved a partial response and 7 patients achieved stable disease.

In clinical trials in melanoma, vemurafenib has been associated with arthralgia, fatigue, rash, photosensitivity reaction, nausea, alopecia and pruritus. AEs have been predominantly mild in severity and transient, even with continuous dosing (over 15 months of treatment in 1 patient). At the recommended Phase 2 and Phase 3 dose of 960 mg b.i.d., AEs have been consistent with the safety profile observed in the Phase 1 setting. Treatment-related Grade 3 AEs and dose-limiting toxicities have been successfully managed by a temporary discontinuation of study drug and/or a reduction in dose.

In mCRC in particular, vemurafenib's safety profile has been characterised in 21 patients treated in the extension cohorts of a Phase 1 dose escalation study (Study PLX06-02; see Vemurafenib Investigator's Brochure 2014). AEs are similar to those observed in patients with metastatic melanoma. All patients experienced at least one AE, the most common (reported in ≥ 30% of patients) of which were fatigue (57.1%), hyperglycemia (42.9%), arthralgia (38.1%), diarrhoea (38.1%), hyperbilirubinemia (33.3%), nausea (33.3%), photosensitivity reaction (33.3%), rash (33.3%), and vomiting (33.3%). Grade 3 or greater study-drug-related AEs were reported in 61.9% of patients, the most common of which was cSCC (23.8%). Eleven (52.4%) patients had their study treatment interrupted and 4 (19.0%) had at least one dose reduction. AEs that led to dose interruption and/or modification for the CRC patients were similar to those reported for melanoma patients in the same study. No mCRC patients in this study experienced an AE that led to vemurafenib treatment discontinuation. All deaths reported during study treatment or within 28 days of the last study drug dose were attributed to disease progression. Seven patients (33.3%) experienced SAEs, the most common of these was cSCC.

Due to its mechanism of action, vemurafenib may cause progression of cancers associated with RAS mutations and should be used with caution in patients with prior or concurrent cancers associated with RAS mutation. Notably, (K)RAS mutations are usually mutually exclusive to BRAF mutations (Van Cutsem et al. 2011, Connolly et al. 2014). One case of progression of NRAS-mutated chronic myelomonocytic leukemia occurred in a male patient with metastatic melanoma treated with vemurafenib for less than two weeks (Callahan et al. 2012) and one case of progression of pancreatic adenocarcinoma in a patient with known (K)RAS mutation has also been reported (Vemurafenib Investigator's Brochure 2014). More details of these events are provided in the Investigator's Brochure.

Other risks identified as important adverse drug reactions (ADRs), based on both post-market use and clinical trial experience, include: cutaneous squamous cell carcinoma (cSCC; most of which are keratoacanthoma [KA] sub-type, or with some features of KA [incompletely expressed or with some features unusual in KA]), liver injury, photosensitivity, QTc prolongation, hypersensitivity and severe cutaneous reactions (including rare cases of Stevens-Johnson syndrome and toxic epidermal necrolysis), uveitis, VIIth nerve paralysis, new primary melanoma, radiation recall and radiation sensitivity. Drug reaction with eosinophilia and systemic symptoms (DRESS), neutropenia, panniculitis, and pancreatitis have also been reported with vemurafenib in the post-marketing setting.

Vemurafenib may also be associated with the development of non-cutaneous squamous cell carcinoma (SCC), bone marrow toxicity, second primary malignancies, GI polyps and retinal

vein occlusion. The association between these events and vemurafenib have not yet been fully characterised.

Complete details of preclinical and clinical studies, all safety events and ADRs observed in vemurafenib clinical trials and post-market use are described in the current vemurafenib Investigator's Brochure.

1.2.6 Clinical Experience with Atezolizumab

Programmed death 1 (PD-1) protein, a T-cell co-inhibitory receptor, and one of its ligands, PD-L1, play a pivotal role in the ability of tumour cells to evade the host's immune system. Atezolizumab is a non-glycosylated human immunoglobulin G1 monoclonal antibody produced in Chinese hamster ovary cells. The antibody is specific for human PD-L1 and inhibits PD-L1 interactions with PD-1 and with B7-1 (also known as CD80) that are thought to otherwise inhibit T-cell activation (Butte et al. 2007, current Atezolizumab Investigator's Brochure). Atezolizumab has also been engineered via a single amino acid heavy chain substitution to eliminate Fc-effector function in order to minimise *in vivo* depletion of tumour specific T cells expressing high levels of PD-L1. The antibody exhibits minimal binding to Fc receptors and prevents Fc-effector function at expected concentrations in humans.

Approximately 4% of patients with Stage IV CRC have tumours with deficiencies in the DNA mismatch repair system. These deficiencies are predominantly nonfamilial (sporadic) and lead to an accumulation of tumour mutations (hyper-mutation) particularly in repetitive sequences (mono-, di-, of higher-order nucleotide repeats) and microsatellites (Cancer Genome Atlas Network 2012). A defining molecular feature of these tumours is high microsatellite instability (MSI-H). Insertions or deletions in microsatellites located in coding regions of the genome can lead to protein truncations or the expression of frameshift peptides, some of which are capable of eliciting T-cell responses (Bauer et al. 2013). The MSI-H phenotype is also associated with mutations in specific oncogenes and tumour suppressors including BRAF and MRE11A (Vilar and Gruber 2010). MSI-H tumours and other hyper-mutated tumours may therefore exhibit higher immunogenicity in comparison to microsatellite-stable (MSS) tumours. One possible correlate of higher immunogenicity MSI-H and other hyper-mutator phenotypes is the presence of high numbers of tumour-infiltrating lymphocytes (Greenson et al. 2003) and a potential role of PDL-1/PD-1 signalling in restraining a pre-existing anti-tumour immune response in the tumour microenvironment. Support for these hypotheses has been borne out in a more recent study showing that inhibition of the PD-1 pathway with pembrolizumab (an anti-PD-1 antibody) is of clinical benefit in MSI-H mCRC but not in MSS cohorts (Le et al. 2015).

Clinical data are available from multiple atezolizumab trials in patients with solid tumours (including CRC) and hematologic malignancies. Of these, one ongoing Phase 1a 0.03-20 mg/kg dose ranging study of atezolizumab monotherapy (Study PCD4989g) and one ongoing Phase 1b combination study (GP28328: atezolizumab with bevacizumab or with bevacizumab plus FOLFOX) included CRC patients. Additional Phase 1, 2, and 3 studies are ongoing or planned. Please refer to the current atezolizumab Investigator's Brochure for study descriptions.

Anti-tumour activity, including RECIST-based responses (i.e., RECIST 1.1 responses), have been observed in patients with different tumour types, including non-small cell lung cancer, renal cell carcinoma, melanoma, gastric cancer, and colorectal cancer, treated with atezolizumab in Phase I and 2 studies. Analyses of PD-L1 expression on baseline tumour tissue collected in these studies suggest that PD-L1 expression is likely to be associated with response to atezolizumab. The definition of PD-L1 positivity is still under investigation and appears to vary by tumour type.

In CRC in particular, 44 evaluable patients were enrolled in Study GP28328. The overall response rate (ORR) ranged from 7% (1/14 patients receiving atezolizumab plus bevacizumab) to 40% (12/30 receiving atezolizumab plus bevacizumab and FOLFOX) with a PFS ranging from 10+ to 61 weeks.

Across all patients receiving atezolizumab alone or in combination with chemotherapy in clinical trials, fatigue was the most frequently reported AE. The incidence of AEs in the treatment arms with combined use was consistent with the known safety profiles of the individual study drugs. Given the mechanism of action of atezolizumab, events associated with inflammation and/or immune-mediated AEs have been closely monitored during the atezolizumab clinical program. These include dermatologic, hepatic, endocrine, and respiratory events, as well as events of hepatitis/elevated liver function tests and influenza-like illness that are considered ADRs associated with atezolizumab. Additional expected ADRs associated with atezolizumab include GI disorders, hypersensitivity/infusion-related reactions, nervous system disorders, pneumonitis, general and metabolic disorders, and vascular disorders. Currently, no maximum tolerated dose (MTD), no dose-limiting toxicities and no clear dose-related trends in the incidence of AEs have been determined.

In Study GP28328 that included CRC patients receiving atezolizumab and bevacizumab with or without FOLFOX, a total of 141 of 144 patients (97.9%) reported at least one AE while on study drug. The majority of these were Grade 2 or 3 in severity. The five most commonly (≥ 10%) reported AEs included fatigue, nausea, diarrhea, decreased appetite, and pyrexia. Seven deaths were reported (6 due to disease progression, 1 due to study treatment related candidemia). Serious adverse events were reported in 55 patients with serious fatigue noted as related to atezolizumab in ≥ 2 patients. Adverse events assessed as related to study drug by the Investigator, and which led to discontinuation, included: neutropenia, pancytopenia, dehydration, proctitis and dermatitis. Immune-mediated AEs were observed in 72 patients and included peripheral neuropathy, rash, rash maculopapular, dermatitis, rash pruritic, rash vesicular, aspartate transaminase (AST) increase, alanine aminotransferase (ALT) increase, blood bilirubin increased, amylase increased, lipase increased, transaminase increased, hypothyroidism, and adrenal insufficiency.

Anti-therapeutic antibodies to atezolizumab have been observed in some patients in Study PCD4989g. A relationship between antibody response and pharmacokinetics, AEs or therapeutic activity has not yet been determined, however, monitoring and characterization of this effect is ongoing in all atezolizumab clinical studies.

Further details of preclinical and clinical studies with atezolizumab and all safety events are found in the current Atezolizumab Investigator’s Brochure.

1.2.7 Clinical Experience with Trastuzumab

Human epidermal growth factor receptor (HER) 2 (also known as c-erbB-2) is a member of the HER family of transmembrane receptor tyrosine kinases which includes EGFR, HER3 and HER4. Binding of ligands to the extracellular domain of EGFR, HER3, or HER4 induces receptor dimerization leading to C-termini tyrosine phosphorylations and initiation of a downstream cascade of transforming effects mediating cell death, division, motility and adhesion. The receptors couple as homo and heterodimers. Though HER2 has no known ligand, it is the preferred dimerization partner amongst the HER family members and is characterised by the most potent kinase catalytic activity capable of amplifying signaling through HER co-receptors (Yarden et al. 2001). HER2 overexpression occurs in a wide variety of tumour types and has been associated with poor outcomes in the absence of HER2-targeted therapies (Slamon et al. 1987, Slamon et al. 1989).

In preclinical studies, single and dual agent HER2 inhibition leads to tumour response in cetuximab resistant, HER2 amplified mCRC patient derived xenografts (Bertotti et al. 2011). HER2 overexpression has been detected by immunohistochemical (IHC) evaluation in a significant proportion of colorectal tumours (estimates occur between 3% and 10%) (Sartore-Bianchi et al. 2016, Seo et al. 2014, Valtorta et al. 2015).

Trastuzumab (Herceptin®) is a recombinant humanised anti-p185^{HER2} monoclonal antibody that binds specifically and with high affinity to the extracellular domain of HER2. Trastuzumab inhibits the proliferation of human tumour cells overexpressing HER2 both *in vitro* and *in vivo* and mediates antibody-dependent cell-mediated cytotoxicity (ADCC) in the presence of human effector cells. Trastuzumab administered either alone, or in combination with chemotherapy or an aromatase inhibitor, is indicated for treatment of HER2-overexpressing early and metastatic breast cancer. It is also indicated in combination with a fluoropyrimidine (5-FU or capecitabine) for first-line treatment of HER-positive (HER2+) advanced carcinoma of the stomach or gastro-esophageal junction. As of 24 March 2015, the total estimated cumulative exposure to Herceptin since the Development International Birth Date (DIBD; 27 May 1992) was approximately 1,935,406 patients worldwide.

Trastuzumab has been evaluated in advanced CRC in a phase II study in combination with irinotecan (Ramanathan et al. 2004). Though the study was closed prematurely due to low accrual attributed to the small proportion of HER2 overexpression in screening population (8% HER2+ by IHC), there was evidence of activity with responses observed in five of seven evaluable patients. More recently, trastuzumab has been combined with lapatinib, a dual tyrosine kinase inhibitor which interrupts the HER2 and epidermal growth factor receptor pathways, in a phase II study or HER2+, treatment refractory, mCRC (Sartore-Bianchi et al. 2016). In this study, trastuzumab was administered at 4 mg/kg IV loading dose followed by 2 mg/kg IV once per week and lapatinib was administered orally at a 1000 mg daily dose. At a median follow-up of 94 weeks, 30% had achieved a partial (7/27 patients) or complete (1/27 patients) and 44% had stable disease. Notably, exploratory analyses found that 6/7 responses occurred in patients that were IHC3+ for HER2 (versus IHC2+) and segregated significantly with high gene copy number. Grade 3 adverse events (fatigue, rash, increased bilirubin) were observed in 22% of patients. No grade 4 or 5 adverse events were reported and there were no treatment related serious adverse events.

Trastuzumab has been investigated in combination with the HER2 dimerization inhibitor, pertuzumab (Perjeta®), in breast cancer, advanced gastric cancer and other solid tumours and is approved in combination with pertuzumab and chemotherapy for the treatment of breast cancer. These studies and clinical experience with combined trastuzumab and pertuzumab are described in Section 1.2.8 below.

Complete details of preclinical and clinical studies conducted in the development of trastuzumab studies are provided in the current Trastuzumab Investigator's Brochure and Summary of Product Characteristics.

1.2.8 Clinical Experience with Pertuzumab

Pertuzumab (Perjeta®) is a recombinant, humanised monoclonal antibody specific for the subdomain 2 epitope of HER2's extracellular domain. Pertuzumab inhibits HER2 heterodimerization with other members of the HER family (EGFR, HER1, HER3 and HER4) thereby blocking ligand-activated downstream signalling. Pertuzumab is also capable of mediating ADCC in cell-based assays.

Pertuzumab and trastuzumab bind to distinct epitopes on the HER2 receptor without competing with each other, and have complementary mechanisms for disrupting HER2 signalling. Combined administration of these agents results in augmented anti-proliferative activity *in vitro* and *in vivo*. Pertuzumab clinical development has focussed on its complimentary activity with trastuzumab and is indicated for the treatment of HER+ breast cancer (metastatic and early) in combination with trastuzumab and chemotherapy.

Overall, data indicate that pertuzumab is well-tolerated as monotherapy and that it can be given in combination with trastuzumab and a range of other therapeutic agents with manageable additional toxicity. No unexpected toxicities have been encountered other than those that are known for agents that target the HER family of receptors. Serious or severe infusion-related symptoms have been rarely observed in patients receiving pertuzumab. A low level of cardiac toxicities, predominantly asymptomatic declines in left ventricular ejection fraction (LVEF), has been reported. In a pivotal Phase III trial WO20698/TOC4129g, the rates of symptomatic and asymptomatic left ventricular systolic dysfunction (LVSD) were not higher in patients receiving pertuzumab combined with trastuzumab and docetaxel than those receiving trastuzumab and docetaxel with placebo. However, patients who have received prior anthracyclines or radiotherapy to the chest area may be at higher risk of decreased LVEF (Pertuzumab Investigator's Brochure 2016).

Pertuzumab has been evaluated in combination with capecitabine in a phase I trial of 19 patients with advanced malignancies (Albanell et al. 2008). Pertuzumab was administered at a fixed dose of 1,050 mg IV on day 1 plus capecitabine at doses up to 1,250 mg/m^2 twice daily orally on days 1 to 14 of each 21-day treatment cycle. The combination was well tolerated at all dose levels and no dose-limiting toxicities were observed. Co-administration of pertuzumab and capecitabine was not found to affect the pharmacokinetics of either agent.

Combined pertuzumab and trastuzumab treatment has been included in a phase IIa study of advanced solid tumours that is being conducted to evaluate the safety and efficacy of targeted therapies in tumour types outside of their approved use (Hurwitz et al. 2016). The results of this study will provide data in patient populations that carry the biomarker target,

but have not been included in comprehensive clinical development, often due to their low incidence. Preliminary clinical activity observed in heavily pre-treated patients with HER2+ CRC included in this study (overall response in 38% or 5/13 patients). Due to these results, the study will expand enrolment of HER2+ CRC patients.

Combination treatment with pertuzumab, trastuzumab and capecitabine is under evaluation in an open-label phase III study comparing the regimen to trastuzumab and capecitabine alone in the treatment of metastatic breast cancer following progression after or during prior trastuzumab-based therapy (Urruticoechea et al. 2016). Patients in the control arm were treated with 8 mg/kg then 6 mg/kg trastuzumab every 3 weeks and 1250 mg/m^2 capecitabine twice daily for 2 weeks followed by a 1 week treatment break. Patients in the experimental arm received the same trastuzumab dosing with 1000 mg/m^2 capecitabine twice daily (same schedule as the control arm) and 840 mg then 420 mg pertuzumab every 3 weeks. In the primary study analysis, there was no significant difference in the primary study endpoint (PFS), however an 8-month improvement was observed in OS with the addition of pertuzumab (HR 0.68, 95% CI 0.51–0.90). No new safety signals were identified in the study. Adverse events were reported in 214/218 patients (98.2%) treated with trastuzumab and capecitabine alone and 222/228 (97.4%) in patients treated with all 3 agents. Diarrhoea, nausea, palmar-plantar erythrodysaesthesia, rash, nasopharyngitis, neutropenia and insomnia occurred in 10% or more of patients in either study arm. Of these, diarrhoea, rash, nasopharyngitis and insomnia occurred more often in the experimental arm. Among the 218 patient safety population treated with pertuzumab, trastuzumab and capecitabine, 5 cases (2.2%) of symptomatic LVSD (all of which resolved) and 15 cases (6.6%) of asymptomatic LVSD were observed. Serious adverse events occurring in 2% or more of this population were diarrhoea (3.5% or 8 patients) and left ventricular dysfunction (4.4% or 10 patients).

Complete details of preclinical and clinical studies conducted in the development of pertuzumab including evaluations of pertuzumab and trastuzumab combined are provided in the current pertuzumab Investigator's Brochure.

1.2.9 Clinical Experience with Cobimetinib

The mitogen-activated protein kinase (MAPK) signaling cascade plays a major role in mediating cell growth and differentiation in response to extracellular signals. The MAPK pathway transduces multiple proliferative and differentiating signals within tumour cells. RAS-GTP activates RAF kinase, which in turn activates the MEK/ERK cascade and subsequent cellular proliferation (Downward et al. 2003, Roberts and Der 2007). To regulate cellular proliferation, activated ERKs translocate to the nucleus and regulate gene expression through the activation of several key transcription factors. ERK promotes cell survival signalling and has been implicated in angiogenesis. Abnormal regulation of the MAPK pathway contributes to uncontrolled proliferation, invasion, metastasis, angiogenesis, and diminished apoptosis.

The RAF-MEK-ERK pathway also has been implicated in the immune resistance of tumours by affecting the tumour microenvironment. Inhibition of this pathway can lead to increases in CD8+ T-cell infiltration. Preclinical models suggest that MEK inhibition increases MHC I expression in tumour cells and enhances activation of dendritic cells. Furthermore, the RAF-

MEK-ERK pathway has been implicated in neutrophil recruitment and activation in the tumour microenvironment, which may lead to overall increased inflammation and decreases in CD8+ T cell infiltration (Kakavand et al. 2015, Liu et al. 2015, current Cobimetinib Investigator's Brochure). MEK inhibition results in increased intratumoural major histocompatibility complex class I expression and tumour antigen presentation, which acts to enhance tumour recognition by the immune system. Notably, MEK inhibition in tumours also increases PD-L1 expression of the checkpoint receptor PD-L1, which could counteract the increased presentation of tumour antigens. Lastly, the MAPK pathway is known to regulate a number of cytokines and chemokines, such as VEGF, interleukin-6, interleukin-8 and granulocyte−macrophage colony-stimulating factor, which may impact recruitment of vascular and other stromal cell types, including myeloid−derived suppressive cells that can inhibit the anti-tumour activity of T cells (Bancroft et al. 2001; Sano et al. 2001; Bancroft et al. 2002; Phan et al. 2013). The activity of MEK inhibition outside of tumour cells may further contribute to the modulation of the immune microenvironment that could enable a more permissive immune reaction against the tumour. These effects include inhibition of tumour vascular maturity and integrity, tumour infiltration, activity of myeloid−derived suppressive cells, neutrophils, increased activity of antigen-presentation cells, such as macrophage and dendritic cells, and recruitment and activation status of T-cell subsets, including CD8-positive cytolytic and CD4−positive helper cells (Giordano et al. 2015; Liu et al. 2015; Loi et al. 2016).

Cobimetinib is a novel and highly selective inhibitor of MEK, and consequently of the intracellular components of the MAPK pathway affecting tumour cell proliferation and survival. Cobimetinib is approved in the United States, European Union, Switzerland, and in multiple other countries across the world for use with vemurafenib for the treatment of unresectable or metastatic melanoma with BRAF mutation at codon 600 ($BRAF^{V600}$).

The combination of cobimetinib and atezolizumab is being developed for the treatment of locally advanced, or metastatic solid tumours for which standard therapies do not exist, have been proven ineffective or are intolerable. Preclinical murine studies have shown that combined treatment with cobimetinib and atezolizumab produces increased tumour growth inhibition compared to either agent alone. In addition, combined treatment results in disease response (partial or complete) in 30% of mice treated versus no responses in mice treated with either agent alone.

Clinical data are available from one ongoing Phase Ib, open-label, multicentre, dose escalation/dose expansion study (study GP28363) designed to assess the safety, tolerability, and pharmacokinetics of cobimetinib and atezolizumab administered to patients with metastatic or locally advanced (unresectable) solid tumours for which no recognised standard therapy exists, including those that carry a KRAS or $BRAF^{V600}$ mutation (Bendell et al. 2016). No dose limiting toxicities were observed in the dose escalation phase and 60 mg cobimetinib administered daily for 3 weeks followed by 1 week off (21/7 schedule) with 800 mg atezolizumab every 2 weeks was determined as the recommended Phase II dose.

In the dose expansion cohort for mCRC patients with KRAS−mutation (n = 23), 4 patients had a partial response, 5 had stable disease, and 14 had progressive disease as of 12 October 2015. Three responses were ongoing (range 4.0 – 7.7 months) at time of data cutoff. Three of the 4 patients responding had MSS tumours. Notably, biomarker evaluation

from a serial tumour biopsy cohort showed a 4-fold increase of CD8−positive T-cell infiltration in 75% of tumours as well as increases in PD-L1 and MHC-I expression.

Median follow-up for safety in CRC patients was 3.78 months (range 1.1 – 11.7 months). The most common treatment-related AEs included diarrhea (69.6%), fatigue (52.2%), dermatitis acneiform (43.5%), rash (34.8%), maculopapular rash (26.1%), pruritus (26.1%) and nausea (26.1%). The incidence of treatment-related grade 3/4 AEs was 34.8%. The only treatment-related grade 3/4 AE occurring in ≥ 2 patients was diarrhea (8.7%). No grade 5 AEs were reported.

A phase III, open-label, multicentre, 3-arm study (study GO30182) comparing cobimetinib (60 mg according to 21/7 schedule) plus atezolizumab (840 mg every 2 weeks) to atezolizumab monotherapy and to regorafenib in patients with previously treated unresectable locally advanced or mCRC is also underway. Data from this study are not yet available.

See the current, respective Investigator's Brochures for atezolizumab and cobimetinib for further details on the clinical studies conducted with each agent and descriptions of risks associated with each agent.

1.3 STUDY RATIONALE AND BENEFIT-RISK ASSESSMENT

Advances in the treatment of mCRC have led to an improvement in survival from 12 months with fluorouracil monotherapy to approximately 2.5 years with current combination regimens (Cunningham et al. 2010, Venook and Saltz, 2013). However, there are significant molecular differences between tumours and between tumour microenvironments that can affect both prognosis and response to treatment. Many new cancer drugs target specific molecular aberrations or cell-signalling pathways, but these drugs are only active in a subset of patients due to molecular differences between tumours. Personalised medicine has made some major advances in CRC, with RAS testing to guide treatment with the anti-EGFR monoclonal antibodies cetuximab and panitumumab now being part of routine clinical practice (Moorcraft et al. 2013). However, not all patients who are RAS^{wt} respond to anti-EGFR therapy and, despite extensive research into other biomarkers for anti-angiogenic drugs, chemotherapy and other targeted agents, these are not yet established in clinical practice, and a validated biomarker for anti-angiogenic therapy is still lacking. Therefore, there is a clear need for both molecular screening approaches to understand the disease better and to fully characterise tumours and identify patients who are most likely to benefit from targeted treatments, as well as for new biomarkers to assist with predicting response to both existing drugs as well as to drugs currently under investigation (Moorcraft et al. 2013).

The current study is a randomised, multi-centre, active-controlled, open-label, parallel-group clinical trial of biomarker-driven maintenance treatment for first-line mCRC. All patients will receive induction treatment with FOLFOX and bevacizumab, a treatment regimen that is considered standard in many countries and that has been shown to improve outcomes compared to FOLFOX alone (see Section 1.2.3; Strickler et al. 2012a). Induction treatment will be followed by maintenance treatment with chemotherapy combined with targeted therapy. Administration of maintenance treatment with fewer cytotoxic drugs until progression, as opposed to complete treatment breaks in the face of accumulating toxicity,

has become an accepted treatment approach (see Section 1.1.3.1). Only those patients who experience disease response or disease control during induction will proceed to further treatment in the Maintenance Treatment Phase of the study.

Patients will be assigned to a maintenance treatment cohort based on their primary tumour biomarker results. In all maintenance treatment cohorts, the control treatment arm consists of a treatment regimen that has been shown to be efficacious in mCRC with a well characterised safety profile (see Section 1.2.3).

The experimental regimens in each maintenance treatment cohort incorporate emerging therapies with or without chemotherapy background treatment.

In Cohort 1, targeted agents delivered in conjunction with 5-FU/LV are vemurafenib and cetuximab. These have each been shown to be beneficial anti-cancer agents and have complementary mechanisms of action expected to inhibit $BRAF^{mut}$ disease while blocking compensation via EGFR pathway signalling. As shown in previous *in vitro* and *in vivo* studies [Corcoran et al. 2012, Prahallad et al. 2012], combined RAF and EGFR inhibition blocked reactivation of mitogen-activated protein kinase (MAPK) signalling in $BRAF^{mut}$ CRC cells, markedly improving anti-tumour efficacy of the combination vs RAF inhibition alone. These preclinical findings support the evaluation of combined RAF and EGFR inhibition in patients with $BRAF^{mut}$ CRC and two recent case reports have demonstrated the potential effectiveness of this approach [Connolly et al. 2014, Al-Marrawi et al. 2013].

The safety profiles of cetuximab in mCRC and vemurafenib in metastatic melanoma are well established from both clinical trial and approved-market use (see Section 1.2.4 and Section 1.2.5). However, a safety review (safety run-in) is being conducted for the initial patients treated with the experimental combination of '5-FU/LV + cetuximab + vemurafenib' prior to continuing treatment in these patients and prior to exposing further patients to the regimen. Initial iDMC reviews (February 2016, April 2016) concluded that 5-FU dose could be increased up to the preplanned maximum of 2400 mg/m^2 with continued safety run-in monitoring of patients treated with 5-FU > 1600 mg/m^2. The iDMC also recommended that patients with an Eastern Cooperative Oncology Group (ECOG) PS of 2 and low body mass index (BMI) must be assessed by the Investigator as adequately fit to receive treatment with this experimental regimen. These recommendations have been incorporated into the protocol guidance to the Investigator and Cohort 1 eligibility criteria.

There are currently no international or national guidelines or recommendations regarding the management of $BRAF^{mut}$ patients, effective treatment options for $BRAF^{mut}$ patients are limited and this population is burdened with a poor prognostic outlook. For these reasons, this experimental regimen will also be offered to $BRAF^{mut}$ patients who progress during induction treatment even though these patients will not contribute to Cohort 1 efficacy analyses.

In Cohort 2, agents delivered in conjunction with a fluoropyrimidine are atezolizumab and bevacizumab. Preliminary data with atezolizumab indicate it produces disease response in a variety of solid tumours and is generally well tolerated with a manageable AE profile (see Section 1.2.6). The safety and anti-cancer activity of bevacizumab have been well described in this setting (see Section 1.2.3).

The rationale for combining anti-PD-L1 therapy and bevacizumab is based on the knowledge that anti-VEGF therapy has immunomodulatory properties, including the increased trafficking of T cells into tumours, and a reduction of suppressive cytokines and infiltrating T regulatory cells and myeloid-derived suppressor cells (Manning et al. 2007, Shrimali et al. 2010, Roland et al. 2009). Preclinical data indicate that combining anti-PD-L1 and anti-VEGF therapy increases tumour suppression compared with either agent given alone in both melanoma and CRC tumour models (Genentech, data on file). Furthermore, a recently presented phase 1b trial (GO28328) evaluated the combination of atezolizumab and bevacizumab ± FOLFOX in patients with locally advanced/metastatic solid tumours (Lieu et al. 2014). Responses were observed in a variety of tumour types, including CRC, and there was no evidence of an exacerbation of bevacizumab- or chemotherapy-associated side effects when adding atezolizumab.

In Cohort 3, trastuzumab and pertuzumab are delivered with capecitabine. Preclinical evidence for tumouricidal activity with dual agent HER2 inhibition in HER2+ colorectal tumours resistant to EGFR-directed therapy have led to clinical evaluations in treatment refractory disease (Sartore-Bianchi et al. 2016). Trastuzumab and pertuzumab combined with a fluoropyrimidine has resulted in improved OS in HER2+ breast cancer patients with reasonable safety and no new safety signals (Urruticoechea et al. 2016; see Section 1.2.7 and Section 1.2.8).

HER2+ overexpression occurs in relatively few CRC patients (see Section 1.2.7). This study provides an opportunity for clinical evaluation of a treatment approach with a known safety profile and potential efficacy that targets this small subset of patients.

In Cohort 4, patients will be treated with cobimetinib combined with atezolizumab. This novel combination is proposed due to the potentially synergistic effect of these agents on the tumour immune microenvironment (see Section 1.2.6 and Section 1.2.9).

To summarize, increased recruitment of immune effector or antigen presenting cells occurring in MSI-H CRCs may at least partially explain the preferential effect of PD-1 pathway inhibition in these tumour types (Llosa et al. 2015, Zhang et al. 2015, Smedt et al. 2015, Le et al. 2015). The pleiotropic effects of MEK inhibition on tumour immune microenvironments suggested by preclinical studies includes increasing CD8−positive T-cell infiltration (Kakavand et al. 2015; Liu et al. 2015). Furthermore, MEK inhibition results in increased intratumoural major histocompatibility complex class I expression and tumour antigen presentation, which acts to enhance tumour recognition by the immune system and increases PD-L1 expression, which could counteract the increased presentation of tumour antigens. Activity of MEK inhibition outside of the tumour cells may further contribute to the modulation of the immune microenvironment that could enable a more permissive immune reaction against the tumour.

These data suggest that MEK inhibition via cobimetinib could modulate the tumour immune microenvironment to enable better tumour recognition and killing by the immune system, particularly when paired with a PD-1 pathway inhibition via atezolizumab. Preliminary clinical data support this hypothesis and have shown reasonable safety of the regimen with no new safety signals observed to date.

The overall and cohort-specific study eligibility criteria have been defined to ensure a patient population with adequate fitness and organ function to undergo treatment and with no contraindications to study drugs. Study patients will be routinely monitored for disease progression and will undergo comprehensive general safety assessments to monitor for any unexpected AEs as well as cohort and treatment arm-specific safety assessments to monitor the known safety risks of each study drug. For example, patients randomised to the experimental arm of Cohort 1 will undergo regular head and neck exams, chest CTs, dermatology evaluations and anal and pelvis exams to check for the development of SCC and cSCC associated with vemurafenib treatment. All study treatments that pose a risk of infusion-related reactions (e.g. cetuximab) will be administered under close supervision according to clear instructions to minimise the likelihood of these events occurring (e.g. premedication and infusion rate specifications).

Further risk mitigation measures include the use of an independent Data Monitoring Committee (iDMC) that is responsible for ongoing monitoring of safety outcomes and risk-benefit balance. When necessary, a safety run-in may be included for experimental regimens 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'). The iDMC will review safety data from these run-ins and make recommendations for subsequent dosing. The iDMC will also oversee interim evaluations of safety and, as necessary, response in each of the study cohorts to assure accrual to any cohort that does not demonstrate risk-benefit balance is terminated early. A separate iDMC Charter further describes the roles and responsibilities of the iDMC and methods for cohort reviews.

In summary, the study treatments offer the potential for clinical benefit in each cohort population. The safety profiles of each study drug have been characterised and patients will be closely monitored both for effects known to be associated with each individual agent as well as overall safety to capture any unexpected events. The study iDMC will provide an additional level of oversight and will ensure that cohorts are not continued if adequate safety and clinical benefit are not indicated throughout each cohort accrual period. Finally, this study represents a unique approach to establishing a signals-seeking platform for different compounds in mCRC. The ability to add new treatment cohorts and/or change existing cohorts once the study is underway allows for future inclusion of novel biomarker findings and corresponding compounds or combinations of compounds thereby allowing for the incorporation of new scientific findings over time. Furthermore, the translational research will foster understanding of CRC and its heterogeneity.

2. OBJECTIVES

2.1 EFFICACY OBJECTIVES

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

The secondary efficacy objectives include the evaluation of efficacy through other endpoints:

- OS
- ORR

- Disease control rate (DCR)
- Time to treatment response (TTR)
- Duration of response (DoR)
- Change in ECOG performance status

2.2 SAFETY OBJECTIVES

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

- Incidence, nature and severity of adverse events (AEs)
- Incidence and reasons for any dose reductions, interruptions or premature discontinuation of any component of study treatment
- Clinically significant laboratory values

AEs refer to all treatment-emergent adverse events occurring after the initiation of study medication (i.e. on or after Day 1, Cycle 1 of the Induction Treatment Phase). AEs will continue to be collected during the Maintenance Treatment Phase and Post-Treatment Follow-up Phase as applicable.

2.3 EXPLORATORY OBJECTIVES

The exploratory efficacy objective of this study is:

- To evaluate PFS measured according to mRECIST in patients treated with atezolizumab

The exploratory biomarker objectives of this study are as follows:

- To explore whether there is differential benefit from treatment in patient subgroups defined by different biomarkers, e.g. but not limited to biomarker panels (mutation and expression profiles), immune panels etc.
- If applicable, to assess correlations between biomarkers/marker panels and safety
- Where possible, to investigate if changes in expression/mutation panels of biomarkers during treatment correlate with treatment efficacy or failure i.e. to explore potential resistance/escape mechanisms to (targeted) treatment
- Explore prognostic and potentially predictive effects of markers/marker profiles
- Explore prevalence of specific markers at Baseline and/or salvage/resistance markers to guide targeted therapy approaches beyond MODUL, e.g. but not limited to programmed cell death-1 (PD-L1)
- Explore and correlate microbiome with other biomarkers, baseline characteristics and clinical outcome

3. STUDY DESIGN

3.1 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 mCRC. The primary study endpoint is PFS determined according to RECIST 1.1 in each maintenance treatment cohort.

Secondary outcomes include other efficacy measurements and safety. In addition, exploratory outcomes will focus on PFS using modified response criteria in patients receiving immunotherapy in the study as well 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 17). The sample must be shipped to the designated laboratory and receipt must be confirmed by the laboratory before a patient may be enrolled. If the tumour block is not available, ≥ 20 slides cut from the primary tumour sample will be accepted as an alternative.

All patients enrolled in the study will be asked to give written informed consent to provide blood samples and to allow all available residual samples of tumour, blood and plasma collected for the study be used for additional exploratory biomarker research using the Roche Clinical Sample Repository (RCR). No additional sampling is required for RCR. Prior to May 2018, an optional metastatic tumour sample was collected from all study patients at screening. 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.

3.1.1 Induction Treatment Phase

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 electronic case report form (eCRF). 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 for all study patients during the Induction Treatment Phase. Tumour assessments will be based on local standard of care, but must include an assessment at the end of the Induction Treatment Phase. See Appendix 1.

No other anti-cancer therapy is permitted during the Induction Treatment Phase except for radiotherapy for pain control or local ablation for liver metastases. Local ablation for liver metastases is allowed 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).

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. Prior to May 2018, patients participating in the Supplemental Biomarker Plan would undergo a tumour core biopsy of metastasis and provide a stool sample at the time of progressive disease. The Supplemental Biomarker Program is now closed (see Appendix 18). 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 who do not have progressive disease and who have completed the Induction Treatment Phase can then proceed to the Maintenance Treatment Phase.

3.1.1.1 *BRAF^{mut} Patients and Early Disease Progression*

BRAF^{mut} patients experiencing early disease progression during induction treatment (called "early progressing BRAF^{mut} patients") 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.

3.1.2 Maintenance Treatment Phase

Prior to May 2018, patients participating in the Supplemental Biomarker Plan would have had an additional tumour core biopsy of metastasis and stool sample collection upon completion of induction treatment prior to initiation of maintenance treatment. The Supplemental Biomarker Program is now closed (see Appendix 18).

For all patients, the assessment of biomarkers for cohort assignment will be based on archival tumour tissue block from the primary tumour obtained at the time of initial diagnosis (see Appendix 17).

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.

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 induction treatment, 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 and will begin maintenance 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. Stratification variables applicable to each cohort are described in Section 4.2.

The study will follow an adaptive design, where additional cohorts can be added and/or existing cohorts changed over the course of the study via protocol amendment (see Figure 2). Refer to Section 6 for the status of cohorts following premature closure of study enrolment.

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 eCRF. For regimens with three week treatment cycles (such as Cohort 3 experimental regimen), clinical laboratory results from every cycle will be collected in the eCRF. Physical examinations will be done every treatment cycle (regimens with three week treatment 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 in accordance with RECIST 1.1 (see Appendix 10) for all patients, and additionally according to mRECIST (see Appendix 11) for patients in the experimental arms

of Cohorts 2 and 4 (all 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 will be evaluated according to local practice. Schedules of Assessments for each cohort are provided in Appendices 2 to 5.

Maintenance treatment IMP dose reductions are only allowed as recommended in the applicable Investigator's Brochures (see Section 5.1.3). If any drug of any study treatment regimen in either the Induction or Maintenance Treatment Phase is discontinued or held for > 21 days, approval of the Sponsor's Medical Monitor must be obtained prior to re-initiation of treatment. Patients not approved to re-initiate treatment after > 21 day delays will come off all study treatment and will enter the Post-Treatment Follow-up Phase.

No other anti-cancer therapy is permitted during the Maintenance Treatment Phase except for radiotherapy for pain control.

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 discontinuing treatment during the Maintenance Treatment Phase, will be followed for new AEs for 28 days following the discontinuation of study treatment if they received treatment in the control arm of any cohort or the experimental arm of Cohort 1. Patients discontinuing from treatment in the experimental arms of Cohorts 2, 3 or 4 will be followed for new AEs for 90 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 if the event is believed to be related to prior study treatment (see Section 5.3.1).

3.1.2.1 *Maintenance Treatment in Cohort 1*

Experimental Arm

- 5-FU/LV with cetuximab and vemurafenib

Control Arm

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

Up to and including May 31, 2019, disease status of patients in Cohort 1 will be assessed by the Investigator according to according to RECIST 1.1 (see Appendix 10) during the Maintenance Treatment Phase. After May 31, 2019, disease status will no longer be collected for study analyses and will be evaluated according to local practice. Maintenance treatment will continue in these patients until disease progression, unacceptable toxicity, initiation of another anti-cancer therapy, patient or physician decision to discontinue, or patient death, whichever occurs first.

A safety run-in review was conducted for the first six patients treated with the experimental combination of '5-FU/LV+ cetuximab + vemurafenib' by the iDMC in February 2016. The iDMC recommended that patients allocated to this regimen may now receive 5-FU at doses

up to 2,400 mg/m^2. The iDMC will continue to monitor initial patients in this regimen treated with 5-FU doses ≥ 1,600 mg/m^2 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. Further details of the safety review are provided in the iDMC Charter.

Prior to May 2018, all patients participating in the Supplemental Biomarker Plan would have undergone a tumour core biopsy of metastasis and stool sample collection at the time of progressive disease. The Supplemental Biomarker Program is now closed (see Appendix 18).

3.1.2.2 *Maintenance Treatment in Cohort 2*

Experimental Arm

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

Control Arm

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

Up to and including May 31, 2019, disease status of patients in the control arm of Cohort 2 will be assessed by the Investigator according to according to RECIST 1.1 (see Appendix 10) during the Maintenance Treatment Phase. After May 31, 2019, disease status will no longer be collected for study analyses and will be evaluated according to local practice. Maintenance treatment will continue in these patients until disease progression, unacceptable toxicity, initiation of another anti-cancer therapy, patient or physician decision to discontinue, or patient death, whichever occurs first.

Up to and including May 31, 2019, disease status of patients in the experimental arm of Cohort 2 (i.e. patients who are receiving atezolizumab), will be assessed according to both RECIST 1.1 (see Appendix 10) and mRECIST (see Appendix 11) during the Maintenance Treatment Phase. After May 31, 2019, disease status will no longer be collected for study analyses and will be evaluated according to local practice. Maintenance treatment may continue in these patients beyond the first tumour assessment showing apparent progression according to 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 hypercalcemia) 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 per RECIST 1.1: unacceptable toxicity, initiation of another anti-cancer therapy, patient or physician decision to discontinue, or patient death, whichever occurs first.

Prior to May 2018, all patients participating in the Supplemental Biomarker Plan would have undergone a tumour core biopsy of metastasis and stool sample collection at the time of progressive disease. The Supplemental Biomarker Program is now closed (see Appendix 18).

3.1.2.3 *Maintenance Treatment in Cohort 3*

Experimental Arm

- capecitabine with trastuzumab and pertuzumab

Control Arm

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

Up to and including May 31, 2019, disease status of patients in Cohort 3 will be assessed by the Investigator according to according to RECIST 1.1 (see Appendix 10) during the Maintenance Treatment Phase. After May 31, 2019, disease status will no longer be collected for study analyses and will be evaluated according to local practice. Maintenance treatment will continue in these patients until disease progression, unacceptable toxicity, initiation of another anti-cancer therapy, patient or physician decision to discontinue, or patient death, whichever occurs first.

Prior to May 2018, all patients participating in the Supplemental Biomarker Plan would have undergone a tumour core biopsy of metastasis and stool sample collection at the time of progressive disease. The Supplemental Biomarker Program is now closed (see Appendix 18).

3.1.2.4 *Maintenance Treatment in Cohort 4*

On February 12, 2018, in accordance with iDMC recommendations following review of safety data, accrual into Cohort 4 was suspended. Based on their subsequent evaluation of additional Cohort 4 safety and efficacy data on July 3, 2018, the iDMC recommended that Cohort 4 accrual be closed. The basis for this recommendation was a higher number of deaths, the occurrence of serious toxicity, and the lack of evidence for clinical benefit (either response or tumour control) in the experimental arm relative to the control arm. Subsequent to the iDMC recommendations, additional deaths occurred in Cohort 4 including in the experimental arm. Even though these additional deaths were due to disease progression, they adversely affect the benefit-risk balance of the cobimetinib plus atezolizumab combination in first-line maintenance therapy for mCRC following induction with FOLFOX and bevacizumab. In an Urgent Safety Measure Letter dated July 25, 2018, the Sponsor strongly advised investigators to consider discontinuing experimental treatment in any ongoing patients. Investigators were advised to explore appropriate next treatment options, including a fluoropyrimidine (5-FU/LV or capecitabine) plus bevacizumab, with patients discontinuing experimental treatment.

Cohort 4 patients discontinuing experimental treatment will undergo a Study Treatment Discontinuation Visit and enter the Post-Treatment Follow-up Phase of the study. Management of these patients, including study assessments and procedures, is as described in this protocol for any Cohort 4 patient discontinuing treatment prior to disease progression.

Following the Sponsor's Urgent Safety Measure notification, continuation of experimental treatment is allowed only with written approval from the Medical Monitor following their review of the patient's case with the investigator. Patients continuing experimental treatment will continue to be managed as described in this protocol for patients in the experimental arm of Cohort 4.

Cohort 4 patients randomized to the control arm receiving standard control treatment are unaffected by the decisions stemming from the benefit risk evaluation of the experimental arm and may continue maintenance treatment in accordance with the protocol.

Experimental Arm

- cobimetinib and atezolizumab

Control Arm

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

Up to and including May 31, 2019, disease status of patients in the control arm of Cohort 4 will be assessed by the Investigator according to according to RECIST 1.1 (see Appendix 10) during the Maintenance Treatment Phase. After May 31, 2019, disease status will no longer be collected for study analyses and will be evaluated according to local practice. Maintenance treatment will continue in these patients until disease progression, unacceptable toxicity, initiation of another anti-cancer therapy, patient or physician decision to discontinue, or patient death, whichever occurs first.

Up to and including May 31, 2019, disease status of patients in the experimental arm of Cohort 4 (i.e. patients who are receiving atezolizumab), will be assessed according to both RECIST 1.1 (see Appendix 10) and mRECIST (see Appendix 11) during the Maintenance Treatment Phase. After May 31, 2019, disease status will no longer be collected for study analyses and will be evaluated according to local practice. Maintenance treatment may continue in these patients beyond the first tumour assessment showing apparent progression according to 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 hypercalcemia) 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

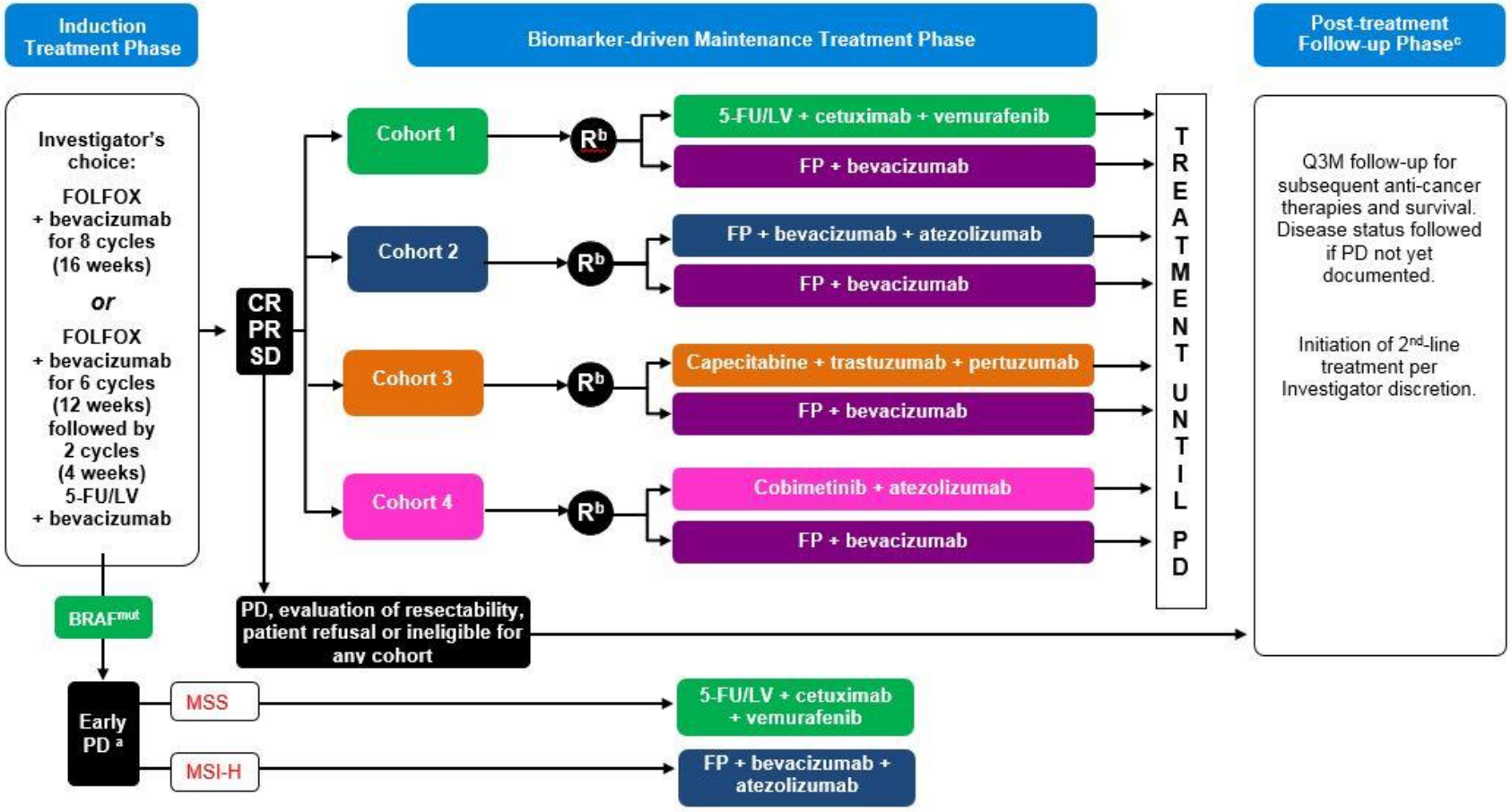
Treatment should be discontinued if the next follow-up tumour assessment continues to demonstrate progression per RECIST 1.1 (as compared to the assessment at the end of

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 per RECIST 1.1: unacceptable toxicity, initiation of another anti-cancer therapy, patient or physician decision to discontinue, or patient death, whichever occurs first.

Prior to May 2018, all study patients participating in the Supplemental Biomarker Plan would have undergone a tumour core biopsy of metastasis and stool sample collection at the time of progressive disease. The Supplemental Biomarker Program is now closed (see Appendix 18).

Figure 2: 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.

3.1.3 Post-Treatment Follow-up Phase

All patients will undergo a Study Treatment Discontinuation visit within 30 days following their last study treatment and will enter the Post-Treatment Follow-up Phase of the study.

Up to and including 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 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 continue to be followed for progression during the Post-Treatment Follow-up Phase with disease assessments conducted according to local practice (patients who discontinued during the Induction Treatment Phase) or every eight weeks (patients who discontinued during 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.

3.1.4 Steering Committee

The SC, composed of sponsor and external clinical representatives, will be responsible for overseeing the scientific validity and general conduct of the study as well as dissemination of the study results.

Further details regarding the roles and responsibilities of the SC and its members are provided in the SC Charter.

3.1.5 Independent Data Monitoring Committee

An iDMC will be responsible for evaluating the safety of the patients participating in the trial at regular intervals throughout the study. The iDMC will also make recommendations as to whether cohort recruitment should continue based on benefit-risk evaluations that include efficacy as well as safety data. The efficacy data included in these reviews will be specified by the iDMC at a preceding iDMC meeting and will be documented in the iDMC meeting

minutes. In addition, the iDMC will evaluate 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').

The schedule of iDMC reviews will be determined by the iDMC and described in the iDMC Charter. Further details regarding the roles and responsibilities of the iDMC are provided in the iDMC Charter.

3.2 END OF STUDY

Study enrolment was suspended in February 2018 and will remain permanently closed. The number of patients included in each cohort is described in Section 6.2.

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 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.

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

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 (see Section 4.3.5).

3.3 RATIONALE FOR STUDY DESIGN

In this Phase 2 study, all patients will receive an induction treatment that is considered standard in many countries and that has been shown to improve outcomes in the first-line setting. Only those patients that experience disease control or response to induction treatment will continue to the randomised Maintenance Treatment Phase of the study wherein the effects of experimental and control arms will be compared. Study treatment blinding is not considered necessary in this Phase 2 setting nor feasible considering the complexity and variation in administration methods and safety monitoring requirements with each regimen.

The distribution of baseline characteristics that could contribute to variations in efficacy and/or safety will be controlled by randomization. Randomization will be stratified within each cohort according to geographic region, response to induction treatment and/or primary tumour biomarkers that are known or expected to affect study outcomes. In addition, randomization in Cohort 3 will be stratified by HER2+ IHC result since there is some evidence that response to HER2-targeted therapy may be dependent on the degree of HER2 overexpression in HER2+ patients (see Section1.2.7). Randomization in Cohort 4 will

be stratified by microsatellite stability status due to the influence of mismatch-repair deficiency on tumour immune environment integral to atezolizumab's mode of action (see Section 1.2.6). Cohort 4 randomization will also be stratified by RAS pathway status. The RAS pathway is well known to affect mCRC outcomes.

The primary study endpoint of PFS determined according to RECIST 1.1 is an established measure of efficacy in the CRC setting. Secondary efficacy endpoints include OS and additional recognised surrogate measures of efficacy (ORR, TTR, DCR, DoR) and clinical benefit (change in ECOG status). Efficacy endpoints will be measured from randomization forward to ensure maintenance experimental and control treatment effects are evaluated distinctly from induction treatment effects.

Safety endpoints will be assessed throughout all study periods (induction, maintenance, and study follow-up) to ensure uninterrupted monitoring of potential treatment effects that continue beyond last study doses, but will be summarised by study treatment phase and by maintenance treatment cohort.

To assure ongoing monitoring of safety outcomes and risk-benefit balance, an iDMC will regularly review safety data as these become available over the course of the study. The efficacy data included in these reviews will be specified by the iDMC at a preceding iDMC meeting and will be documented in the iDMC meeting minutes. When necessary due to the nature of prior experience with a particular experimental regimen, a safety run-in will be included. The iDMC will review data from such safety run-ins and make recommendations for subsequent dosing. Accrual into any cohort may be terminated prior to attaining the planned PFS events should the iDMC find the available data do not support an adequate balance of benefit to risk.

Notably, the modular study design accommodates the addition of further maintenance treatment cohorts consisting of regimens that include targeted therapies with potential efficacy in mCRC when the data to support biomarker-based assignment to such cohorts are established.

3.3.1 Rationale for mRECIST and Allowing Treatment beyond Progression in Atezolizumab-treated Patients

Anti-tumour immune responses such as those associated with atezolizumab may result in objective responses that are delayed and that can be preceded by initial apparent radiological progression. This initial apparent progression may occur as a result of either delayed anti-tumour activity and/or robust tumour immune cell infiltration with a concomitant increase in tumour size. In addition, lesions that might otherwise be undetectable with conventional imaging may increase in size as a result of these processes and be recorded as new lesions (Hales et al. 2010). As a result, conventional response criteria may not adequately assess the activity of immunotherapeutic agents because PD determined from initial radiographic evaluations using these criteria may not necessarily reflect therapeutic failure. Because of the potential for such pseudo-progression/tumour immune infiltration, this study will allow patients randomised to the experimental arms of Cohort 2 and 4 to remain on study maintenance treatment after apparent radiographic progression, provided the benefit-risk ratio is judged to be favourable. These patients will be discontinued for unacceptable

toxicity or symptomatic deterioration attributed to disease progression as determined by the Investigator after an integrated assessment of radiographic data and clinical status (see Section 4.6.2).

In addition, while the primary and secondary efficacy endpoint measures will be assessed according to RECIST 1.1, an exploratory analysis of PFS using mRECIST (see Appendix 11) will be conducted for patients randomised to receive atezolizumab in this study. These mRECIST criteria allow the incorporation of new lesions into the calculation of total tumour burden after baseline. Similar to other immune-related response criteria (Wolchok et al. 2009), it is recommended that radiological progression be confirmed at a subsequent tumour assessment to take into account the potential for pseudo-progression/tumour immune infiltration.

3.3.2 Rationale for Investigational Medicinal Product Maintenance Treatment Dosages

3.3.2.1 *Cetuximab*

Cetuximab will be administered to patients in the experimental arm of Cohort 1 in combination with 5-FU/LV and vemurafenib at a dose of 500 mg/m^2 via IV infusion on Day 1 of every 2-week cycle. This dose and schedule varies from the approved weekly schedule (400 mg/m^2 loading dose then 250 mg/m^2 weekly thereafter) but has been found to exhibit predictable pharmacokinetics similar to the approved weekly regimen (Tabernero et al. 2008). Findings from a phase II study of this biweekly cetuximab schedule given with irinotecan in patients with mCRC progressing after at least one previous line of chemotherapy showed similar efficacy and safety to that seen with weekly cetuximab (Martín-Martorell et al. 2008). Furthermore, in a recent study of chemotherapy with or without cetuximab in mCRC patients with resectable liver disease, this dose and schedule was not associated with any new safety concerns (Primrose et al. 2014). This biweekly dose and schedule of cetuximab is also included in the most recent NCCN guidelines (version 2, 2015).

A description of the safety run-in iDMC review of patients treated with 5-FU/LV + cetuximab + vemurafenib is provided in Section 3.3.2.2 below.

3.3.2.2 *Vemurafenib*

Vemurafenib will be administered in this combination regimen at a dose of 960 mg b.i.d by mouth consistent with the dose and schedule approved for its use in the treatment of melanoma. Combined treatment with cetuximab (doses up to 400 mg/m^2 loading dose then 250 mg/m^2 weekly) and vemurafenib (doses up to 960 mg b.i.d) has been found to have a manageable safety profile in CRC patients in an ongoing Phase 2 study (Tabernero et al. 2014). A safety review (safety run-in) was conducted for the first six patients with the experimental combination of '5-FU/LV + cetuximab + vemurafenib' in February 2016. The iDMC recommended that 5-FU dosing could be increased up to 2,400 mg/m^2 with no changes vemurafenib or cetuximab doses. The iDMC will continue to monitor initial patients in this regimen treated with 5-FU doses ≥ 1,600 mg/m^2.

3.3.2.3 *Atezolizumab*

Atezolizumab will be administered to patients in the experimental arm of Cohort 2 in combination with a fluoropyrimidine and bevacizumab at a fixed dose of 800 mg on Day 1 of every 2-week treatment cycle. The atezolizumab dose and schedule were determined based on both nonclinical studies and available clinical data as described in the current Investigator's Brochure.

Atezolizumab will be administered to patients in the experimental arm of Cohort 4 at a fixed dose of 840 mg on Day 1 of every 2-week treatment cycle. This dose was selected for further evaluation in the ongoing phase III mCRC study (GO30182) in combination with cobimetinib. It is expected to be pharmacologically similar to 800 mg atezolizumab every 2 weeks recommended for phase II testing.

As described in Section 3.3.1, due to the potential for pseudo-progression with immunotherapy, patients receiving atezolizumab may continue treatment beyond the first tumour assessment showing disease progression per RECIST 1.1 until loss of clinical benefit (unless the next follow-up tumour assessment also shows progression). These patients may also be discontinued due to unacceptable toxicity or patient or Investigator decision to discontinue therapy as is consistent with standard practice in the first-line maintenance setting.

3.3.2.4 *Bevacizumab*

Bevacizumab will be administered in the experimental arm of Cohort 2 in combination with atezolizumab and a fluoropyrimidine at a dose of 5 mg/kg IV on Day 1 of every 2-week cycle. This dose and schedule represents the lowest dose found to be efficacious and safe in combination chemotherapy regimens for CRC and is approved in many countries in combination with 5-FU (see Section 1.2.3 and current Bevacizumab Investigator's Brochure or local labelling as applicable).

3.3.2.5 *Trastuzumab*

Trastuzumab will be administered to patients in the experimental arm of Cohort 3 on Day 1 every 3 weeks at an initial loading dose of 8 mg/kg followed by 6 mg/kg for subsequent doses. This dose is indicated in the treatment of metastatic breast cancer as monotherapy and in combination with pertuzumab. It was administered in the phase III study evaluating trastuzumab in combination with pertuzumab and capecitabine with reasonable safety (see Section 1.2.8).

3.3.2.6 *Pertuzumab*

Pertuzumab will be administered to patients in the experimental arm of Cohort 3 on Day 1 every 3 weeks at an initial fixed loading dose of 840 mg followed by a fixed dose of 420 mg for subsequent doses. This dose is indicated in the treatment of metastatic breast cancer in combination with trastuzumab. This dose was administered in a phase III study evaluating pertuzumab in combination with trastuzumab and capecitabine with reasonable safety (see Section 1.2.8).

3.3.2.7 *Cobimetinib*

Cobimetinib will be administered to patients in the experimental arm of Cohort 4 at a dose of 60 mg orally once daily for 3 weeks followed by a 1 week treatment break (21/7 schedule) in combination with atezolizumab. As such, 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. This dose was determined as the recommended phase II dose in the phase I dose-escalation/dose-expansion study GP28363 of combined atezolizumab and cobimetinib (see Section 1.2.9).

3.3.3 Rationale for Patient Populations

The study patient population was defined to ensure participants are suitable to receive the study mandated induction treatment in terms of both available treatment options (e.g. previously untreated, unresectable metastatic disease) and overall fitness (e.g. ECOG status ≤ 2, adequate organ function).

Cohort populations were defined primarily upon biomarker criteria considered appropriate to the cohort's experimental treatment arm regimen and to avoid contraindications to the experimental regimen.

3.3.4 Rationale for Control Group

Each maintenance cohort will include the same control arm regimen consisting of a fluoropyrimidine and bevacizumab. Treatment with these agents is considered standard in many countries for the treatment of mCRC with or without oxaliplatin and regardless of biomarker status. The doses of each agent are consistent with applicable local prescribing information. In countries where bevacizumab is not approved in this indication, the lowest biweekly dose recommended for use in any jurisdiction (5 mg/kg q2w) is mandated.

As a consequence of using the same control treatment regimens across study cohorts, study outcomes may be compared between the different cohorts' control arm populations.

3.3.5 Rationale for Biomarker Assessments

Overall, biomarker assessments conducted in this study are fundamental to the general study goal of further characterizing biomarkers in mCRC treatment. Tumour biomarker testing (e.g. BRAF gene analysis) for cohort assignment is required to determine which cohort's experimental treatment may be appropriate to the particular patient. Importantly, biomarker testing for cohort assignment will be conducted on archived primary tumour samples already obtained as part of routine care that are available for all study patients.

Additional biomarker assessments conducted on tumour, blood and stool samples will provide insight into factors which affect the efficacy and safety of specific treatments in an individual patient. These evaluations are critical to the development of individualised care including optimal treatment selection. These assessments will be conducted on tumour samples that have already been collected as part of routine care, on peripheral blood samples obtained at the same time as blood sampling for safety monitoring, or on stool samples collected by the patient at home. Additional tumour biopsies will be done solely for

study purposes but these will only be obtained from patients who have provided written informed consent for these additional biopsies.

3.4 OUTCOME MEASURES

3.4.1 Efficacy Outcome Measures

The primary efficacy outcome measure of PFS will be assessed within each cohort (experimental arm vs. control arm) during the Maintenance Treatment Phase. PFS is defined as the time from randomisation into the Maintenance Treatment Phase until disease progression according to RECIST 1.1 per Investigator assessment or death from any cause, whichever occurs first.

Secondary

- 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

3.4.2 Safety Outcome Measures

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.

3.4.3 Exploratory Outcome Measures

The exploratory efficacy outcome of the study is 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.

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.

Further details of biomarkers that may be assessed in the exploratory biomarker analyses are provided in Appendix 17.

4. MATERIALS AND METHODS

4.1 PATIENTS

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.

The cohort-specific exclusion criteria must be assessed within 3 weeks of completing the Induction Treatment Phase. Biomarker assessment for cohort assignment 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.

4.1.1 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.

4.1.2 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. VEGF or vascular endothelial growth factor receptor [VEGFR] therapies or tyrosine kinase inhibitors)
3. Current or recent (within 10 days of start of 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 start of study induction treatment for patients not receiving anti-coagulation therapy. 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 the last 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, post ovulation 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

Cohort 1 Exclusion Criteria

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 (see Appendix 8)

   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 Section 4.3.2.2.2).

Cohort 2 Exclusion Criteria

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 antibody test) are eligible.

   Note: Patients positive for hepatitis C virus (HCV) antibody are eligible only if polymerase chain reaction testing is negative for HCV ribonucleic acid (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 four weeks prior to start of maintenance treatment or anticipation that such a live attenuated vaccine will be required during the remainder of the study
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 four weeks or five half-lives of the drug, whichever is longer, prior to start of 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 agents) within 2 weeks prior to start of maintenance treatment, or requirement for systemic immunosuppressive medications during the remainder of the study.

    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.

    Note: 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.

Cohort 3 Exclusion Criteria

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. 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

Cohort 4 Exclusion Criteria

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 x 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 test for HIV
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).

4.2 METHOD OF TREATMENT ASSIGNMENT

Within 3 weeks of completion of the Induction Treatment Phase of the study (based on the last day of the last cycle of induction treatment), patients who have not progressed may continue to the biomarker-driven Maintenance Treatment Phase.

Patients will be randomised by an independent interactive voice or web-based response system (IxRS) system. At the time of enrolment to the Induction Treatment Phase, the site will enter demographic and Screening/Baseline patient characteristics into the IxRS. For patients who are eligible for enrolment, the site will obtain the patient's identification number from the IxRS.

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 (see Appendix 17). If the primary tumour block is not available, ≥ 20 slides cut from the primary tumour sample will be accepted as an alternative. The determination of primary tumour tissue availability must be made before a potential participant undergoes any screening procedures and the sample (block or slides) must be shipped to the designated laboratory with confirmation of receipt by the laboratory before a patient may be enrolled in this study. Patients for whom a sufficient primary tumour sample was submitted but who do not have a definitive biomarker status due to indeterminate assay results (e.g. due to technical issues) may still be included in the study depending on the addition of future cohorts. At the time of randomization to the Maintenance Treatment Phase, the site will enter the patient's biomarker status. Once assigned to a cohort, patients will be randomised on a 2:1 (experimental:control) basis to either the experimental treatment arm or the control arm of that cohort. Randomization will be stratified by specific biomarkers, geographical region and/or by patient response after the Induction Treatment Phase as follows:

- Cohort 1: geographical region (EU, Americas, Africa or Asia), patient response after induction treatment (CR/PR vs. SD).
- Cohort 2: geographical region (EU, Americas, Africa or Asia), patient response after induction treatment (CR/PR vs. SD).
- Cohort 3: patient response after induction treatment (CR/PR vs. SD), HER2 IHC result (IHC0/IHC1+/IHC2+ vs. IHC3+)

- Cohort 4: geographical region (EU vs. rest of the world), patient response after induction treatment (CR/PR vs. SD), microsatellite stability (MSI-H vs. MSS) and RAS status (wild-type KRAS and NRAS vs. mutant KRAS and/or NRAS)

4.2.1 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 and the sample must have been shipped to the Sponsor's designated laboratory. Confirmation of sample receipt by the laboratory is required. The sample must be shipped to the designated laboratory with the corresponding pathology report. 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.

4.3 STUDY TREATMENT

Study treatment includes induction treatment (FOLFOX regimens, bevacizumab) and maintenance treatments (5-FU/LV, capecitabine, bevacizumab, and other agents comprising the experimental arm regimen in each cohort).

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.

4.3.1 Formulation, Packaging, and Handling

4.3.1.1 *Induction Treatment Phase*

5-FU, LV, Oxaliplatin (FOLFOX)

5-FU, LV and oxaliplatin will be used in commercially available formulations. Refer to local prescribing information for details of these formulations, as well as packaging, and handling requirements.

Bevacizumab

Bevacizumab will be used in commercially available formulation. Refer to local prescribing information for details of the formulation as well as packaging and handling requirements.

4.3.1.2 *Maintenance Treatment Phase*

4.3.1.2.1 *Control Arm- All Cohorts*

Fluoropyrimidine (5-FU or Capecitabine)

The fluoropyrimidine (5-FU or capecitabine) and LV (if applicable) selected for use in the maintenance treatment control arms will be used in commercially available formulations. Refer to local prescribing information for details of these formulations as well as packaging and handling requirements.

Bevacizumab

Bevacizumab will be used in commercially available formulation. Refer to local prescribing information for details of the formulation as well as packaging and handling requirements.

4.3.1.2.2 *Experimental Arm Cohort 1*

5-FU

5-FU and LV will be used in commercially available formulations. Refer to local prescribing information for details of these formulations, as well as packaging, and handling requirements.

Cetuximab

Cetuximab is provided in single-use, ready-to-use, 100 mL vials containing 500 mg of cetuximab as a sterile, preservative-free injectable liquid.

Chemical and physical in-use stability of cetuximab 5 mg/mL has been demonstrated for 48 hours at 25 ºC, if the solution is prepared as described in the current cetuximab SmPC. Cetuximab does not contain any antimicrobial preservative or bacteriostatic agent. From a microbiological point of view, the product shall be used immediately after opening. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2 – 8 ºC, unless opening has taken place in controlled and validated aseptic conditions.

For further details of cetuximab formulation, packaging and handling are provided in the cetuximab Package Insert (Appendix 14).

Vemurafenib

Vemurafenib is provided as 240 mg film-coated tablets for oral administration. Excipients include croscarmellose sodium, colloidal anhydrous silica, magnesium stearate, and hydroxypropylcellulose in addition to the film coat ingredients (polyvinyl alcohol, titanium dioxide, polyethylene glycol 3350, talc, iron oxide red).

Vemurafenib tablets should be stored at ≤ 25 °C (77°F) and should be protected from excessive exposure to light. Patients will be requested to store vemurafenib at the recommended storage conditions noted on the label, out of reach of children or other vulnerable persons. Under hot weather conditions, vemurafenib may be stored in a refrigerator to avoid exceeding the 25 °C maximum storage temperature.

For further details, refer to the current Vemurafenib Investigator's Brochure.

4.3.1.2.3 *Experimental Arm Cohort 2*

Fluoropyrimidine (5-FU/LV, Capecitabine)

5-FU or capecitabine, and LV (if applicable) will be used in commercially available formulations. Refer to local prescribing information for details of these formulations, as well as packaging, and handling requirements.

Bevacizumab

Bevacizumab will be used in commercially available formulation. Refer to local prescribing information for details of the formulation as well as packaging and handling requirements.

Atezolizumab

The atezolizumab drug product is formulated as 60 mg/mL atezolizumab in 20 mM histidine acetate, 120 mM sucrose, 0.04% polysorbate 20, pH 5.8. It is provided in a single-use, 20-cc glass vial as a colourless to slightly yellow, sterile, preservative-free clear liquid solution intended for IV administration. The vial is designed to deliver 20.0 mL (1200 mg) of atezolizumab solution but may contain more than the stated volume to enable delivery of the entire 20.0 mL volume.

Atezolizumab must be refrigerated at 2 °C – 8 °C (36 °F – 46 °F) upon receipt until use. Atezolizumab vials should not be used beyond the expiration date provided by the manufacturer. No preservative is used in the atezolizumab drug product; therefore, each vial is intended for single use only. Vial contents should not be frozen or shaken and should be protected from direct sunlight.

Atezolizumab must be administered from infusion bags with IV infusion lines with product contacting surfaces of polyvinylchloride or polyolefin and 0.2 µm in-line filters (filter membrane of polyethersulfone). No incompatibilities have been observed between atezolizumab and polyvinylchloride or polyolefin infusion materials (bags and infusion lines).

For further details, refer to the Atezolizumab Pharmacy Manual and current Investigator's Brochure.

4.3.1.2.4 *Experimental Arm Cohort 3*

Capecitabine

Capecitabine will be used in commercially available formulation. Refer to local prescribing information for details of the formulation, as well as packaging, and handling requirements.

Trastuzumab

Only trastuzumab (Herceptin) may be used in the study. Substitution with biosimilar drugs is not allowed.

Trastuzumab for IV administration is a sterile, white to pale yellow, preservative-free lyophilised powder. Each vial of trastuzumab contains 150 mg of trastuzumab with L-histidine HCl; L-histidine; α,α-trehalose dihydrate and polysorbate 20. Each vial is reconstituted with 7.2 mL of water for injections (not supplied). Use of other reconstitution solvents should be avoided. This yields a 7.4 mL solution for single-dose use, containing approximately 21 mg/mL trastuzumab. A volume overage of 4% ensures that the labelled dose of 150 mg can be withdrawn from each vial.

Vials of trastuzumab must be stored in the closed original pack at a temperature of 2 ºC – 8 ºC in a refrigerator. Trastuzumab reconstituted with sterile water for injection is stable for 48 hours at 2 ºC – 8 ºC after reconstitution and must not be frozen.

The appropriate amount of reconstituted trastuzumab should be withdrawn from the vial and added to a polyvinylchloride, polyethylene or polypropylene infusion bag containing 250 mL of 0.9% sodium chloride solution. Do not use with glucose-containing solutions. The bag should be gently inverted to mix the solution in order to avoid foaming. Parenteral solutions should be inspected visually for particulates and discoloration prior to administration. Once the infusion is prepared it should be administered immediately. If diluted aseptically, it may be stored for 24 hours (do not store above 30 °C).

For further details refer to the current Trastuzumab Investigator's Brochure.

Pertuzumab

Pertuzumab for IV administration is provided as a single use formulation containing 30 mg/mL pertuzumab in 20 mM L-histidine acetate (pH 6.0), 120 mM sucrose, and 0.02% polysorbate 20. Each 20-mL vial contains approximately 420 mg of pertuzumab (14.0 mL/vial).

Vials of pertuzumab must be placed in a refrigerator 2 °C – 8 °C (36 °F – 46 °F) immediately upon receipt to ensure optional retention of physical and biochemical integrity and should remain refrigerated until immediately prior to use. DO NOT FREEZE and DO NOT SHAKE the pertuzumab vial. Protect from light.

The solution of pertuzumab diluted for infusion in polyvinylchloride or non-polyvinylchloride polyolefin bags (including polyethylene) containing 0.9% sodium chloride injection may be stored at 2 °C – 8 °C (36 °F – 46 °F) for up to 24 hours prior to use. Diluted pertuzumab has been shown to be stable for up to 24 hours at room temperature (2 °C – 25 °C). However, since pertuzumab contains no preservative, the aseptically diluted solution should be stored refrigerated (2 °C – 8 °C) for no more than 24 hours.

For further details, see the current Pertuzumab Investigator's Brochure.

Note: Trastuzumab and pertuzumab should not be administered at the same time and should not be mixed in the same infusion bag.

4.3.1.2.5 *Experimental Arm Cohort 4*

Cobimetinib

Cobimetinib is supplied as 20 mg, film-coated, white, round, immediate-release tablets packaged in blister packs. The inactive ingredients in cobimetinib are as follows: lactose monohydrate, microcrystalline cellulose, croscarmellose sodium, and magnesium stearate for the tablet core. The tablet coating consists of polyvinyl alcohol, part hydrolyzed, titanium dioxide, polyethylene glycol 3350, and talc. Cobimetinib should be stored below 30 °C (86 °F).

For further details, see the current Cobimetinib Investigator's Brochure.

Atezolizumab

The atezolizumab drug product is formulated as 60 mg/mL atezolizumab in 20 mM histidine acetate, 120 mM sucrose, 0.04% polysorbate 20, pH 5.8. It is provided in a single-use, 20-cc glass vial as a colourless to slightly yellow, sterile, preservative-free clear liquid solution intended for IV administration. The vial is designed to deliver 20.0 mL (1200 mg) of atezolizumab solution but may contain more than the stated volume to enable delivery of the entire 20.0 mL volume.

Atezolizumab must be refrigerated at 2 °C – 8 °C (36 °F – 46 °F) upon receipt until use. Atezolizumab vials should not be used beyond the expiration date provided by the manufacturer. No preservative is used in the atezolizumab drug product; therefore, each vial is intended for single use only. Vial contents should not be frozen or shaken and should be protected from direct sunlight.

Atezolizumab must be administered from infusion bags with IV infusion lines with product contacting surfaces of polyvinylchloride or polyolefin and 0.2 µm in-line filters (filter membrane of polyethersulfone). No incompatibilities have been observed between atezolizumab and polyvinylchloride or polyolefin infusion materials (bags and infusion lines).

For further details, refer to the Atezolizumab Pharmacy Manual and current Investigator's Brochure.

4.3.2 Dosage and Administration

Guidelines for dosage modification and treatment interruption or discontinuation of study treatment are described in Section 5.1. Please refer to the MODUL Treatment Administration Guide for detailed study treatment administration instructions.

Any overdose or incorrect administration of study drug should be noted on the Study Drug Administration electronic Case Report Form (eCRF). AEs associated with an overdose or incorrect administration of study drug should be recorded on the Adverse Event eCRF.

4.3.2.1 *Induction Treatment Phase*

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

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). The selected regimen should be administered in accordance with locally approved prescribing information including any recommendations for pre-treatment (i.e. antiemetic therapies).

4.3.2.2 *Maintenance Treatment Phase*

Following cohort assignment based on biomarker status, patients will be randomised to receive study maintenance treatment in either the control or experimental treatment arm of their assigned cohort as described below. Maintenance treatment will begin within 3 weeks of their last dose of induction treatment.

For patients in Cohorts 1 and 3, and the control arms of Cohorts 2 and 4 only, maintenance treatment 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.

Patients randomised to the experimental arms of Cohorts 2 and 4 (i.e. patients who are receiving atezolizumab) may continue maintenance treatment 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 per RECIST 1.1: unacceptable toxicity, initiation of another anti-cancer therapy, patient or physician decision to discontinue, or patient death, whichever occurs first.

For all patients, dose reductions or dose delays of any IMP are only allowed as recommended in the applicable Investigator's Brochure (see Section 5.1.3). 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 may be re-initiated. Patients not approved by the Medical Monitor to re-initiate treatment will come off all study treatment and will enter the Post-Treatment Follow-up Phase.

4.3.2.2.1 *Control Arm-All Cohorts*

Control arm treatment is the same in all cohorts and should be administered as follows:

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. 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 systemic premedication is not warranted.

Detailed treatment administration instructions are provided in the MODUL Treatment Administration Guide. Guidelines for dosage modification and treatment interruption or discontinuation of study maintenance treatment are provided in Section 5.1.3.

4.3.2.2.2 *Experimental Arm Cohort 1*

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.

Treatment in the experimental arm of Cohort 1 should be administered as follows:

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. Subsequent patients in this cohort will receive 1,600 - 2,400 mg/m^2 5-FU administered via 46-hour IV infusion (IV bolus is not permitted), 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 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. If a patient misses a dose (e.g., due to emesis), the patient should be instructed not to take or make up that dose and to resume dosing with the next scheduled dose.

Note: A safety run-in was conducted for the first six patients treated with the experimental combination of '5-FU/LV + cetuximab + vemurafenib' in February 2016. The iDMC recommended that patients allocated to this regimen may now receive 5-FU at doses up to 2,400 mg/m^2. The iDMC will continue to monitor initial patients in this regimen treated with 5-FU doses ≥ 1,600 mg/m^2 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. Further details of the review are provided in the iDMC Charter.

Detailed treatment administration instructions are provided in the MODUL Treatment Administration Guide. Guidelines for dosage modification and treatment interruption or discontinuation of study maintenance treatment are provided in Section 5.1.3.

4.3.2.2.3 *Experimental Arm Cohort 2*

Treatment in the experimental arm of Cohort 2 should be administered as follows:

Fluoropyrimidine (5-FU/LV or capecitabine): 1,600 – 2,400 mg/m^2 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/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.

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: 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. Guidelines for appropriate infusion rate adjustments are provided in the current Atezolizumab Investigator's Brochure.

Detailed treatment administration instructions are provided in the MODUL Treatment Administration Guide. Guidelines for dosage modification and treatment interruption or discontinuation of study maintenance treatment are provided in Section 5.1.3.

4.3.2.2.4 *Experimental Arm Cohort 3*

Capecitabine, trastuzumab and pertuzumab should be administered in the experimental arm of Cohort 3 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 to 14 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.

Detailed treatment administration instructions are provided in the MODUL Treatment Administration Guide. Guidelines for dosage modification and treatment interruption or discontinuation of study maintenance treatment are provided in Section 5.1.3.

4.3.2.2.5 *Experimental Arm Cohort 4*

Treatment in the experimental arm of Cohort 4 should be administered as follows:

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 Table 3 in 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.

Detailed treatment administration instructions are provided in the MODUL Treatment Administration Guide. Guidelines for dosage modification and treatment interruption or discontinuation of study maintenance treatment are provided in Section 5.1.3.

4.3.2.3 *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.

4.3.3 Study Treatment Compliance

A Drug Dispensing Log will be maintained for all study treatments and must be kept current with the following information:

- the identification of the subject to whom the study medication was dispensed
- the date(s), and quantity of study medication administered or dispensed to the subject.

In addition, patients receiving self-administered oral study medications (i.e. capecitabine, vemurafenib) will be asked to record each study treatment dose in a daily drug diary which will be collected at regular study visits.

4.3.4 Investigational Medicinal Product Accountability

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

All IMPs required for completion of this study will be provided by the Sponsor where required by local health authority regulations. The study site will acknowledge receipt of IMPs and confirm the shipment condition and content. Any damaged shipments will be replaced.

IMPs will either be disposed of at the study site according to the study site's institutional standard operating procedure or returned to the Sponsor with the appropriate documentation. The site's method of IMP destruction must be agreed to by the Sponsor. The site must obtain written authorization from the Sponsor before any IMP is destroyed, and IMP destruction must be documented on the appropriate form.

Accurate records of all IMPs received at, dispensed from, returned to, and disposed of by the study site should be recorded on the Drug Inventory Log.

4.3.5 Continued Access to Roche Investigational Medicinal Products

The Sponsor will offer continued access to Roche IMPs (atezolizumab, bevacizumab, cobimetinib, pertuzumab, trastuzumab, and vemurafenib) free of charge to eligible patients in accordance with the Roche Global Policy on Continued Access to Investigational Medicinal Product, as outlined below.

A patient will be eligible to receive Roche IMPs (atezolizumab, bevacizumab, cobimetinib, pertuzumab, trastuzumab, or vemurafenib) after completing the study if all of the following conditions are met:

- The patient has a life-threatening or severe medical condition and requires continued Roche IMP treatment for his or her well-being
- There are no appropriate alternative treatments available to the patient
- The patient and his or her doctor comply with and satisfy any legal or regulatory requirements that apply to them

A patient will not be eligible to receive Roche IMPs (atezolizumab, bevacizumab, cobimetinib, pertuzumab, trastuzumab, or vemurafenib) after completing the study if any of the following conditions are met:

- The Roche IMP is commercially marketed in the patient's country and is reasonably accessible to the patient (e.g., is covered by the patient's insurance or wouldn't otherwise create a financial hardship for the patient)
- The Sponsor has discontinued development of the IMP or data suggest that the IMP is not effective for mCRC
- The Sponsor has reasonable safety concerns regarding the IMP as treatment for mCRC
- Provision of the Roche IMP is not permitted under the laws and regulations of the patient's country

The Roche Global Policy on Continued Access to Investigational Medicinal Product is available at:

http://www.roche.com/policy_continued_access_to_investigational_medicines.pdf

4.4 CONCOMITANT THERAPY AND FOOD

Concomitant medication includes any prescription medications or over-the-counter preparations used by a patient during the period 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.

4.4.1 Permitted Therapy

During the study, patients on allowed, ongoing therapies such as oral contraceptives, hormone-replacement therapy, or thyroid replacement therapy should continue their use. Patients should also receive full supportive care as medically warranted (including transfusion of blood products and antibiotics) and in accordance with local standards of oncology care and the Investigator's clinical judgement. These treatment details should be recorded in the eCRF.

During the Induction Treatment Phase, local prescribing information for contraindicated medications and medications to manage study treatment-related AEs should be followed.

Patients who require palliative radiotherapy, liver metastases ablation (during Induction Treatment Phase only) or initiation of bisphosphonates during therapy should be evaluated carefully for possible disease progression before starting these treatments and these treatments must be recorded in the eCRF. Irradiated or ablated lesions will thereafter be evaluable for progression only. See Section 4.4.2.2.2 regarding radiotherapy use in the experimental arm of Cohort 1.

Patients who experience infusion-associated symptoms from study treatment may be treated symptomatically with antipyretics, diphenhydramine and/or other antihistamines according to local standard practice. Serious infusion-associated events manifested by dyspnoea, hypotension, wheezing, bronchospasm, tachycardia, reduced oxygen saturation, or respiratory distress should be managed with supportive therapies as clinically indicated (e.g. supplemental oxygen and β_2-adrenergic agonists).

Low-dose oral coumarin-derived anticoagulants, heparin or low-molecular weight heparins and/or clopidogrel (≤ 75 mg/day) are permitted during study only if treatment has started prior to study entry or during the Induction Treatment Phase and the patient isn't experiencing any unstable cardiovascular symptoms. Prophylactic low-dose aspirin (≤ 325 mg/day) is a recommended standard of care in patients at high-risk of an arterial thromboembolic event and is permitted in this study. Patients who experience Grades 1-3 venous thromboembolic events during study treatment are permitted to receive full dose anticoagulants and to remain on study medication. INR and aPTT will be assessed at baseline for all patients receiving anticoagulant treatment. INR and aPTT should be monitored during study treatment in these patients, and those initiating anticoagulant therapy during the study according to the local standard of care.

Experimental Arm of Cohort 1 Only

Photosensitivity has been reported in patients treated with vemurafenib in clinical trials. The majority of cases were mild or moderate in severity. All patients randomised to the Experimental Arm Cohort 1 (i.e. receiving vemurafenib) in this study should be advised to avoid sun exposure and wear protective clothing and use sun block and lip balm (minimum of sun protection factor (SPF) 30, re-applied every 2 to 3 hours) during vemurafenib treatment and for at least 5 to 10 days after study drug discontinuation.

Should hypomagnesaemia occur in a patient receiving cetuximab, magnesium supplementation should be provided. No dose adjustment is required, however careful monitoring should continue.

4.4.2 Therapy Permitted with Caution

4.4.2.1 *Induction Treatment Phase*

During the Induction Treatment Phase, local prescribing information for contraindicated medications and medications to manage study treatment-related AEs should be followed.

4.4.2.2 *Maintenance Treatment Phase*

4.4.2.2.1 *Control Arms*

All Cohorts

Anticoagulants

There is no information on the safety profile of bevacizumab in patients receiving full dose of anticoagulants for the treatment of thromboembolism prior to starting bevacizumab treatment, as such patients were excluded from clinical trials (Bevacizumab Investigator's Brochure 2011). Therefore, caution should be exercised before initiating bevacizumab therapy in these patients. Notably, patients who developed venous thrombosis while receiving bevacizumab therapy in clinical trials did not appear to have an increased rate of ≥ Grade 3 events when treated with full dose of warfarin and bevacizumab concomitantly.

Altered coagulation parameters and/or bleeding have been reported in patients taking capecitabine concomitantly with coumarin-derivative anticoagulants such as warfarin and phenprocoumon. These reactions occurred within several days and up to several months after initiating capecitabine therapy and, in a few cases, within 1 month after stopping capecitabine. In a clinical pharmacokinetic interaction study, after a single 20 mg dose of warfarin, capecitabine treatment increased the area under the curve (AUC) of S-warfarin by 57% with a 91% increase in INR value. Since metabolism of R-warfarin was not affected, these results indicate that capecitabine down-regulates isozyme 2C9, but has no effect on isozymes 1A2 and 3A4 (Capecitabine Summary of Product Characteristics 2010). INR and aPTT will be assessed at baseline for all patients receiving anticoagulant treatment. INR and aPTT should be monitored during study treatment in these patients, and those initiating anticoagulant therapy during the study according to the local standard of care.

Phenytoin

Increased phenytoin plasma concentrations have been reported during concomitant use of capecitabine with phenytoin (Capecitabine Summary of Product Characteristics 2010). Formal drug-drug interaction studies with phenytoin have not been conducted. Patients taking phenytoin concomitantly with capecitabine should be regularly monitored for increased phenytoin plasma concentrations and associated clinical symptoms.

4.4.2.2.2 *Experimental Arm Cohort 1*

CYP3A4 substrates

In a Phase I study of CYP450 metabolism conducted in melanoma patients (study NP22676; Vemurafenib Investigator's Brochure 2014), vemurafenib induced CYP3A4 activity by approximately two-fold. Thus, medications predominantly metabolised via CYP3A4 may have decreased exposure when administered concomitantly with vemurafenib.

The clinical significance of this observation depends on the therapeutic index of the specific CYP3A4 substrate administered concomitantly with vemurafenib. If CYP3A4 substrates must be co-administered with vemurafenib, the Investigator should monitor the signs of reduced benefit of CYP3A4 drugs due to potential decrease in their plasma concentration.

Doses of the concomitant CYP3A4 drug, but not the dose of vemurafenib, may be adjusted as necessary to alleviate the impact of drug interaction.

Appendix 13 includes a non-exhaustive list of CYP3A4 substrates.

CYP1A2 substrates

In CYP450 metabolism study NP22676 (Vemurafenib Investigator's Brochure 2014), vemurafenib inhibited CYP1A2 in metastatic melanoma patients by approximately three-fold. Similarly, other pharmacokinetic assessments have demonstrated drug-drug interactions between vemurafenib and caffeine that are consistent with CYP1A2 inhibition. Thus, medications predominantly metabolised via CYP1A2 may have increased exposure when administered concomitantly with vemurafenib.

The clinical significance of these observations depends on the therapeutic index of the specific CYP1A2 substrate administered with vemurafenib. The Investigator should assess the safety risk associated with a potential increase in plasma concentrations of any concomitantly administered CYP1A2 metabolised drug. If there is a concern, doses of the concomitant CYP1A2 drug, but not the dose of vemurafenib, may be adjusted as necessary to alleviate the impact of drug interaction.

Appendix 13 includes a non-exhaustive list of CYP1A2 substrates.

CYP2C9 substrates including warfarin

Vemurafenib exhibited a strong signal for CYP2C9 inhibition *in vitro* studies in human hepatic microsomes. This *in vitro* inhibition did not appear to be as significant in the NP22676 study of CYP450 metabolism in melanoma patients where the observed increase in warfarin exposure was not significant. However, warfarin has a narrow therapeutic index and the potential increase in warfarin exposure, in addition to the *in vitro* evidence of CYP2C9 inhibition and the inherent propensity for coagulation disorders in patients with malignant disease, indicate the necessity for caution when vemurafenib is co-administered with warfarin. The same considerations are true of other medications with narrow therapeutic indices that are metabolised primarily by CYP2C9.

Appendix 13 includes a non-exhaustive list of CYP2C9 substrates.

Drugs that may cause QTc prolongation or cardiac arrhythmia

Due to a potential preclinical signal for human Ether-à-go-go Related Gene (hERG) ion channel blockade by vemurafenib *in vitro,* as well as clinical evidence that vemurafenib may prolong QTc interval, caution should be taken when vemurafenib is co-administered with drugs that cause QTc prolongation or cardiac arrhythmia, or when there is a pre-existing cardiac disease or electrocardiogram (ECG) abnormality that may indicate a predisposition to cardiac dysrhythmia.

Investigators should closely monitor patients who are on medications and/or supplements that may affect QT interval prolongation. Such agents include, but are not limited to, terfenadine, quinidine, procainamide, disopyramide, sotalol, probucol, bepridil, haloperidol, risperidone, indapamide, and other drugs with potential to cause disrythmia. Alternative treatment options for medications known to affect QT interval should be discussed with each

patient prior to their inclusion into this study. Please refer to QT Drug List by Risk Groups (http://www.azcert.org) for additional information and Appendix 12.

Radiation

Vemurafenib should be used with caution when given concomitantly or sequentially with radiation treatment. Cases of radiation recall and radiation sensitization have been reported in patients treated with radiation either prior, during, or subsequent to vemurafenib treatment. Refer to the current Vemurafenib Investigator's Brochure for further details of these events. Radiotherapy is permitted only for pain control during the study treatment periods.

4.4.2.2.3 *Experimental Arm Cohort 2*

Anticoagulants

There is no information on the safety profile of bevacizumab in patients receiving full dose of anticoagulants for the treatment of thromboembolism prior to starting bevacizumab treatment, as such patients were excluded from clinical trials (Bevacizumab Investigator's Brochure 2011). Therefore, caution should be exercised before initiating bevacizumab therapy in these patients. Notably, patients who developed venous thrombosis while receiving bevacizumab therapy in clinical trials did not appear to have an increased rate of ≥ Grade 3 events when treated with full dose of warfarin and bevacizumab concomitantly.

Altered coagulation parameters and/or bleeding have been reported in patients taking capecitabine concomitantly with coumarin-derivative anticoagulants such as warfarin and phenprocoumon. These reactions occurred within several days and up to several months after initiating capecitabine therapy and, in a few cases, within 1 month after stopping capecitabine. In a clinical pharmacokinetic interaction study, after a single 20 mg dose of warfarin, capecitabine treatment increased the (AUC of S-warfarin by 57% with a 91% increase in INR value. Since metabolism of R-warfarin was not affected, these results indicate that capecitabine down-regulates isozyme 2C9, but has no effect on isozymes 1A2 and 3A4 (Capecitabine Summary of Product Characteristics 2010). INR and aPTT will be assessed at baseline for all patients receiving anticoagulant treatment. INR and aPTT should be monitored during study treatment in these patients, and those initiating anticoagulant therapy during the study according to the local standard of care.

Phenytoin

Increased phenytoin plasma concentrations have been reported during concomitant use of capecitabine with phenytoin (Capecitabine Summary of Product Characteristics 2010). Formal drug-drug interaction studies with phenytoin have not been conducted. Patients taking phenytoin concomitantly with capecitabine should be regularly monitored for increased phenytoin plasma concentrations and associated clinical symptoms.

Corticosteroids and TNF Inhibitors

Systemic corticosteroids and TNF-α inhibitors may attenuate the potential beneficial effects of atezolizumab, therefore alternatives in Cohort 2 patients randomised to the experimental arm should be considered where feasible. If there are no feasible alternatives, systemic corticosteroids and TNF-α inhibitors may be administered at the discretion of the treating physician except in the case of patients for whom CT scans with contrast are contraindicated

(i.e. patients with contrast allergy or impaired renal clearance). Treatment with oral or parenteral steroids treatment may be warranted in the event of immune-related adverse effects, colitis, rash, pruritus or pulmonary toxicity occurring with atezolizumab treatment. See the current Atezolizumab Investigator's Brochure further information. The use if inhaled corticosteroids for chronic obstructive pulmonary disease (≤ 10 mg oral prednisone or equivalent), mineralocorticoids (e.g. fludrocortisone) for patients with orthostatic hypertension, and megastrol as an appetite stimulant are allowed.

4.4.2.2.4 *Experimental Arm Cohort 3*

Anticoagulants

Altered coagulation parameters and/or bleeding have been reported in patients taking capecitabine concomitantly with coumarin-derivative anticoagulants such as warfarin and phenprocoumon. These reactions occurred within several days and up to several months after initiating capecitabine therapy and, in a few cases, within 1 month after stopping capecitabine. In a clinical pharmacokinetic interaction study, after a single 20 mg dose of warfarin, capecitabine treatment increased the AUC of S-warfarin by 57% with a 91% increase in INR value. Since metabolism of R-warfarin was not affected, these results indicate that capecitabine down-regulates isozyme 2C9, but has no effect on isozymes 1A2 and 3A4 (Capecitabine Summary of Product Characteristics 2010). INR and aPTT will be assessed at baseline for all patients receiving anticoagulant treatment. INR and aPTT should be monitored during study treatment in these patients, and those initiating anticoagulant therapy during the study according to the local standard of care.

Phenytoin

Increased phenytoin plasma concentrations have been reported during concomitant use of capecitabine with phenytoin (Capecitabine Summary of Product Characteristics 2010). Formal drug-drug interaction studies with phenytoin have not been conducted. Patients taking phenytoin concomitantly with capecitabine should be regularly monitored for increased phenytoin plasma concentrations and associated clinical symptoms.

4.4.2.2.5 *Experimental Arm Cohort 4*

Corticosteroids and TNF Inhibitors

Systemic corticosteroids and TNF-α inhibitors may attenuate the potential beneficial effects of atezolizumab, therefore alternatives in Cohort 4 patients randomised to the experimental arm should be considered where feasible. If there are no feasible alternatives, systemic corticosteroids and TNF-α inhibitors may be administered at the discretion of the treating physician except in the case of patients for whom CT scans with contrast are contraindicated (i.e. patients with contrast allergy or impaired renal clearance). Treatment with oral or parenteral steroids treatment may be warranted in the event of immune-related adverse effects, colitis, rash, pruritus or pulmonary toxicity occurring with atezolizumab treatment. See the current Atezolizumab Investigator's Brochure further information. The use if inhaled corticosteroids for chronic obstructive pulmonary disease (≤ 10 mg oral prednisone or equivalent), mineralocorticoids (e.g. fludrocortisone) and megastrol as an appetite stimulant are allowed.

4.4.3 Prohibited Therapy

The use of any other experimental medications during the study is prohibited.

4.4.3.1 *Induction Treatment Phase*

No anti-cancer therapy other than the protocol specified induction regimen is permitted during the study with the following exceptions:

- local ablation for liver metastases 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

Patients who require local ablation or radiotherapy for pain control should be assessed for evidence of progression first.

During the Induction Treatment Phase, local prescribing information for contraindicated medications and medications to manage study treatment-related AEs should be followed.

4.4.3.2 *Maintenance Treatment Phase*

4.4.3.2.1 *All Cohorts*

With the exception of radiotherapy for pain control, no anti-cancer treatments other than the protocol-specified maintenance regimens are allowed during the Maintenance Treatment Phase. Patients who require radiotherapy for pain control should be assessed for evidence of progression first.

Low-dose oral coumarin-derived anticoagulants, heparin or low-molecular weight heparins and/or clopidogrel (≤ 75 mg/day) are prohibited during the Maintenance Treatment Phase unless treatment started prior to maintenance treatment (i.e. prior to study entry or during the Induction Treatment Phase) and the patient is not experiencing any unstable cardiovascular symptoms.

During treatment with 5-FU/LV, capecitabine and/or bevacizumab, local prescribing information for contraindicated medications should be followed.

Allopurinol

Interactions with allopurinol have been observed for 5-FU with possible decreased efficacy of 5-FU. Concomitant use of allopurinol with capecitabine or 5-FU should be avoided.

Antivirals and Antiprotozoals

Capecitabine or 5-FU should not be administered together with the antiviral drug sorivudine or its chemically-related analogues, such as brivudine. A clinically significant drug-drug interaction between sorivudine and 5-FU, resulting from the inhibition of dihydropyrimidine dehydrogenase by sorivudine, has been described in the literature. This interaction, which leads to increased fluoropyrimidine toxicity, is potentially fatal.

Laxatives

The use of drugs with laxative properties should be avoided.

4.4.3.2.2 *Experimental Arm Cohort 1*

There are no additional therapies specifically prohibited during treatment in the experimental arm of Cohort 1.

4.4.3.2.3 *Experimental Arm Cohort 2*

Patients receiving atezolizumab should not receive any of the following during the study Maintenance Phase:

- traditional herbal medicines; herbal therapies intended for the treatment of cancer are prohibited. Herbal therapies are not fully studied and their pharmacokinetics, safety profiles, and potential drug-drug interactions are generally unknown therefore their concomitant use is not recommended. However, herbal therapies not intended for the treatment of cancer may allowed at the discretion of the Investigator, provided that there are no known interactions with any study treatment.
- RANKL inhibitor (denosumab)
- immunomodulatory agents, including but not limited to interferons or interleukin-2; these agents could potentially increase the risk for autoimmune conditions when received in combination with atezolizumab treatment
- Steroids for premedication of patients for whom CT scans with contrast are contraindicated (i.e. patients with contrast allergy or impaired renal clearance). In such patients, non-contrast CT of the chest and non-contrast CT or MRIs of the abdomen and pelvis should be performed.
- live, attenuated vaccines (e.g. live attenuated influenza virus [FluMist®]) including for 5 months after last atezolizumab dose. Inactivated influenza vaccines are allowed.

Initiation or increased dose of granulocyte colony-stimulating factors (e.g., granulocyte colony-stimulating factor, granulocyte/macrophage colony-stimulating factor, and/or pegfilgrastim) is prohibited.

In addition, patients treated with atezolizumab should not receive other immunomodulatory agents for 10 weeks after study treatment discontinuation.

4.4.3.2.4 *Experimental Arm Cohort 3*

Folinic Acid

Folinic acid has an effect on the pharmacodynamics of capecitabine, and its toxicity may be enhanced by folinic acid and should be avoided.

Allopurinol

Interactions with allopurinol have been observed for 5-FU with possible decreased efficacy of 5-FU. Concomitant use of allopurinol with capecitabine should be avoided.

Antivirals and Antiprotozoals

Capecitabine should not be administered together with the antiviral drug sorivudine or its chemically-related analogues, such as brivudine. A clinically significant drug-drug interaction between sorivudine and 5-FU, resulting from the inhibition of dihydropyrimidine

dehydrogenase by sorivudine, has been described in the literature. This interaction, which leads to increased fluoropyrimidine toxicity, is potentially fatal.

4.4.3.2.5 *Experimental Arm Cohort 4*

Patients receiving atezolizumab should not receive any of the following during the study Maintenance Phase:

- traditional herbal medicines; herbal therapies intended for the treatment of cancer are prohibited. Herbal therapies are not fully studied and their pharmacokinetics, safety profiles, and potential drug-drug interactions are generally unknown therefore their concomitant use is not recommended. However, herbal therapies not intended for the treatment of cancer may allowed at the discretion of the Investigator, provided that there are no known interactions with any study treatment.
- RANKL inhibitor (denosumab)
- immunomodulatory agents, including but not limited to interferons or interleukin-2; these agents could potentially increase the risk for autoimmune conditions when received in combination with atezolizumab treatment
- Steroids for premedication of patients for whom CT scans with contrast are contraindicated (i.e. patients with contrast allergy or impaired renal clearance). In such patients, non-contrast CT of the chest and non-contrast CT or MRIs of the abdomen and pelvis should be performed.
- live, attenuated vaccines (e.g. live attenuated influenza virus [FluMist®]) including for 5 months after last atezolizumab dose. Inactivated influenza vaccines are allowed.

Initiation or increased dose of granulocyte colony-stimulating factors (e.g., granulocyte colony-stimulating factor, granulocyte/macrophage colony-stimulating factor, and/or pegfilgrastim) is prohibited.

In addition, patients treated with atezolizumab should not receive other immunomodulatory agents for 10 weeks after study treatment discontinuation.

Patients receiving cobimetinib should not receive any of the following during the Maintenance Treatment Phase:

- strong and moderate inhibitors of CYP3A (e.g. clarithromycin, grapefruit juice, itraconazole, ketoconazole, posaconazole, telithromycin, and voriconazole) should be avoided as cobimetinib is a sensitive substrate of CYP3A and exposures will be increased in presence of these agents (approximately 7-fold increase in presence of itraconazole in healthy subjects).
- strong and moderate CYP3A inducers (e.g. rifampin, phenytoin, carbamazepine, phenobarbital, and St. John's wort) as they increase the metabolism of cobimetinib. Strong inducers of CYP3A4 should be avoided, or selection of an alternate concomitant medicinal product, with no or minimal potential to induce CYP3A4 should be considered.

4.4.4 Food

Other than the two exceptions listed below, there are no other food-related study requirements or recommendations (including no prohibited foods).

Capecitabine

All patients receiving capecitabine as part of their maintenance treatment regimen in any cohort should take each dose no later than 30 minutes after meals. Administration of capecitabine with food decreases the rate of capecitabine absorption. All current safety and efficacy data for capecitabine are based upon administration with food.

Vemurafenib

All patients receiving vemurafenib as part of their maintenance treatment regimen should take each dose in the same manner with respect to meals i.e. all doses with a meal or all doses without a meal.

4.5 STUDY ASSESSMENTS

Please see Appendices 1 to 5 for the Schedule of Assessments performed during the study.

4.5.1 Induction Treatment Phase

4.5.1.1 *Informed Consent Forms and Screening Log*

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. Informed Consent Forms for enrolled patients and for patients who are not subsequently enrolled will be maintained at the study site.

The “All Cohort” eligibility criteria are evaluated prior to initiating the first cycle of study treatment during the Induction Treatment Phase. Patients who do not have archival primary tumour tissue available for shipping to the Sponsor’s designated laboratory during the Screening Phase should not undergo any screening procedures. Informed consent must be obtained prior to shipping the tumour sample to the designated laboratory. The Investigator will maintain a screening log to record details of all patients screened and to confirm eligibility or record reasons for screening failure, as applicable.

4.5.1.2 *Demographic Data and Medical History*

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.

The location of the primary tumour defined as either right colon (up to the splenic flexure) or left colon (below the splenic flexure including the rectum) will also be recorded.

Demographic data will include age, sex, and self-reported race/ethnicity (where permitted by federal regulations).

4.5.1.3 *Vital Signs*

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

4.5.1.4 *Physical Examinations*

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 recorded as AEs is appropriate.

4.5.1.5 *ECOG Performance Status*

See Appendix 8.

4.5.1.6 *Concomitant Medications*

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 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.

4.5.1.7 *Laboratory Samples*

Samples for the following laboratory tests will be sent to the study site's local laboratory for analysis:

- Haematology (haemoglobin, haematocrit, platelet count, red blood cell count, white blood cell count, and differential)
- Blood chemistry (ALT, AST, alkaline phosphatase, total bilirubin, total protein, albumin, blood urea nitrogen or urea, lactate dehydrogenase (LDH), creatinine, glucose, calcium, phosphorus, sodium, potassium, chloride and bicarbonate)
- Pregnancy Test (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
- Coagulation (INR and aPTT; only for patients receiving anticoagulants while on protocol-specified treatment)

- 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

Test results must be available to the Investigator prior to start of each treatment cycle. Clinical laboratory results constituting a clinically significant AE should be recorded as such.

4.5.1.8 *Whole Blood and Plasma Samples*

Whole blood and plasma samples will be collected from all study patients for exploratory biomarker analyses. If genomic (inheritable) analysis is not allowed per local regulations, only plasma testing (non-inheritable) will be conducted. All samples will be sent to a Central Laboratory. Samples during treatment should be taken within 48 hours before study treatment administration on Day 1 of cycle, unless otherwise specified (see Appendix 17 and the Laboratory Manual).

Data arising from clinical genotyping (inheritable) conducted on whole blood samples will be subject to the confidentiality standards described in Section 4.5.3.4.

4.5.1.9 *Tumour and Response Evaluations*

Tumour assessments will include radiology, chest and abdominal computed tomography (CT) or magnetic resonance imaging (MRI), and other scans to document all sites of disease. Upper abdomen imaging should be included at Baseline. If there is a clinical suspicion of CNS metastases during screening, at Baseline or at any time during the study, a CT or MRI scan of the brain must be conducted. 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.

Response will be determined by the Investigator according to RECIST 1.1.

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.

4.5.1.10 *Archival Tumour Tissue*

For all patients, the assessment of biomarkers for cohort assignment will be based on archival tumour FFPET block from the primary tumour obtained at the time of initial diagnosis (see Appendix 17). If the tumour block is not available, ≥ 20 slides cut from the primary tumour sample will be accepted as an alternative. After the patient has provided informed consent to participate in the study but before they are enrolled, their sample (block or slides) must be shipped to the designated laboratory with receipt of shipment confirmed by the laboratory. An associated pathology report must also be sent with all samples.

The remainder of the block will be returned to the study site.

Only biomarker results from the designated laboratory which will be available during the Induction Treatment Phase will guide treatment allocation for the Maintenance Treatment Phase. For testing details please refer to Appendix 17.

4.5.1.11 *Optional Metastatic Tumour Sample*

Prior to May 2018, a core biopsy of metastatic tumour was collected from all patients who provided specific consent to provide this optional sample. Biopsies already done as part of routine practice within two months of the 28-day Screening Phase were acceptable. These samples will be included in the exploratory biomarker analyses as described in Appendix 17.

4.5.1.12 *Stool Sample-Supplemental Biomarker Program Participants Only*

Prior to May 2018, stool samples were collected from Supplemental Biomarker Program participants for exploratory biomarker analyses as described in Appendix 17. The Supplemental Biomarker Program was closed in May 2018.

4.5.2 Maintenance Treatment Phase

4.5.2.1 *Cohort-Specific Informed Consent*

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.

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.

4.5.2.2 *Confirmation of Cohort-Specific Eligibility*

All Cohorts

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 primary tumour tissue from initial diagnosis are known. Biomarker results will be available during the Induction Treatment Phase. 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. Patients should start the Maintenance Treatment Phase within 3 weeks of completing induction treatment (based on the last day of the last cycle of induction treatment).

4.5.2.3 *Screening Log*

The Investigator will update the screening log to record details of all patients who complete the Induction Treatment Phase and to confirm continued eligibility according to the cohort-specific exclusion criteria or record reasons for ineligibility, as applicable.

4.5.2.4 *Randomization*

All Cohorts

Each cohort will consist of an experimental treatment arm and a control arm. Randomization will be on a 2:1 (experimental:control) basis to either the experimental or control arm within each cohort (see Section 4.2).

4.5.2.5 *Vital Signs*

All Cohorts

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

4.5.2.6 *Physical Examinations*

All Cohorts

Physical examinations will be symptom-directed, and will include changes from Baseline (pre-induction). New or worsened clinically significant abnormalities should be recorded as AEs on the Adverse Event eCRF.

4.5.2.7 *ECOG Performance Status*

All Cohorts

See Appendix 8.

4.5.2.8 *Concomitant Medications*

All Cohorts

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.

4.5.2.9 *Laboratory Samples*

All Cohorts

Samples for the following laboratory tests will be sent to the study site's local laboratory for analysis:

- Haematology (haemoglobin, haematocrit, platelet count, red blood cell count, white blood cell count, and differential)
- Blood chemistry (ALT, AST, alkaline phosphatase, total bilirubin, total protein, albumin, blood urea nitrogen or urea, LDH, creatinine, glucose, calcium, phosphorus, sodium, potassium, chloride, and bicarbonate).
- Pregnancy Test (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

- Coagulation (INR and aPTT; only for patients receiving anticoagulants while on protocol-specified treatment)
- 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

Test results must be available to the Investigator prior to start of each treatment cycle. Laboratory results constituting a clinically significant AE should be recorded as such.

4.5.2.9.1 *Experimental Treatment Arm Cohort 1*

- Magnesium, amylase and lipase (experimental treatment arm only)

4.5.2.9.2 *Cohort 2*

The following tuberculosis (TB) and virology laboratory tests are required for assessment of eligibility for Cohort 2 and will be sent to the study site's local laboratory for analysis:

- TB test
- HIV testing (performed in accordance with national and/or institutional guidelines)
- HBV serology (HBsAg, anti-HBc)
- HCV serology (anti-HCV)

4.5.2.9.3 *Experimental Treatment Arm Cohort 2*

Thyroid function testing will be conducted at the study site’s local laboratory.

- Thyroid function testing (thyroid-stimulating hormone [TSH], free or total triiodothyronine [T3], free or total thyroxine [T4]) (experimental treatment arm only)

4.5.2.9.4 *Cohort 3*

The following virology laboratory tests are required for assessment of eligibility for Cohort 3 and will be sent to the study site's local laboratory for analysis:

- HIV testing (performed in accordance with national and/or institutional guidelines)
- HBV serology (HBsAg, anti-HBc)
- HCV serology (anti-HCV)

4.5.2.9.5 *Cohort 4*

The following TB and virology laboratory tests are required for assessment of eligibility for Cohort 4 and will be sent to the study site's local laboratory for analysis:

- TB test
- HIV testing (performed in accordance with national and/or institutional guidelines)
- HBV serology (HBsAg, anti-HBc)
- HCV serology (anti-HCV)

4.5.2.9.6 *Experimental Treatment Arm Cohort 4*

- Thyroid function testing including TSH, free or total T3, and free or total T4 conducted at the study site's local laboratory (experimental treatment arm only)
- Magnesium, amylase, creatine phosphokinase (CPK), lipase (experimental treatment arm only)

4.5.2.10 *Plasma Samples*

All Cohorts

Plasma samples will be collected from all study patients for exploratory biomarker analyses.

All samples will be sent to a Central Laboratory. Samples during treatment should be taken within 48 hours before study treatment administration on Day 1 of cycle, unless otherwise specified (see Appendix 17 and the Laboratory Manual).

4.5.2.11 *Tumour and Stool Samples- Supplemental Biomarker Program Participants Only*

Prior to May 2018, metastatic tumour samples (if clinically feasible) and stool samples were collected from all Supplemental Biomarker Program participants for exploratory analyses as described in Appendix 17. Since May 2018, the Supplemental Biomarker Program is closed and no further samples are being collected.

4.5.2.12 *Tumour and Response Evaluations*

All Cohorts

Up to and including May 31, 2019, tumour 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 must be conducted at any time there is a clinical suspicion of CNS metastases. Tumour assessments will be conducted every eight weeks with disease status during maintenance treatment determined based on comparison with the tumour assessment done at the end of induction treatment according to RECIST 1.1 (all treatment arms in all cohorts) and mRECIST (experimental arms of Cohorts 2 and 4 only) as described below.

After May 31, 2019, disease status will not be documented for the study and tumour assessments may be conducted according to 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 conducted every eight weeks until progression, or May 31, 2019, whichever comes first.

4.5.2.12.1 *Cohorts 1 and 3*

For patients in Cohorts 1 and 3 disease status will be assessed by the Investigator according to RECIST 1.1 (see Appendix 10) based on comparison with the tumour assessment conducted at the end of induction treatment.

Target lesions identified at start of induction treatment will be considered target lesions for the entire study period regardless of decreases below sizes considered measurable by

RECIST 1.1 (e.g. < 10 mm by CT scan) during or following induction treatment. As such, all target lesions, including those that decrease below the minimum measurable size, will continue to be followed through the Maintenance Treatment Phase and until disease progression. An increase in size of any target lesion that had previously decreased to below measurability (per RECIST 1.1) to the minimum measurable size or greater will be considered indicative of disease progression.

4.5.2.12.2 *Cohorts 2 and 4*

For all patients in Cohorts 2 and 4, disease status will be assessed by the Investigator according to RECIST 1.1 (see Appendix 10) based on comparison with the tumour assessments done at the end of induction treatment.

For patients in the experimental arms of Cohorts 2 and 4, disease status will additionally be assessed for the purpose of treatment management and exploratory efficacy analysis by the Investigator according to mRECIST (see Appendix 11) based on comparison with the tumour assessment done at the end of induction treatment.

Target lesions identified at start of induction treatment will be considered target lesions for the entire study period regardless of decreases below sizes considered measurable by RECIST 1.1 (e.g. < 10 mm by CT scan) during or following induction treatment. As such, all target lesions, including those that decrease below the minimum measurable size, will continue to be followed through the Maintenance Treatment Phase and until disease progression. An increase in size of any target lesion that had previously decreased to below measurability (per RECIST 1.1) to the minimum measurable size or greater will be considered indicative of disease progression.

4.5.2.13 *Additional Assessments for Cohort 1*

All patients will require a 12-lead ECG to determine cohort eligibility. Cohort 1 experimental arm patients only will require subsequent ECGs. ECGs will include measurements includes heart rate, PR interval, QRS duration, and QT and QTc intervals.

4.5.2.14 *Additional Assessments for Experimental Arm Cohort 1*

The following assessments only apply to patients randomised to the experimental treatment arm of Cohort 1.

Head and neck assessment for SCC

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.

Chest CT assessment for SCC

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.

Dermatology evaluation

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

Anal and pelvic exam

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.

12-lead Electrocardiograms

See Section 4.5.2.13.

4.5.2.15 *Additional Assessment for Experimental Arm Cohort 2*

Blood oxygen saturation will be measured only in patients randomised to the experimental treatment arm of Cohort 2. Blood oxygen saturation will be measured by pulse oximetry.

4.5.2.16 *Additional Assessment for Cohort 3*

Left ventricular ejection fraction

All Cohort 3 patients will require evaluation of LVEF to determine cohort eligibility. Cohort 3 experimental arm patients only will require subsequent LVEF evaluations.

Evaluation of LVEF must be performed by the same method (ECHO or MUGA) for each patient. It is strongly encouraged that the same laboratory and operator perform ECHO/MUGA scans for each individual patient. Investigators must be aware of local institution regulations regarding repeat MUGA scans. The repeat administration of radioisotopes is limited in some nuclear medicine laboratories, and some patients in this study could require monitoring on four or more occasions.

4.5.2.17 *Additional Assessments for Cohort 4*

Left ventricular ejection fraction

All Cohort 4 patients will require evaluation of LVEF to determine cohort eligibility. Cohort 4 experimental arm patients only will require subsequent LVEF evaluations.

Evaluation of LVEF must be performed by the same method (ECHO or MUGA) for each patient. It is strongly encouraged that the same laboratory and operator perform ECHO/MUGA scans for each individual patient. Investigators must be aware of local institution regulations regarding repeat MUGA scans. The repeat administration of radioisotopes is limited in some nuclear medicine laboratories, and some patients in this study could require monitoring on four or more occasions.

Ophthalmology Examination

All Cohort 4 patients will require an ophthalmology exam to determine cohort eligibility. Cohort 4 experimental arm patients only will require subsequent ophthalmology exams.

Ophthalmologic examination must be performed by a qualified ophthalmologist to evaluate potential risk factors for, or evidence of, central serous retinopathy or retinal vein occlusion. The exam will include visual acuity testing, intraocular pressure measurements by tonometry, slit-lamp ophthalmoscopy, indirect ophthalmoscopy and spectral−domain optical coherence tomography. Spectral domain optical coherence tomography, if not available, may be substituted with time-domain optical coherence tomography.

4.5.2.18 *Additional Assessment for Experimental Arm Cohort 4*

Blood oxygen saturation will be measured only in patients randomised to the experimental treatment arm of Cohort 4. Blood oxygen saturation will be measured by pulse oximetry.

4.5.3 Samples for Roche Clinical Repository

4.5.3.1 *Overview of the Roche Clinical Repository*

The Roche Clinical Repository (RCR) is a centrally administered group of facilities used for the long-term storage of human biologic specimens, including body fluids, solid tissues, and derivatives thereof (e.g., DNA, RNA, proteins, peptides). The collection and analysis of RCR specimens will facilitate the rational design of new pharmaceutical agents and the development of diagnostic tests, which may allow for individualised drug therapy for patients in the future.

RCR specimens will be used to achieve the following objectives:

- To further study the association of biomarkers with efficacy, adverse events, or disease progression
- To increase knowledge and understanding of disease biology
- To study drug response, including drug effects and the processes of drug absorption and disposition
- To develop biomarker or diagnostic assays and establish the performance characteristics of these assays

4.5.3.2 *Approval by the Institutional Review Board or Ethics Committee*

Collection and submission of biological samples to the RCR is contingent upon the review and approval of the exploratory research and the RCR portion of the Informed Consent Form by each site's Institutional Review Board or Ethics Committee (IRB/EC) and, if applicable, an appropriate regulatory body. If a site has not been granted approval for RCR sampling, this section of the protocol (Section 4.5.3) will not be applicable at that site.

4.5.3.3 *Sample Collection*

All blood, tissue and stool samples collected in this study and derivatives thereof will be destroyed no later than 5 years after the date of final closure of the clinical study database. However, patients who enrol in this study will have the option, at the time of enrolment, to

consent to RCR sampling to allow the remainder of these samples and derivatives thereof to be stored and used for exploratory research. If the patient provides consent for this optional exploratory research, these samples will be sent to and stored in the RCR and will be destroyed no later than 15 years after the date of final closure of the clinical study database.

These specimens will be used for research purposes to identify biomarkers that are predictive of response to study treatment (in terms of dose, safety, and tolerability) and will help to better understand the pathogenesis, course, and outcome of CRC. Specimens for non-inherited biomarker discovery will be single coded like any other clinical sample (labelled and tracked using the patient's study identification number (see Section 8.4). Genetic specimens will undergo additional processes to maintain confidentiality upon receipt by the RCR (see Section 4.5.3.4).

Residual tumour tissue, whole blood, plasma and stool samples and derivatives thereof collected throughout the study for purposes of biomarker assessment (see Section 2.3 and Schedule of Assessments listed in Appendices 1 to 5 and Appendix 17) will be collected and stored for research purposes, including:

- Tissue slides and blocks. These include core biopsies of metastases (including those collected at Baseline from all patients and those collected at completion of induction and at disease progression from patients participating in the Supplemental Biomarker Program). Archival tumour tissue blocks from the initial diagnosis will be returned to the site.
- Whole blood samples collected at Baseline (unless genomic analysis not allowed per federal regulations)
- Plasma samples taken during the Induction Treatment Phase, Maintenance Treatment Phase, at time of progressive disease and during post-study follow-up
- Stool samples taken at baseline, post-induction (but prior to start of maintenance treatment) and at study discontinuation from patients participating in the Supplemental Biomarker Program

The specimens in the RCR will be made available for future biomarker research toward further understanding of study treatment, CRC and related diseases, adverse events and toward development of potential associated diagnostic assays. The implementation and use of the RCR specimens is governed by the RCR policy to ensure the appropriate use of the RCR specimens.

For all samples, dates of consent and specimen collection should be recorded on the associated RCR page of the eCRF. For sampling procedures, storage conditions, and shipment instructions, see the Laboratory Manual.

4.5.3.4 *Confidentiality*

The dynamic biomarker specimens will be subject to the confidentiality standards described in Section 8.4. The genetic biomarker specimens will undergo additional processes to ensure confidentiality, as described in the section below.

Given the sensitive nature of genetic data, Roche has implemented additional processes to ensure patient confidentiality for RCR specimens collected for genetic research. Upon

receipt by the RCR, specimens for genetic research are "double-coded" by replacing the patient identification number with a new independent number. Data generated from the use of these specimens and all clinical data transferred from the clinical database and considered relevant are also labelled with this same independent number. A "linking key" between the patient identification number and this new independent number is stored in a secure database system. Access to the linking key is restricted to authorised individuals and is monitored by audit trail. Legitimate operational reasons for accessing the linking key are documented in a standard operating procedure. Access to the linking key for any other reason requires written approval from the Pharma Repository Governance Committee and Roche's Legal Department, as applicable.

Data generated from RCR specimens must be available for inspection upon request by representatives of national and local health authorities, and Roche monitors, representatives, and collaborators, as appropriate.

Patient medical information associated with RCR specimens is confidential and may be disclosed to third parties only as permitted by the Informed Consent Form (or separate authorization for use and disclosure of personal health information) signed by the patient (or where applicable, their legally authorised representative) unless permitted or required by law.

Data derived from RCR specimen analysis on individual patients will generally not be provided to study Investigators unless a request for research use is granted. The aggregate results of any research conducted using RCR specimens will be available in accordance with the effective Roche policy on study data publication.

Any inventions and resulting patents, improvements, and/or know-how originating from the use of the RCR data will become and remain the exclusive and unburdened property of Roche, except where agreed otherwise.

4.5.3.5 *Consent to Participate in the Roche Clinical Repository*

The Informed Consent Form administered at study enrolment will contain a separate section that addresses participation in the RCR. The Investigator or authorised designee will explain to each patient the objectives, methods, and potential hazards of participation in the RCR. Patients will be told that they are free to refuse to participate and may withdraw their specimens at any time and for any reason during the storage period. A separate, specific signature will be required to document a patient's agreement to participate in the optional RCR research. Patients who decline to participate will not provide a separate signature.

The Investigator should document whether or not the patient has given consent to participate by completing the RCR Research Sample Informed Consent eCRF.

In the event of an RCR participant's death or loss of competence, the participant's specimens and data will continue to be used as part of the RCR research.

4.5.3.6 *Withdrawal from the Roche Clinical Repository*

Patients who give consent to RCR research have the right to withdraw their specimens from the RCR at any time for any reason. However, if RCR samples have been tested prior to withdrawal of consent, results from those tests will remain as part of the overall research

data. If a patient wishes to withdraw consent to the testing of his or her specimens, the Investigator must inform the Medical Monitor in writing of the patient's wishes through use of the RCR Subject Withdrawal Form and, if the trial is ongoing, must enter the date of withdrawal on the RCR Research Sample Withdrawal of Informed Consent eCRF. If a patient wishes to withdraw consent to the testing of his or her RCR samples after closure of the study site, the investigator must inform the Sponsor by emailing the study number and patient number to the following email address:

global_rcr-withdrawal@roche.com.

A patient's withdrawal from Study MO29112 does not, by itself, constitute withdrawal of specimens from the RCR. Likewise, a patient's withdrawal from the RCR does not constitute withdrawal from Study MO29112.

4.5.3.7 *Monitoring and Oversight*

RCR specimens will be tracked in a manner consistent with Good Clinical Practice by a quality-controlled, auditable, and appropriately validated laboratory information management system, to ensure compliance with data confidentiality as well as adherence to authorised use of specimens as specified in this protocol and in the Informed Consent Form. Roche monitors and auditors will have direct access to appropriate parts of records relating to patient participation in the RCR for the purposes of verifying the data provided to Roche. The site will permit monitoring, audits, IRB/EC review, and health authority inspections by providing direct access to source data and documents related to the RCR samples.

4.6 PATIENT, TREATMENT, STUDY, AND SITE DISCONTINUATION

4.6.1 Patient Discontinuation

Patients have the right to voluntarily withdraw from the study at any time for any reason. In addition, the Investigator has the right to withdraw a patient from the study at any time. Reasons for withdrawal from the study may include, but are not limited to, the following:

- Patient withdrawal of consent at any time
- Any medical condition that the Investigator or Sponsor determines may jeopardise the patient’s safety if he or she continues in the study
- Investigator or Sponsor determines it is in the best interest of the patient

Every effort should be made to obtain information on patients who withdraw from the study. The primary reason for withdrawal from the study should be documented on the appropriate eCRF. However, patients will not be followed for any reason after consent has been withdrawn. Patients who withdraw from the study will not be replaced.

4.6.2 Study Treatment Discontinuation

Patients must discontinue study treatment if they experience any of the following:

- Pregnancy
- Progressive disease per RECIST 1.1 with the following exception:

Patients randomised to the experimental arms of Cohort 2 and 4 (i.e. patients who are receiving atezolizumab), may continue maintenance treatment after the first tumour assessment showing progression according to RECIST 1.1 if 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 will 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, maintenance treatment may be continued 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

- Any medical condition that the Investigator or Sponsor determines may jeopardise the patient's safety if he or she continues on study treatment
- Hold in administration of any drug in any study treatment regimen for > 21 days without Medical Monitor approval to re-initiate treatment and continue in the study
- Initiation of treatment with any other anti-cancer medication
- Are not eligible for any maintenance treatment cohort
- Found to be resectable at the end of the Induction Treatment Phase

The primary reason for study treatment discontinuation should be documented on the appropriate eCRF. Patients who discontinue study treatment prematurely will not be replaced.

4.6.3 Study and Site Discontinuation

The Sponsor has the right to terminate this study at any time. Reasons for terminating the study may include, but are not limited to, the following:

- The incidence or severity of AEs in this or other studies indicates a potential health hazard to patients.
- Patient enrolment is unsatisfactory.

The Sponsor will notify the Investigator if the Sponsor decides to discontinue the study.

The Sponsor has the right to close a site at any time. Reasons for closing a site may include, but are not limited to, the following:

- Excessively slow recruitment
- Poor protocol adherence
- Inaccurate or incomplete data recording

- Non-compliance with the International Conference on Harmonisation (ICH) guideline for Good Clinical Practice
- No study activity (i.e., all patients have completed and all obligations have been fulfilled)

5. ASSESSMENT OF SAFETY

5.1 SAFETY PLAN

Study medications, or the combination of study medications may not be approved and may be currently in clinical development. Thus, the entire safety profile of all study medications (or their combinations) are not known at this time. The safety plan for this study is designed to ensure patient safety and will include specific eligibility criteria and monitoring assessments as detailed below.

Patients will be assessed by prior medical history, vital signs, weight, physical examination, AEs and concomitant medications. A complete medical history (including prior treatments for cancer) will be documented at Screening. A complete physical exam will be performed at Screening, with symptom-directed physical exams performed throughout study treatment. Changes in concomitant medication will be recorded at each study visit. Concomitant medications for treatment of AEs related to study medication will continue to be recorded while the AE is being followed.

Additional safety-related tests and procedures will be performed as required for patients who are receiving specific study medications during the Maintenance Treatment Phase (see Schedule of Assessments, Appendices 2 to 5). When necessary, preplanned safety run-ins will be conducted for experimental combinations (e.g. as required for initial patients treated with the experimental combination of '5-FU/LV + cetuximab + vemurafenib'). Safety data from safety run-in patients will be reviewed by the iDMC to ensure acceptable safety prior to continuing treatment in these patients and prior to exposing further patients to the regimen. Safety run-ins will be indicated in the study protocol. Further details of the safety run-in procedures are provided in the iDMC Charter.

AEs will be monitored and documented continuously during the study and SAEs will also be documented and reported (see Section 5.4.2). All AEs will be graded according to NCI CTCAE version 4.0.

Patients who discontinue study treatment prior to start of maintenance treatment or were treated in the control arm of any maintenance cohort or the experimental arm of Cohort 1 will be followed for new AEs for 28 days following the discontinuation of study treatment. Patients who discontinue maintenance treatment in the experimental arm of Cohorts 2, 3 or 4 will continue be followed for new AEs for 90 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. 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.

5.1.1 Management of Specific Adverse Events

For each IMP administered in the study, guidelines for management of AEs including dose reductions and treatment interruptions are described in the applicable, current Investigator's Brochures and SmPCs and this protocol. Please refer to Section 5.1.2 and Section 5.1.3 where the appropriate resources for AE management guidelines for induction treatment and each maintenance treatment cohort are indicated. It is important to note that any revisions or additions to AE management and dosing recommendations introduced with an Investigator's Brochure update are indicated in the summary of changes at the front of the document.

For each non-IMP administered in the study, guidelines for the management of specific AEs including dose reductions and treatment interruptions are described in the Summary of Product Characteristics.

5.1.2 Induction Treatment Phase

Dose reductions and treatment interruptions of the selected FOLFOX regimen should be based on standard clinical practice and the Investigator's discretion. Please refer to the Summary of Product Characteristics for each FOLFOX treatment component.

If any drug of any study treatment regimen is delayed > 21 days, approval must be obtained from the Medical Monitor prior to re-initiation of treatment. Patients not approved to continue treatment in the study will be discontinued from study treatment and enter the Post-Treatment Follow-up Phase.

Bevacizumab

No dose reduction of bevacizumab is foreseen for an individual patient. Skipped doses or termination of treatment will be based on the observed toxicities specified in the current Investigator's Brochure for bevacizumab. No dose adjustments are allowed except for body weight changes of more than 10%. Missed doses will not be made up for.

5.1.3 Maintenance Treatment Phase

As described in this section, dose modifications or delays may be allowed for certain agents in the maintenance treatment regimens.

If any drug of any study treatment regimen is delayed > 21 days, approval must be obtained from the Medical Monitor prior to re-initiation of treatment. Patients not approved to continue treatment in the study will be discontinued from study treatment and enter the Post-Treatment Follow-up Phase.

5.1.3.1 *Control Arms*

Fluoropyrimidine (5-FU/LV or capecitabine)

Dose reductions and treatment interruptions of the fluoropyrimidine should be based on standard clinical practice and the Investigator's discretion. Please refer to the Summary of Product Characteristics.

Bevacizumab

Refer to Induction Treatment Section 5.1.2 above.

5.1.3.2 *Experimental Arm Cohort 1*

5-FU/LV

Dose reductions and treatment interruptions of 5-FU/LV should be based on standard clinical practice and the Investigator's discretion. Please refer to the 5-FU/LV Summary of Product Characteristics (SmPC).

Cetuximab

Cetuximab dose modifications or interruptions may be required due to toxicity. Please refer to the Erbitux SmPC (see Appendix 14).

Vemurafenib

Vemurafenib dose modifications or interruptions may be required due to toxicity. Please refer to the current Vemurafenib Investigator's Brochure.

5.1.3.3 *Experimental Arm Cohort 2*

Fluoropyrimidine (5-FU/LV or capecitabine)

Dose reductions and treatment interruptions of the fluoropyrimidine should be based on standard clinical practice and the Investigator's discretion. Please refer to the capecitabine or 5-FU/LV Summary of Product Characteristics (SmPC) as applicable.

Bevacizumab

Refer to Induction Treatment Section 5.1.2 above.

Atezolizumab

There will be no dose reductions of atezolizumab however atezolizumab may be delayed for toxicity as described in the current Atezolizumab Investigator's Brochure.

Atezolizumab has been associated with risks such as the following: infusion-related reactions and immune-mediated hepatitis, pneumonitis, colitis, pancreatitis, diabetes mellitus, hypothyroidism, hyperthyroidism, adrenal insufficiency, hypophysitis, Guillain-Barré syndrome, myasthenic syndrome or myasthenia gravis, meningoencephalitis, myocarditis, nephritis, and myositis. Refer to the Investigator's Brochure for further details of risks associated with atezolizumab and the management of these events.

If a patient must be tapered off steroids used to treat AEs, atezolizumab may be withheld for additional time from the last dose until steroids are discontinued or reduced to prednisone dose (or dose equivalent) ≤ 10 mg/day. Patients must be discontinued from study treatment for delays > 21 days unless approval to continue is obtained from the Medical Monitor.

Immune-mediated reactions with atezolizumab may involve any organ system and may lead to hemophagocytic lymphohistiocytosis (HLH) and macrophage activation syndrome (MAS). Patients with suspected HLH should be diagnosed according to published criteria by McClain and Eckstein (2014). A patient should be classified as having HLH if five of the following eight criteria are met:

- Fever ≥ 38.5°C
- Splenomegaly

- Peripheral blood cytopenia consisting of at least two of the following:
  - Haemoglobin < 90 g/L (9 g/dL) (< 100 g/L [10 g/dL] for infants < 4 weeks old)
  - Platelet count < 100 x 10^9/L (100,000/µL)
  - ANC < 1.0 x 10^9/L (1000/µL)
- Fasting triglycerides > 2.992 mmol/L (265 mg/dL) and/or fibrinogen < 1.5 g/L (150 mg/dL)
- Haemophagocytosis in bone marrow, spleen, lymph node, or liver
- Low or absent natural killer cell activity
- Ferritin > 500 mg/L (500 ng/mL)
- Soluble interleukin-2 (IL-2) receptor (soluble CD25) elevated ≥ 2 standard deviations above age-adjusted laboratory-specific norms

Patients with suspected MAS should be diagnosed according to published criteria for systemic juvenile idiopathic arthritis by Ravelli et al. (2016). A febrile patient should be classified as having MAS if the following criteria are met:

- Ferritin > 684 mg/L (684 ng/mL)
- At least two of the following:
  - Platelet count ≤ 181 x 10^9/L (181,000/µL)
  - AST ≥ 48 U/L
  - Triglycerides > 1.761 mmol/L (156 mg/dL)
  - Fibrinogen ≤ 3.6 g/L (360 mg/dL)

Patients with suspected HLH or MAS should be treated according to the following guidelines:

- Permanently discontinue atezolizumab and contact Medical Monitor.
- Consider patient referral to haematologist.
- Initiate supportive care, including intensive care monitoring if indicated per institutional guidelines.
- Consider initiation of IV corticosteroids and/or an immunosuppressive agent.
- If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent.
- If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month.

5.1.3.4 *Experimental Arm Cohort 3*

Capecitabine

Capecitabine dose reductions and treatment interruptions should be based on standard clinical practice and the Investigator's discretion. Capecitabine dose calculations by body surface area with corresponding tablet counts are provided in Appendix 7. Please refer to the current capecitabine SmPC as applicable.

Trastuzumab and Pertuzumab

Trastuzumab and pertuzumab dose reductions are not allowed. The dose of trastuzumab should be recalculated if the patient's body weight has changed by more than 10% from start of trastuzumab treatment.

If a delay in either trastuzumab or pertuzumab is required for toxicity, both drugs should be held.

If a trastuzumab dose is delayed by > 7 days, a re-loading dose (8 mg/kg) should be given. If re-loading is required for a given cycle the three study drugs should be given on the same schedule as Cycle 1 (i.e. pertuzumab on Day 1 and trastuzumab and capecitabine on Day 2).

If a pertuzumab dose is delayed for < 21 days, re-loading is not required (the next dose should be 420 mg). If a pertuzumab dose is delayed for ≥ 21 days, a re-loading dose (840 mg) should be given. If re-loading is required for a given cycle, the three study drugs should be given on the same schedule as Cycle 1 (i.e. pertuzumab on Day 1 and trastuzumab and capecitabine on Day 2). Note: If treatment is delayed for > 21 days, approval must be obtained from the Medical Monitor before study treatment can be re-initiated.

For dose delays of trastuzumab and pertuzumab, please refer to the current trastuzumab and pertuzumab Investigator's Brochures. Appropriate management of safety events other than left ventricular dysfunction (see below) associated with combined trastuzumab and pertuzumab treatment is described in the current Pertuzumab Investigator's Brochure.

Guidelines for the management and reporting of cardiac toxicity in patients treated with trastuzumab and pertuzumab are provided in Appendix 15.

5.1.3.5 *Experimental Arm Cohort 4*

Cobimetinib and Atezolizumab

Cobimetinib dose modifications or interruptions may be required due to toxicity. There will be no dose reductions of atezolizumab, however, atezolizumab may delayed for toxicity. With the exception of guidelines for infusion-related reactions to atezolizumab, guidelines for management of toxicities and specific AEs in patients treated with cobimetinib and atezolizumab are provided in Appendix 16.

Guidelines for infusion-related reactions to atezolizumab are provided in the current Atezolizumab Investigator's Brochure. Anaphylaxis precautions are provided in Appendix 16.

Immune-mediated reactions with atezolizumab may involve any organ system and may lead to HLH and MAS. Refer to Section 5.1.3.3 for initial evaluation and management of possible cases of HLH or MAS.

5.2 SAFETY PARAMETERS AND DEFINITIONS

Safety assessments will consist of monitoring and recording AEs, including serious adverse events (SAEs) and AEs of special interest; measurement of protocol-specified safety laboratory assessments; measurement of protocol-specified vital signs; and other protocol-specified tests that are deemed critical to the safety evaluation of the study.

Certain types of events require immediate reporting to the Sponsor, as outlined in Section 5.4.

5.2.1 Adverse Events

According to the ICH guideline for Good Clinical Practice, an AE is any untoward medical occurrence in a clinical investigation subject administered a pharmaceutical product, regardless of causal attribution. An AE can therefore be any of the following:

- Any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product
- Any new disease or exacerbation of an existing disease (a worsening in the character, frequency, or severity of a known condition), except as described in Section 5.3.5.10
- Recurrence of an intermittent medical condition (e.g., headache) not present at baseline
- Any deterioration in a laboratory value or other clinical test (e.g., ECG, X-ray) that is associated with symptoms or leads to a change in study treatment or concomitant treatment or discontinuation from study drug
- AEs that are related to a protocol-mandated intervention, including those that occur prior to assignment of study treatment (e.g., screening invasive procedures such as biopsies)

5.2.2 Serious Adverse Events (Immediately Reportable to the Sponsor)

An SAE is any AE that meets any of the following criteria:

- Fatal (i.e., the AE actually causes or leads to death).
- Life threatening (i.e., the AE, in the view of the Investigator, places the patient at immediate risk of death).
- This does not include any AE that had it occurred in a more severe form or was allowed to continue might have caused death.
- Requires or prolongs inpatient hospitalization (see Section 5.3.5.11)
- Results in persistent or significant disability/incapacity (i.e., the AE results in substantial disruption of the patient's ability to conduct normal life functions)
- Congenital anomaly/birth defect in a neonate/infant born to a mother exposed to study drug
- Significant medical event in the Investigator's judgment (e.g., may jeopardise the patient or may require medical/surgical intervention to prevent one of the outcomes listed above)

The terms "severe" and "serious" are not synonymous. Severity refers to the intensity of an AE (e.g., rated according to NCI CTCAE criteria; see Section 5.3.3); the event itself may be of relatively minor medical significance (such as severe headache without any further findings).

Severity and seriousness need to be independently assessed for each AE recorded on the eCRF.

SAEs are required to be reported by the Investigator to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2 for reporting instructions).

5.2.3 Adverse Events of Special Interest (Immediately Reportable to the Sponsor)

Adverse events of special interest are required to be reported by the Investigator to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2 for reporting instructions).

These events may or may not be SAEs and they may or may not be considered related to study medication. Regardless of relationship or severity, these events will be recorded if they start from the time of the first dose of study treatment and will be followed until resolution.

After the end of the adverse event reporting period, the Sponsor should be notified if the Investigator becomes aware of any AEs of special interest that are believed to be related to prior study treatment.

5.2.3.1 *Adverse Events of Special Interest in Both Induction and Maintenance Treatment Phases*

AEs of special interest for all patients in both the Induction and Maintenance Treatment Phases of the study include the following:

- Cases of potential drug-induced liver injury that include an elevated ALT or AST in combination with either an elevated bilirubin or clinical jaundice, as defined by Hy's law (see Section 5.3.5.7)
- Suspected transmission of an infectious agent by a study drug, as defined below

  Any organism, virus, or infectious particle (e.g., prion protein transmitting transmissible spongiform encephalopathy), pathogenic or non-pathogenic, is considered an infectious agent. A transmission of an infectious agent may be suspected from clinical symptoms or laboratory findings that indicate an infection in a patient exposed to a medicinal product. This term applies only when a contamination of the study drug is suspected.

5.2.3.2 *Adverse Events of Special Interest in the Induction Treatment Phase*

There are no additional AEs of special interest for induction treatment.

5.2.3.3 *Adverse Events of Special Interest in the Maintenance Treatment Phase*

5.2.3.3.1 *Control Arms*

Bevacizumab

For patients receiving bevacizumab, the following are considered additional AEs of special interest:

- Hypertension ≥ Grade 3
- Proteinuria ≥ Grade 3

- GI perforation, abscesses and fistulae (any grade)
- Wound healing complications ≥ Grade 3
- Haemorrhage ≥ Grade 3 (any grade CNS bleeding; ≥ Grade 2 haemoptysis)
- Arterial thromboembolic events (any grade)
- Venous thromboembolic events ≥ Grade 3
- PRES (or RPLS; any grade)
- CHF ≥ Grade 3
- Non-GI fistula or abscess ≥ Grade 2

5.2.3.3.2 *Experimental Arm Cohort 1*

Cetuximab

No additional AEs of special interest.

Vemurafenib

For patients receiving vemurafenib, the following are considered additional AEs of special interest:

- Cutaneous SCC
- Keratoacanthoma (KA)
- GI polyps
- Photosensitivity
- Adverse events potentially associated with prolongation of cardiac repolarization or arrhythmia ("cardiac events")
- Potentiation of radiation toxicity

Any lesion at baseline or during treatment clinically suspected of representing cutaneous, basal cell carcinoma, actinic keratosis, KA or other skin conditions identified should be treated as per local standard of care.

If more than one SCC lesion occurs in more than one location on the skin, and the multiple lesions are detected during the same observation period (i.e. clinic visit), then these SCC lesions should be reported together as one AE. Locations of each lesion can be listed in the event term and narrative.

If more than one SCC lesion occurs in more than one location on the skin and the lesions are detected during separate observation periods (i.e., separate clinic visits), then these SCC lesions should be reported as separate AEs.

Cases in which patients rapidly develop multiple lesions within a limited time-frame (e.g., 5–10 lesions over a 2-week period) will be handled on a case by case basis in terms of reporting. Please contact the Medical Monitor when these cases occur, for additional discussion.

Skin biopsies should be performed by a dermatologist, as necessary, with histopathologic interpretation of suspected lesions. Biopsy-proven non-melanoma skin cancers should be excised.

When completing the AE and SAE forms in the eCRF, the following guidelines should be followed:

- Cutaneous SCC events should be reported using the event term of “Squamous Cell Carcinoma of the skin” or “Cutaneous Squamous Cell Carcinoma”. The event should be designated as Grade 3 severity.
- The term “Squamous Cell Carcinoma” should only be used if there is a confirmed non-cutaneous squamous cell carcinoma.
- If SCC is confirmed to be cutaneous the term “Cutaneous Squamous Cell Carcinoma” or “Squamous Cell Carcinoma of the skin” should be used. Do not report the event term of “treatment-related secondary malignancy” or “Squamous Cell Carcinoma”.
- If cSCC or SCC is suspected, an SAE with the event term “suspected cutaneous SCC” or “suspected non-cutaneous of <insert organ site>”and onset date of admission has to be submitted to the Sponsor within 24 hours.

For all SCC cases, the tick box medically significant must be ticked. The onset date for an SCC SAE is always the date of when the suspicion of an SCC occurred regardless of when and if the suspected diagnosis was confirmed.

5.2.3.3.3 *Experimental Arm Cohort 2*

Bevacizumab

See Section 5.2.3.3.1.

Atezolizumab

For patients receiving atezolizumab in Cohort 2, the following are considered additional AEs of special interest:

- Confirmed treatment-emergent immune related conditions including the following:
  - Pneumonitis
  - Colitis
  - Endocrinopathies: diabetes mellitus, pancreatitis, adrenal insufficiency, hypothyroidism or hyperthyroidism
  - Vasculitis
  - Hepatitis
  - Transaminitis: AST/ALT > 10 x ULN
  - Systemic lupus erythematosus
  - Neurologic: Guillain-Barré syndrome, myasthenia gravis, meningoencephalitis
  - Nephritis
- Events suggestive of hypersensitivity, cytokine release syndrome, influenza like illness, systemic inflammatory response system (SIRS), systemic immune activation (SIA) or infusion reaction syndromes

5.2.3.3.4 *Experimental Arm Cohort 3*

For patients in the experimental arm of Cohort 3, the following are considered additional AEs of special interest:

- Asymptomatic decline in LVEF requiring treatment or leading to discontinuation of trastuzumab or pertuzumab

5.2.3.3.5 *Experimental Arm Cohort 4*

For patients in the experimental arm of Cohort 4, the following are considered additional AEs of special interest:

- Pneumonitis
- Colitis
- Endocrinopathies: diabetes mellitus, pancreatitis, adrenal insufficiency, hypothyroidism or hyperthyroidism
- Systemic lupus erythematosus
- Neurologic: Guillain-Barré syndrome, myasthenia gravis, meningoencephalitis
- Nephritis
- Events suggestive of hypersensitivity, cytokine release, influenza-like illness, systemic inflammatory response system, or infusion-reaction syndromes
- Retinal vein occlusion
- Serous retinopathy, including events of retinal detachment, retinal pigment epithelium detachment, neurosensory retinal detachment, and central serous chorioretinopathy
- Rhabdomyolysis or Grade ≥ 3 CPK elevation
- Grade ≥ 3 hemorrhage or any grade cerebral hemorrhage
- Grade ≥ 3 rash
- Grade ≥ 3 diarrhea
- Significant liver toxicity
- AST and/or ALT > 10 × ULN
- Symptomatic heart failure or Grade ≥ 3 LVEF reduction

5.3 METHODS AND TIMING FOR CAPTURING AND ASSESSING SAFETY PARAMETERS

The Investigator is responsible for ensuring that all AEs (see Section 5.2.1 for definition) are recorded on the Adverse Event eCRF and reported to the Sponsor in accordance with instructions provided in this section and in Sections 5.4–5.6.

For each AE recorded on the Adverse Event eCRF, the Investigator will make an assessment of seriousness (see Section 5.2.2 for seriousness criteria), severity (see Section 5.3.3), and causality (see Section 5.3.4).

5.3.1 Adverse Event Reporting Period

Investigators will seek information on AEs at each patient contact. All AEs, whether reported by the patient or noted by study personnel, will be recorded in the patient's medical record and on the Adverse Event eCRF.

After informed consent has been obtained **but prior to initiation of study drug**, only SAEs caused by a protocol-mandated intervention (e.g., invasive procedures such as biopsies, discontinuation of medications) should be reported (see Section 5.4.2 for instructions for reporting SAEs).

After initiation of study drug, all AEs, regardless of relationship to study drug, will be documented at every cycle during treatment. All AEs, regardless of relationship to study drug, will continue to be reported for all patients who discontinue study treatment prior to the start of maintenance treatment, all patients treated in the control arm of any maintenance cohort and all patients treated in the experimental arm of Cohort 1 until 28 days after their last dose of study drug. Patients treated in the experimental arm of Cohorts 2, 3 or 4 will continue to be followed until 90 days after their last dose of study drug.

After the 28 or 90 day post-treatment period as described above, the Investigator is not required to actively monitor patients for AEs; however, the Sponsor should be notified if the Investigator becomes aware of any death, other SAE or AEs of special interest if the event is believed to be related to prior study treatment (see Section 5.6).

Note that patients in the experimental arm of Cohort 1 must complete assessments for SCC and cuSCC six months after their last study treatment (see Appendix 2) and all female patients of childbearing potential in the experimental arm of Cohort 3 must have a final pregnancy test 7 months after their last trastuzumab/pertuzumab dose (see Appendix 4). The study will not be considered to have ended until all patients in the experimental arm of Cohort 1 and all female patients of childbearing potential in the experimental arm of Cohort 3 have completed these follow-up safety assessments.

5.3.2 Eliciting Adverse Event Information

A consistent methodology of non-directive questioning should be adopted for eliciting AE information at all patient evaluation timepoints. Examples of non-directive questions include the following:

"How have you felt since your last clinic visit?"

"Have you had any new or changed health problems since you were last here?"

5.3.3 Assessment of Severity of Adverse Events

The AE severity grading scale for the NCI CTCAE (v4.0) will be used for assessing AE severity. Table 3 will be used for assessing severity for AEs that are not specifically listed in the NCI CTCAE.

Table 3: Adverse Event Severity Grading Scale for Events Not Specifically Listed in NCI CTCAE

Grade	Severity
1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; or intervention not indicated
2	Moderate; minimal, local, or non-invasive intervention indicated; or limiting age-appropriate instrumental activities of daily living a
3	Severe or medically significant, but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; or limiting self-care activities of daily living b,c
4	Life-threatening consequences or urgent intervention indicated d
5	Death related to AE d

NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events.

Note: Based on the most recent version of NCI CTCAE (v4.0), which can be found at: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm

a. Instrumental activities of daily living refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

b. Examples of self-care activities of daily living include bathing, dressing and undressing, feeding oneself, using the toilet, and taking medications, as performed by patients who are not bedridden.

c. If an event is assessed as a "significant medical event," it must be reported as a SAE (see Section 5.4.2 for reporting instructions), per the definition of SAE in Section 5.2.2.

d. Grade 4 and 5 events must be reported as SAEs (see Section 5.4.2 for reporting instructions), per the definition of SAE in Section 5.2.2

5.3.4 Assessment of Causality of Adverse Events

Investigators should use their knowledge of the patient, the circumstances surrounding the event, and an evaluation of any potential alternative causes to determine whether or not an AE is considered to be related to the study drug, indicating "yes" or "no" accordingly. The following guidance should be taken into consideration (see also Table 4):

- Temporal relationship of event onset to the initiation of study drug
- Course of the event, considering especially the effects of dose reduction, discontinuation of study drug, or reintroduction of study drug (as applicable)
- Known association of the event with the study drug or with similar treatments
- Known association of the event with the disease under study
- Presence of risk factors in the patient or use of concomitant medications known to increase the occurrence of the event
- Presence of non-treatment-related factors that are known to be associated with the occurrence of the event

Table 4: Causal Attribution Guidance

Is the AE suspected to be caused by the study drug on the basis of facts, evidence, science-based rationales, and clinical judgment?	
YES	There is a plausible temporal relationship between the onset of the AE and administration of the study drug, and the AE cannot be readily explained by the patient's clinical state, intercurrent illness, or concomitant therapies; and/or the AE follows a known pattern of response to the study drug; and/or the AE abates or resolves upon discontinuation of the study drug or dose reduction and, if applicable, reappears upon re-challenge.
NO	An AE will be considered related, unless it fulfils the criteria specified below. Evidence exists that the AE has an etiology other than the study drug (e.g., pre-existing medical condition, underlying disease, intercurrent illness, or concomitant medication); and/or the AE has no plausible temporal relationship to administration of the study drug (e.g., cancer diagnosed 2 days after first dose of study drug).

For patients receiving combination therapy, causality will be assessed individually for each protocol-mandated therapy.

5.3.5 Procedures for Recording Adverse Events

Investigators should use correct medical terminology/concepts when recording AEs on the Adverse Event eCRF. Avoid colloquialisms and abbreviations.

Only one AE term should be recorded in the event field on the Adverse Event eCRF.

5.3.5.1 *Infusion-Related Reactions*

AEs that occur during or within 24 hours after study drug administration and are judged to be related to study drug infusion should be captured as a diagnosis (e.g., "infusion-related reaction" or "anaphylactic reaction") on the Adverse Event eCRF. If possible, avoid ambiguous terms such as "systemic reaction." Associated signs and symptoms should be recorded on the dedicated Infusion-Related Reaction eCRF. If a patient experiences both a local and systemic reaction to the same dose of study drug, each reaction should be recorded separately on the Adverse Event eCRF, with signs and symptoms also recorded separately on the dedicated Infusion-Related Reaction eCRF.

5.3.5.2 *Diagnosis versus Signs and Symptoms*

Reactions Temporally Associated with Infusions

AEs that occur during or within 24 hours after study drug infusion should be captured as individual signs and symptoms unless assessed as secondary to an allergic reaction or infusion reaction.

Other Adverse Events

For AEs other than infusion-related or injection reactions (see Section 5.3.5.1), a diagnosis (if known) should be recorded on the Adverse Event eCRF rather than individual signs and symptoms (e.g., record only liver failure or hepatitis rather than jaundice, asterixis, and elevated transaminases). However, if a constellation of signs and/or symptoms cannot be medically characterised as a single diagnosis or syndrome at the time of reporting, each individual event should be recorded on the Adverse Event eCRF. If a diagnosis is

subsequently established, all previously reported AEs based on signs and symptoms should be nullified and replaced by one AE report based on the single diagnosis, with a starting date that corresponds to the starting date of the first symptom of the eventual diagnosis.

5.3.5.3 *Adverse Events That Are Secondary to Other Events*

In general, AEs that are secondary to other events (e.g., cascade events or clinical sequelae) should be identified by their primary cause, with the exception of severe or serious secondary events. A medically significant secondary AE that is separated in time from the initiating event should be recorded as an independent event on the Adverse Event eCRF. For example:

- If vomiting results in mild dehydration with no additional treatment in a healthy adult, only vomiting should be reported on the eCRF.
- If vomiting results in severe dehydration, both events should be reported separately on the eCRF.
- If a severe gastrointestinal haemorrhage leads to renal failure, both events should be reported separately on the eCRF.
- If dizziness leads to a fall and consequent fracture, all three events should be reported separately on the eCRF.
- If neutropenia is accompanied by an infection, both events should be reported separately on the eCRF.

All AEs should be recorded separately on the Adverse Event eCRF if it is unclear as to whether the events are associated.

5.3.5.4 *Persistent or Recurrent Adverse Events*

A persistent adverse event is one that extends continuously, without resolution, between patient evaluation time points. Such events should only be recorded once on the Adverse Event eCRF. The initial severity (intensity or grade) of the event will be recorded at the time the event is first reported. If a persistent adverse event becomes more severe, the most extreme severity should also be recorded on the Adverse Event eCRF. If the event becomes serious, it should be reported to the Sponsor immediately (i.e., no more than 24 hours after learning that the event became serious; see Section 5.4.2 for reporting instructions). The Adverse Event eCRF should be updated by changing the event from "non-serious" to "serious," providing the date that the event became serious, and completing all data fields related to serious adverse events. A recurrent AE is one that resolves between patient evaluation time points and subsequently recurs. Each recurrence of an AE should be recorded as a separate event on the Adverse Event eCRF.

5.3.5.5 *Abnormal Laboratory Values*

Not every laboratory abnormality qualifies as an AE. A laboratory test result must be reported as an AE if it meets any of the following criteria:

- Accompanied by clinical symptoms

- Results in a change in study treatment (e.g., dosage modification, treatment interruption, or treatment discontinuation)
- Results in a medical intervention (e.g., potassium supplementation for hypokalemia) or a change in concomitant therapy
- Clinically significant in the Investigator's judgment

It is the Investigator's responsibility to review all laboratory findings. Medical and scientific judgment should be exercised in deciding whether an isolated laboratory abnormality should be classified as an AE.

If a clinically significant laboratory abnormality is a sign of a disease or syndrome (e.g., alkaline phosphatase and bilirubin $5 \times$ ULN associated with cholestasis), only the diagnosis (i.e., cholestasis) should be recorded on the Adverse Event eCRF.

If a clinically significant laboratory abnormality is not a sign of a disease or syndrome, the abnormality itself should be recorded on the Adverse Event eCRF, along with a descriptor indicating if the test result is above or below the normal range (e.g., "elevated potassium," as opposed to "abnormal potassium"). If the laboratory abnormality can be characterised by a precise clinical term per standard definitions, the clinical term should be recorded as the AE. For example, an elevated serum potassium level of 7.0 mEq/L should be recorded as "hyperkalemia."

Observations of the same clinically significant laboratory abnormality from visit to visit should not be repeatedly recorded on the Adverse Event eCRF, unless the etiology changes. The initial severity of the event should be recorded, and the severity or seriousness should be updated any time the event worsens.

5.3.5.6 *Abnormal Vital Sign Values*

Not every vital sign abnormality qualifies as an AE. A vital sign result must be reported as an AE if it meets any of the following criteria:

- Accompanied by clinical symptoms
- Results in a change in study treatment (e.g., dosage modification, treatment interruption, or treatment discontinuation)
- Results in a medical intervention or a change in concomitant therapy
- Clinically significant in the Investigator's judgment

It is the Investigator's responsibility to review all vital sign findings. Medical and scientific judgment should be exercised in deciding whether an isolated vital sign abnormality should be classified as an AE.

If a clinically significant vital sign abnormality is a sign of a disease or syndrome (e.g., high blood pressure), only the diagnosis (i.e., hypertension) should be recorded on the Adverse Event eCRF.

Observations of the same clinically significant vital sign abnormality from visit to visit should not be repeatedly recorded on the Adverse Event eCRF, unless the etiology changes. The

initial severity of the event should be recorded, and the severity or seriousness should be updated any time the event worsens.

5.3.5.7 *Abnormal Liver Function Tests*

The finding of an elevated ALT or AST (> 3 × baseline value) in combination with either an elevated total bilirubin (> 2 × ULN) or clinical jaundice in the absence of cholestasis or other causes of hyperbilirubinemia is considered to be an indicator of severe liver injury (as defined by Hy's Law). Therefore, Investigators must report as an AE the occurrence of either of the following:

- Treatment-emergent ALT or AST > 3 × baseline value in combination with total bilirubin > 2 ×ULN (of which ≥ 35% is direct bilirubin)
- Treatment-emergent ALT or AST > 3 × baseline value in combination with clinical jaundice

The most appropriate diagnosis or (if a diagnosis cannot be established) the abnormal laboratory values should be recorded on the Adverse Event eCRF (see Section 5.3.5.5) and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event), either as a SAE or an AE of special interest (see Section 5.4.2).

5.3.5.8 *Deaths*

For this protocol, mortality is an efficacy endpoint. Deaths that occur during the protocol-specified adverse event reporting period (see Section 5.3.1) that are attributed by the Investigator solely to progression of mCRC should be recorded only on the Study Completion/Early Discontinuation eCRF. All other on-study deaths, regardless of relationship to study drug, must be recorded on the Adverse Event eCRF and immediately reported to the Sponsor (see Section 5.4.2). The iDMC will monitor the frequency of deaths from all causes.

Death should be considered an outcome and not a distinct event. The event or condition that caused or contributed to the fatal outcome should be recorded as the single medical concept on the Adverse Event eCRF. Generally, only one such event should be reported. The term **"sudden death"** should be used only for the occurrence of an abrupt and unexpected death due to presumed cardiac causes in a patient with or without pre-existing heart disease, within 1 hour after the onset of acute symptoms or, in the case of an unwitnessed death, within 24 hours after the patient was last seen alive and stable. If the cause of death is unknown and cannot be ascertained at the time of reporting, **"unexplained death"** should be recorded on the Adverse Event eCRF. If the cause of death later becomes available (e.g., after autopsy), "unexplained death" should be replaced by the established cause of death.

During survival follow-up, deaths attributed to progression of mCRC should be recorded only on the eCRF.

5.3.5.9 *Pre-existing Medical Conditions*

A pre-existing medical condition is one that is present at the screening visit for this study. Such conditions should be recorded on the General Medical History and Baseline Conditions eCRF.

A pre-existing medical condition should be recorded as an AE only if the frequency, severity, or character of the condition worsens during the study. When recording such events on the Adverse Event eCRF, it is important to convey the concept that the pre-existing condition has changed by including applicable descriptors (e.g., "more frequent headaches").

5.3.5.10 *Lack of Efficacy or Worsening of mCRC*

Events that are clearly consistent with the expected pattern of progression of the underlying disease should not be recorded as AEs. These data will be captured as efficacy assessment data only. In most cases, the expected pattern of progression will be based on RECIST 1.1 or mRECIST. In rare cases, the determination of clinical progression will be based on symptomatic deterioration. However, every effort should be made to document progression through use of objective criteria. If there is any uncertainty as to whether an event is due to disease progression, it should be reported as an AE.

5.3.5.11 *Hospitalization or Prolonged Hospitalization*

Any AE that results in hospitalization (i.e., in-patient admission to a hospital) or prolonged hospitalization should be documented and reported as a SAE (per the definition of SAE in Section 5.2.2), except as outlined below.

The following hospitalization scenarios are not considered to be AEs:

- Hospitalization for respite care
- Planned hospitalization required by the protocol (e.g., for study drug administration or insertion of access device for study drug administration)
- Hospitalization for a pre-existing condition, provided that all of the following criteria are met:
  - The hospitalization was planned prior to the study or was scheduled during the study when elective surgery became necessary because of the expected normal progression of the disease
  - The patient has not experienced an AE
- Hospitalization due solely to progression of the underlying cancer

5.3.5.12 *Adverse Events Associated with an Overdose*

An overdose is the accidental or intentional use of a drug in an amount higher than the dose being studied. An overdose or incorrect administration of study treatment is not itself an AE, but it may result in an AE. All AEs associated with an overdose or incorrect administration of study drug should be recorded on the Adverse Event eCRF. If the associated AE fulfils serious criteria, the event should be reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2).

5.4 IMMEDIATE REPORTING REQUIREMENTS FROM INVESTIGATOR TO SPONSOR

Certain events require immediate reporting to allow the Sponsor to take appropriate measures to address potential new risks in a clinical trial. The Investigator must report such events to the Sponsor immediately; under no circumstances should reporting take place more than 24 hours after the Investigator learns of the event. The following is a list of events that the Investigator must report to the Sponsor within 24 hours after learning of the event, regardless of relationship to study drug:

- SAEs
- AEs of special interest
- Pregnancies

The Investigator must report new significant follow-up information for these events to the Sponsor immediately (i.e., no more than 24 hours after becoming aware of the information). New significant information includes the following:

- New signs or symptoms or a change in the diagnosis
- Significant new diagnostic test results
- Change in causality based on new information
- Change in the event's outcome, including recovery
- Additional narrative information on the clinical course of the event

Investigators must also comply with local requirements for reporting SAEs to the local health authority and IRB/EC.

5.4.1 Emergency Medical Contacts

To ensure the safety of study patients, an Emergency Medical Call Centre Help Desk will access the Roche Medical Emergency List, escalate emergency medical calls, provide medical translation service (if necessary), connect the Investigator with a Roche Medical Monitor, and track all calls. The Emergency Medical Call Centre Help Desk will be available 24 hours per day, 7 days per week. Toll-free numbers for the Help Desk and Medical Monitor contact information will be distributed to all Investigators (see "Protocol Administrative and Contact Information & List of Investigators").

5.4.2 Reporting Requirements for SAEs and AEs of Special Interest

5.4.2.1 *Events That Occur prior to Study Drug Initiation*

After informed consent has been obtained but prior to initiation of study drug, only SAEs caused by a protocol-mandated intervention should be reported. A paper Serious Adverse Event Reporting Form and fax cover sheet should be completed and faxed to Roche Safety Risk Management or its designee immediately (i.e., no more than 24 hours after learning of the event), using the fax numbers provided to Investigators (see "Protocol Administrative and Contact Information & List of Investigators").

5.4.2.2 *Events That Occur after Study Drug Initiation*

After initiation of study drug, SAEs and AEs of special interest will be reported. After the end of the adverse event reporting period, the Sponsor should be notified if the Investigator becomes aware of any SAE or AEs of special interest if the event is believed to be related to prior study treatment. Investigators should record all case details that can be gathered immediately (i.e., within 24 hours after learning of the event) on the Adverse Event eCRF and submit the report via the electronic data capture (EDC) system. A report will be generated and sent to Roche Safety Risk Management by the EDC system.

In the event that the EDC system is unavailable, a paper Serious Adverse Event Reporting Form and fax cover sheet should be completed and faxed to Roche Safety Risk Management or its designee immediately (i.e., no more than 24 hours after learning of the event), using the fax numbers provided to Investigators (see "Protocol Administrative and Contact Information & List of Investigators"). Once the EDC system is available, all information will need to be entered and submitted via the EDC system.

Instructions for reporting post-study AEs are provided in Section 5.6.

5.4.3 Reporting Requirements for Pregnancies

5.4.3.1 *Pregnancies in Female Patients*

Female patients 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]) will be instructed to immediately inform the Investigator if they become pregnant during the study or within 7 months after the last dose of study drug. A Clinical Trial Pregnancy Reporting Form provided to investigators should be completed and submitted to Roche or its designee immediately (i.e., no more than 24 hours after learning of the pregnancy), either by faxing or by scanning and emailing the form using the fax number or email address provided to Investigators.

Pregnancy should not be recorded on the Adverse Event eCRF. The Investigator should discontinue study drug and counsel the patient, discussing the risks of the pregnancy and the possible effects on the fetus.

Monitoring of the patient should continue until conclusion of the pregnancy. Any SAEs associated with the pregnancy (e.g., an event in the fetus, an event in the mother during or after the pregnancy, or a congenital anomaly/birth defect in the child) should be reported on the Adverse Event eCRF. In addition, the investigator will submit a Clinical Trial Pregnancy Reporting Form when updated information on the course and outcome of the pregnancy becomes available.

Additional information on any pertuzumab and trastuzumab-exposed pregnancy and infant will be requested by Roche Drug Safety at specific time points (i.e. after having received the initial report during the first trimester, at the end of the second trimester, 2 weeks after the expected date of delivery and at 3, 6, and 12 months of the infant's life). In case of a report of a congenital abnormality, a guided questionnaire will be sent out by Roche Drug Safety.

5.4.3.2 *Pregnancies in Female Partners of Male Patients*

Male patients will be instructed through the Informed Consent Form to immediately inform the Investigator if their partner becomes pregnant during the study or within 6 months after the last dose of study drug. A Clinical Trial Pregnancy Reporting Form should be completed and submitted to the Roche or its designee immediately (i.e., no more than 24 hours after learning of the pregnancy) either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators. Attempts should be made to collect and report details of the course and outcome of any pregnancy in the partner of a male patient exposed to study drug. The pregnant partner will need to sign an Authorization for Use and Disclosure of Pregnancy Health Information to allow for follow-up on her pregnancy. Once the authorization has been signed, the Investigator will submit a Clinical Trial Pregnancy Reporting Form when updated information on the course and outcome of the pregnancy becomes available. An Investigator who is contacted by the male patient or his pregnant partner may provide information on the risks of the pregnancy and the possible effects on the fetus, to support an informed decision in cooperation with the treating physician and/or obstetrician.

5.4.3.3 *Abortions*

Any abortion should be classified as an SAE (as the Sponsor considers abortions to be medically significant), recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2).

5.4.3.4 *Congenital Anomalies/Birth Defects*

Any congenital anomaly/birth defect in a child born to a female patient exposed to study drug or the female partner of a male patient exposed to study drug should be classified as an SAE, recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2).

5.5 FOLLOW-UP OF PATIENTS AFTER ADVERSE EVENTS

5.5.1 Investigator Follow-Up

The Investigator should follow each AE until the event has resolved to baseline grade or better, the event is assessed as stable by the Investigator, the patient is lost to follow-up, or the patient withdraws consent. Every effort should be made to follow all SAEs considered to be related to study drug or trial-related procedures until a final outcome can be reported.

During the study period, resolution of AEs (with dates) should be documented on the Adverse Event eCRF and in the patient's medical record to facilitate source data verification. If, after follow-up, return to baseline status or stabilization cannot be established, an explanation should be recorded on the Adverse Event eCRF.

All pregnancies reported during the study should be followed until pregnancy outcome.

5.5.2 Sponsor Follow-Up

For SAEs, AEs of special interest, and pregnancies, the Sponsor or a designee may follow up by telephone, fax, electronic mail, and/or a monitoring visit to obtain additional case

details and outcome information (e.g., from hospital discharge summaries, consultant reports, autopsy reports) in order to perform an independent medical assessment of the reported case.

5.6 POST-STUDY ADVERSE EVENTS

At the time of study completion or study discontinuation, the Investigator should instruct each patient to report to the Investigator any subsequent AEs that the patient's personal physician believes could be related to prior study drug treatment or study procedures.

The Investigator is not required to actively monitor patients for AEs after the end of the adverse event reporting period (defined as either 28 or 90 days after the last dose of study drug). However, the Sponsor should be notified if the Investigator becomes aware of any death, other SAE, or AE 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. The Sponsor should also be notified if the Investigator becomes aware of the development of cancer or a congenital anomaly/birth defect in a subsequently conceived offspring of a female patient exposed to study drug or the female partner of a male patient exposed to study drug.

The Investigator should report these events directly to Roche Safety Risk Management via telephone or via fax machine using the Serious Adverse Event Reporting Form and fax cover sheet (see "Protocol Administrative and Contact Information & List of Investigators").

5.7 EXPEDITED REPORTING TO HEALTH AUTHORITIES, INVESTIGATORS, INSTITUTIONAL REVIEW BOARDS, AND ETHICS COMMITTEES

The Sponsor will promptly evaluate all SAEs and AEs of special interest against cumulative product experience to identify and expeditiously communicate possible new safety findings to Investigators, IRBs, ECs, and applicable health authorities based on applicable legislation.

To determine reporting requirements for single AE cases, the Sponsor will assess the expectedness of these events using the following Investigator's Brochures, local prescribing information or Core Data sheets as reference documents, as described below.

- Refer to European Medicines Agency (EMA) website for Summary of Product Characteristics (SmPC):
  - cetuximab
- Investigator's Brochure
  - bevacizumab
  - vemurafenib
  - atezolizumab
  - trastuzumab
  - pertuzumab
  - cobimetinib

The Sponsor will compare the severity of each event and the cumulative event frequency reported for the study with the severity and frequency reported in the applicable reference document.

Reporting requirements will also be based on the Investigator's assessment of causality and seriousness, with allowance for upgrading by the Sponsor as needed.

Certain AEs are anticipated to occur in the study population at some frequency independent of study drug exposure and will be excluded from expedited reporting. These anticipated events include, but are not limited to, the following:

- Death due to progressive disease
- Disease progression

An iDMC will monitor the incidence of the above-listed anticipated events during the study. An aggregate report of any clinically relevant imbalances that do not favour the test products will be submitted to health authorities.

6. STATISTICAL CONSIDERATIONS AND ANALYSIS PLAN

Update on Statistical Analysis Plans and Cohort Status Following Premature Closure of Study Enrolment

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 iDMC. Accrual to Cohort 4 was not re-opened after February 2018 due to iDMC recommendations. No new or modified cohorts with broad biomarker eligibility have been identified for addition to the study. In the absence of a cohort with broad biomarker eligibility to replace Cohort 4, the majority of patients eligible for study entry would not be eligible for maintenance cohort assignment. For this reason, study enrolment will not be re-opened following the February 2018 suspension.

Accrual to Cohort 2 was completed in November 2016 after reaching its target sample size. Accrual to Cohort 4 was closed in February 2018, prior to reaching its target sample size. 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; however, Cohorts 1 and 3 did not reach their target sample size.

The clinical cut-off for the primary analysis of Cohort 2 occurred on May 31, 2017. The primary analyses for Cohorts 1, 3 and 4 will be conducted based on the same clinical cut-off as the update analysis of Cohort 2 occurring on May 31, 2019 (24 months from Cohort 2 primary analysis clinical cut-off date). Following May 31, 2019, disease status data will not be collected for any cohort. Since survival follow-up at 24 months after the primary analysis clinical cut-off date will have been reported in Cohort 2, and only five patients were accrued in Cohort 3 (see Section 6.2), no further survival (other than during the adverse event reporting period) or subsequent anti-cancer therapy data will be collected for patients in Cohorts 2 and 3 after May 31, 2019. Survival and subsequent anti-cancer therapy will continue to be collected for Cohorts 1 and 4 until the end of the study.

6.1 OVERVIEW

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 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 for the cohort will occur when the target number of PFS events has been reached. Secondary endpoints will also be summarised at this time. An updated analysis of time-to-event and safety endpoints will be conducted for such cohorts once 24 months of survival follow-up has been completed.

The final study analysis 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.

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.

The following is an outline of the statistical methodology that will be used to analyse this study. More detailed descriptions will be provided in statistical analysis plans (SAPs) applicable to each cohort which may also include additional exploratory analyses not explicitly mentioned in the following sections. The timing and methods of analyses for any cohort closed to accrual before its target sample size is reached may differ from descriptions provided below. These will be described in the SAP applicable to the cohort and will depend on accrual at the time of early closure. The SAPs will be finalised before closure of the study database. Deviations from the SAPs will be reported and justified in the clinical study reports.

6.1.1 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.

6.1.2 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 (evaluated per RECIST v1.1) 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%.

6.2 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 target sample size in each maintenance cohort. The target sample size was reached in Cohort 2 (final n=445). Target sample sizes were not reached in Cohort 1 (final n=60), Cohort 3 (final n=5), or Cohort 4 (final n=99) due to premature closure of study enrolment.

The calculated sample size for each study cohort has been based on an estimated recruitment period for 11 months for Cohorts 2 and 4 and on the comparison between PFS in the experimental and control arms of that cohort. Estimated proportions of the patients enrolled into the study that are eligible for each cohort are based on published reports

(Cohorts 1, 2 and 4: di Nicolantonio et al. 2008; Cohort 3: Seo et al. 2014). The prevalence of mCRC patients with HER2+ or $BRAF^{mut}$ disease is relatively low. The formal statistical tests for Cohorts 1 and 3 will therefore be one-sided and performed with a higher alpha level and lower power to limit intercohort differences in the timing primary efficacy endpoint maturation that would affect study feasibility. 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 5.

As of February 12, 2018, study enrolment was suspended due to considerations around early closure of accrual into Cohort 4 (see Section 3.1.2.4). The study will remain closed to enrolment and no additional cohorts are planned.

Table 5: Sample Size Determination per Cohort

	Cohort 1	Cohort 2	Cohort 3	Cohort 4
Percent of study population eligible for cohort based on biomarker status	10%	90%	6%	84%
Percent of patients eligible for cohort based on biomarker status expected to have disease progression prior to randomization	25%	25%	25%	25%
Average randomization rate (pts/month) [a]	3.5	31.5	2.5	31.5
Estimated median PFS [b] (months) - Experimental arm	7	11.5	11.5	11.5
Estimated median PFS [b] (months) - Control arm	4.9	7.5	7.5	7.5
HR	0.70	0.65	0.65	0.65
Number of expected PFS events	96	259	69	259
Statistical test	1-sided	2-sided	1-sided	2-sided
Alpha level	10%	5%	10%	5%
Power	65%	90%	65%	90%
Randomised patients	126	405	90	405
Randomization ratio (experimental vs control)	2:1	2:1	2:1	2:1
Recruitment period (months)	36	11	36	11
Time to primary analysis of PFS (months) [c]	36	22	43	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

6.3 SUMMARIES OF CONDUCT OF STUDY

Enrolment, study treatment administration, and discontinuations from the study will be summarised by Induction Treatment Phase, study cohort and treatment arm. The incidence of, and reasons for, treatment discontinuation and major protocol violations will also be summarised.

6.4 SUMMARIES OF TREATMENT GROUP COMPARABILITY

Demographic and baseline characteristics (e.g. age, sex, ethnicity) and baseline disease characteristics (e.g. prior treatment, sites of metastatic disease, ECOG performance status) for experimental and control arms of each cohort will be summarised.

6.5 EFFICACY ANALYSES

Efficacy analyses will be conducted separately for each study cohort.

No adjustment will be made for multiplicity of endpoints or subgroup analyses.

6.5.1 Primary Efficacy Endpoints

All Cohorts

The primary study endpoint within each cohort is PFS evaluated according to RECIST 1.1.

PFS is defined as the time from randomisation into the Maintenance Treatment Phase until disease progression evaluated according to 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.

6.5.2 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. 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. 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).

DoR will be assessed for all patients after randomisation until PD. Only patients with a best overall response of CR or PR 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.

The above efficacy outcomes will be evaluated using RECIST 1.1.

ECOG performance status will be summarised over time.

6.5.3 Exploratory Efficacy Endpoints

Cohorts 2 and 4

PFS defined as the time from randomisation into the Maintenance Treatment Phase until disease progression evaluated according to mRECIST or death from any cause (whichever occurs first) will be evaluated as an exploratory endpoint. This endpoint will only be assessed in patients treated with atezolizumab. 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.

6.6 SAFETY ANALYSES

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 (including partial doses) 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 Phase and those reported during follow-up after treatment completion/discontinuation will be summarised by treatment group.

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.

6.7 EXPLORATORY BIOMARKER ANALYSES

All Cohorts

Biomarker and microbiome analyses will be of exploratory nature only, utilizing all available data obtained from archival tumour samples from the initial diagnosis and all other tumour, blood and stool samples 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 summarised. Relevant findings will be discussed with the study's SC in order to conduct further exploratory biomarker analyses accordingly.

6.8 INTERIM ANALYSES

All Cohorts

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 the 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.

6.9 SUBGROUP ANALYSES

Subgroup analysis will be defined in the SAP.

7. DATA COLLECTION AND MANAGEMENT

7.1 DATA QUALITY ASSURANCE

The Sponsor will supply eCRF specifications for this study. A contract research organization (CRO) will be responsible for data management of this study, including quality checking of

the data. Data entered manually will be collected via EDC using eCRFs. Sites will be responsible for data entry into the EDC system. In the event of discrepant data, the CRO will request data clarification from the sites, which the sites will resolve electronically in the EDC system.

The CRO will produce a Data Quality Plan that describes the quality checking to be performed on the data. Central laboratory data will be sent directly to the CRO using the CRO's standard procedures to handle and process the electronic transfer of these data.

The Sponsor will perform oversight of the data management of this study, including approval of the CRO's data management plans and specifications. Data will be periodically transferred electronically from the CRO to the Sponsor, and the Sponsor's standard procedures will be used to handle and process the electronic transfer of these data.

eCRFs and correction documentation will be maintained in the EDC system's audit trail. System backups for data stored at the CRO and records retention for the study data will be consistent with the CRO's standard procedures.

7.2 ELECTRONIC CASE REPORT FORMS

eCRFs are to be completed through use of a Sponsor-designated EDC system. Sites will receive training and have access to a manual for appropriate eCRF completion. eCRFs will be submitted electronically to the Sponsor and should be handled in accordance with instructions from the Sponsor.

All eCRFs should be completed by designated, trained site staff. eCRFs should be reviewed and electronically signed and dated by the Investigator or a designee.

At the end of the study, the Investigator will receive patient data for his or her site in a readable format on a compact disc that must be kept with the study records. Acknowledgement of receipt of the compact disc is required.

7.3 SOURCE DATA DOCUMENTATION

Study monitors will perform ongoing source data verification to confirm that critical protocol data (i.e., source data) entered into the eCRFs by authorised site personnel are accurate, complete, and verifiable from source documents.

Source documents (paper or electronic) are those in which patient data are recorded and documented for the first time. They include, but are not limited to, hospital records, clinical and office charts, laboratory notes, memoranda, patient-reported outcomes, evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies of transcriptions that are certified after verification as being accurate and complete, microfiche, photographic negatives, microfilm or magnetic media, X-rays, patient files, and records kept at pharmacies, laboratories, and medico-technical departments involved in a clinical trial.

Before study initiation, the types of source documents that are to be generated will be clearly defined in the Trial Monitoring Plan. This includes any protocol data to be entered directly into the eCRFs (i.e., no prior written or electronic record of the data) and considered source data.

Source documents that are required to verify the validity and completeness of data entered into the eCRFs must not be obliterated or destroyed and must be retained per the policy for retention of records described in Section 7.5.

To facilitate source data verification, the Investigators and institutions must provide the Sponsor direct access to applicable source documents and reports for trial-related monitoring, Sponsor audits, and IRB/EC review. The study site must also allow inspection by applicable health authorities.

7.4 USE OF COMPUTERISED SYSTEMS

When clinical observations are entered directly into a study site's computerised medical record system (i.e., in lieu of original hardcopy records), the electronic record can serve as the source document if the system has been validated in accordance with health authority requirements pertaining to computerised systems used in clinical research. An acceptable computerised data collection system allows preservation of the original entry of data. If original data are modified, the system should maintain a viewable audit trail that shows the original data as well as the reason for the change, name of the person making the change, and date of the change.

7.5 RETENTION OF RECORDS

Records and documents pertaining to the conduct of this study and the distribution of IMP, including eCRFs, Informed Consent Forms, laboratory test results, and medication inventory records, must be retained by the Principal Investigator for at least 15 years after completion or discontinuation of the study, or for the length of time required by relevant national or local health authorities, whichever is longer. After that period of time, the documents may be destroyed, subject to local regulations.

No records may be disposed of without the written approval of the Sponsor. Written notification should be provided to the Sponsor prior to transferring any records to another party or moving them to another location.

8. ETHICAL CONSIDERATIONS

8.1 COMPLIANCE WITH LAWS AND REGULATIONS

This study will be conducted in full conformance with the ICH E6 guideline for Good Clinical Practice and the principles of the Declaration of Helsinki, or the laws and regulations of the country in which the research is conducted, whichever affords the greater protection to the individual. The study will comply with the requirements of the ICH E2A guideline (Clinical Safety Data Management: Definitions and Standards for Expedited Reporting). Studies conducted in the EU or European Economic Area will comply with the EU Clinical Trial Directive (2001/20/EC).

8.2 INFORMED CONSENT

Due to the complexity of the study and the number of different maintenance regimens a patient could potentially receive, the informed consent process including signing of the informed consent form, may be conducted twice unless the individual study center chooses

to obtain informed consent including all potential regimens in a single process (i.e. provide all induction and maintenance treatment information prior to study entry). Sites conducting two informed consent procedures will obtain the first informed consent prior to study screening and enrolment into the Induction Treatment Phase. The second informed consent will be obtained prior to cohort-specific eligibility assessments and randomization into the Maintenance Treatment Phase. The informed consent just prior to Maintenance Treatment Phase will be based on only those regimens in the assigned maintenance cohort. Patients will have the option of reviewing informed consent information for all maintenance treatment cohorts before entry into the study.

The Sponsor's sample Informed Consent Forms will be provided to each site. If applicable, they will be provided in a certified translation of the local language. The Sponsor or its designee must review and approve any proposed deviations from the Sponsor's sample Informed Consent Forms or any alternate consent forms proposed by the site (collectively, the "Consent Forms") before IRB/EC submission. The final IRB/EC–approved Consent Forms must be provided to the Sponsor for health authority submission purposes according to local requirements.

The Informed Consent Form signed before entry into the study will contain a separate section that addresses the use of remaining samples for optional exploratory research. The Investigator or authorised designee will explain to each patient the objectives of the exploratory research. Patients will be told that they are free to refuse to participate and may withdraw their specimens at any time and for any reason during the storage period. A separate, specific signature will be required to document a patient's agreement to allow any remaining specimens to be used for exploratory research. Patients who decline to participate will not provide a separate signature.

The Consent Forms must be signed and dated by the patient, or, where applicable, their legally authorised representative, before his or her initial participation in the study and again prior to entry into the Maintenance Phase. The case history or clinical records for each patient shall document the informed consent processes and that written informed consents were obtained prior to participation in the study and entry into the Maintenance Treatment Phase.

The Consent Forms should be revised whenever there are changes to study procedures or when new information becomes available that may affect the willingness of the patient to participate. The final revised IRB/EC-approved Consent Forms must be provided to the Sponsor for health authority submission purposes.

Patients must be re-consented to the most current version of the Consent Forms (or to a significant new information/findings addendum in accordance with applicable laws and IRB/EC policy) during their participation in the study. For any updated or revised Consent Forms, the case history or clinical records for each patient shall document the informed consent process and that written informed consent was obtained using the updated/revised Consent Forms for continued participation in the study.

A copy of each signed Consent Form must be provided to the patient, or, where applicable, their legally authorised representative. All signed and dated Consent Forms must remain in

each patient's study file or in the site file and must be available for verification by study monitors at any time.

An additional consent form will be provided to patients who agree to also participate in the Supplemental Biomarker Program outlined in Appendix 18.

8.3 INSTITUTIONAL REVIEW BOARD OR ETHICS COMMITTEE

This protocol, the Informed Consent Forms, any information to be given to the patient, and relevant supporting information must be submitted to the IRB/EC by the Principal Investigator and reviewed and approved by the IRB/EC before the study is initiated. In addition, any patient recruitment materials must be approved by the IRB/EC.

The Principal Investigator is responsible for providing written summaries of the status of the study to the IRB/EC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/EC. Investigators are also responsible for promptly informing the IRB/EC of any protocol amendments (see Section 9.6).

In addition to the requirements for reporting all AEs to the Sponsor, Investigators must comply with requirements for reporting SAEs to the local health authority and IRB/EC. Investigators may receive written Investigational New Drug (IND) safety reports or other safety-related communications from the Sponsor. Investigators are responsible for ensuring that such reports are reviewed and processed in accordance with health authority requirements and the policies and procedures established by their IRB/EC, and archived in the site's study file.

8.4 CONFIDENTIALITY

The Sponsor maintains confidentiality standards by coding each patient enrolled in the study through assignment of a unique patient identification number. This means that patient names are not included in data sets that are transmitted to any Sponsor location.

Patient medical information obtained by this study is confidential and may be disclosed to third parties only as permitted by the Informed Consent Form (or separate authorization for use and disclosure of personal health information) signed by the patient (or where applicable, their legally authorised representative) unless permitted or required by law.

Medical information may be given to a patient's personal physician or other appropriate medical personnel responsible for the patient's welfare, for treatment purposes.

Data generated by this study must be available for inspection upon request by representatives of the U.S. Food and Drug Administration (FDA) and other national and local health authorities, Sponsor monitors, representatives, and collaborators, and the IRB/EC for each study site, as appropriate.

8.5 FINANCIAL DISCLOSURE

Investigators will provide the Sponsor with sufficient, accurate financial information in accordance with local regulations to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate health authorities.

Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

9. STUDY DOCUMENTATION, MONITORING, AND ADMINISTRATION

9.1 STUDY DOCUMENTATION

The Investigator must maintain adequate and accurate records to enable the conduct of the study to be fully documented, including but not limited to the protocol, protocol amendments, Informed Consent Forms, and documentation of IRB / EC and governmental approval. In addition, at the end of the study, the Investigator will receive the patient data, including an audit trail containing a complete record of all changes to data.

9.2 PROTOCOL DEVIATIONS

The Investigator should document and explain any protocol deviations. The Investigator should promptly report any deviations that might have an impact on patient safety and data integrity to the Sponsor and to the IRB / EC in accordance with established IRB / EC policies and procedures.

9.3 SITE INSPECTIONS

Site visits will be conducted by the Sponsor or an authorised representative for inspection of study data, patients' medical records, and eCRFs. The Investigator will permit national and local health authorities, Sponsor monitors, representatives, and collaborators, and the IRBs/ECs to inspect facilities and records relevant to this study.

9.4 ADMINISTRATIVE STRUCTURE

This study is sponsored by Roche, who has overall responsibility for this study.

A CRO will be responsible for clinical operations oversight, data management support, and medical monitoring.

A 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, providing recommendations regarding continued enrolment in each study cohort, and conducting pre-planned safety run-in reviews.

Tumour tissue and exploratory blood / plasma samples will be sent to a Roche-approved designated laboratory for analysis of biomarker status.

9.5 PUBLICATION OF DATA AND PROTECTION OF TRADE SECRETS

The results of this study may be published or presented at scientific meetings. If this is foreseen, the Investigator agrees to submit all manuscripts or abstracts to the Sponsor prior to submission. This allows the Sponsor to protect proprietary information and to provide comments based on information from other studies that may not yet be available to the Investigator.

The Sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the Sponsor will generally support publication of multi-centre trials only in their entirety and not as individual centre data. In this case, a coordinating Investigator will be designated by mutual agreement.

Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements. Any formal publication of the study in which contribution of Sponsor personnel exceeded that of conventional monitoring will be considered as a joint publication by the Investigator and the appropriate Sponsor personnel.

Any inventions and resulting patents, improvements, and/or know-how originating from the use of data from this study will become and remain the exclusive and unburdened property of the Sponsor, except where agreed otherwise.

9.6 PROTOCOL AMENDMENTS

Any protocol amendments will be prepared by the Sponsor. Protocol amendments will be submitted to the IRB/EC and to regulatory authorities in accordance with local regulatory requirements.

Approval must be obtained from the IRB / EC and regulatory authorities (as locally required) before implementation of any changes, except for changes necessary to eliminate an immediate hazard to patients or changes that involve logistical or administrative aspects only (e.g., change in Medical Monitor or contact information).

10. REFERENCES

A'Hern RP. Sample size tables for exact single-stage phase II designs. Stat Med 2001;20:859-66.

Albanell J, Montagut C, Jones ET, et al. A phase I study of the safety and pharmacokinetics of the combination of pertuzumab (rhuMab 2C4) and capecitabine in patients with advanced solid tumors. Clin Cancer Res 2008;14(9):2726−31.

Al-Marrawi MY, Saroya BS, Brennan MC, et al. Off-label use of cetuximab plus sorafenib and panitumumab plus regorafenib to personalize therapy for a patient with V600E BRAF-mutant metastatic colon cancer. Cancer Biol Ther 2013;14:703-10.

Alymani N, Smith M, Williams D, et al. Predictive biomarkers for personalised anticancer drug use: discovery to clinical implementation. Eur J Cancer 2010;46: 869-79.

Arnold D, Graeven U, Lerchenmuller CA et al. Brigitta Maintenance strategy with fluoropyrimidines (FP) plus bevacizumab (Bev), bev alone, or no treatment, following a standard combination of FP, oxaliplatin (Ox), and Bev as first-line treatment for patients with metastatic colorectal cancer (mCRC): A phase III non-inferiority trial (AIO KRK 0207). J Clin Oncol 32:5s, 2014 (suppl; abstr 3503)

Avastin® (Bevacizumab) Investigator's Brochure Nineteenth Version, November 2011.

Bancroft CC, Chen Z, Dong G, et al. Coexpression of proangiogenic factors IL-8 and VEGF by human head and neck squamous cell carcinoma involves coactivation by MEK-MAPK and IKK-NF-kappaB signal pathways. Clin Cancer Res 2001;7:435−42.

Bancroft CC, Chen Z, Yeh J, et al. Effects of pharmacologic antagonists of epidermal growth factor receptor, PI3K and MEK signal kinases on NF-kappaB and AP-1 activation and IL-8 and VEGF expression in human head and neck squamous cell carcinoma lines. Int J Cancer 2002;99:538−48.

Basso M, Strippoli A, Orlandi A, et al. KRAS mutational status affects oxaliplatin-based chemotherapy independently from basal mRNA ERCC-1 expression in metastatic colorectal cancer patients. Br J Cancer. 2013;108:115–20.

Bauer K, Nelius N, Reuschenbach M, et al. T cell responses against microsatellite instability-induced frameshift peptides and influence of regulatory T cells in colorectal cancer. Cancer Immunol Immunother 2013;62:27-37.

Bekaii-Saab T, Wu C. Seeing the forest through the trees: A systematic review of the safety and efficacy of combination chemotherapies used in the treatment of metastatic colorectal cancer. Crit Rev Oncol Hematol. 2014 Jan 15. pii: S1040-8428(14)00011-0. doi: 10.1016/j.critrevonc.2014.01.001.

Bendell J, Kim TW, Goh B, et al. Clinical activity and safety of cobimetinib (cobi) and atezolizumab in colorectal cancer (CRC). Abstract 3502. June 2016, Chicago, USA.

Bertotti A, Migliardi G, Galimi F et al. A molecularly annotated platform of patient-derived xenografts ("xenopatients") identifies HER2 as an effective therapeutic target in cetuximab-

resistant colorectal cancer. Cancer Discov. 2011 Nov;1(6):508-23. doi: 10.1158/2159-8290.CD-11-0109.

Bokemeyer C, Bondarenko I, Hartmann JT, et al. Efficacy according to biomarker status of cetuximab plus FOLFOX-4 as first-line treatment for metastatic colorectal cancer: the OPUS study. Ann Oncol 2011; 22: 1535–46.

Bokemeyer C, Bondarenko I, Makhson A, et al. Fluorouracil, leucovorin, and oxaliplatin with and without cetuximab in the first-line treatment of metastatic colorectal cancer. J Clin Oncol. 2009;27:663-71.

Bokemeyer C, Van Cutsem E, Rougier P, et al. Addition of cetuximab to chemotherapy as first-line treatment for KRAS wild-type metastatic colorectal cancer: pooled analysis of the CRYSTAL and OPUS randomised clinical trials. Eur J Cancer. 2012 Jul;48(10):1466-75. doi: 10.1016/j.ejca.2012.02.057.

Brahmer JR, Tykodi SS, Chow LQ, et al. Safety and activity of anti-PD-L1 antibody in patients with advanced cancer. N Engl J Med. 2012 Jun 28;366(26):2455-65. doi: 10.1056/NEJMoa1200694.

Butte MJ, Keir ME, Phamduy TB et al. PD-L1 interacts specifically with B7-1 to inhibit T cell proliferation. Immun 2007; 27(1):111-22.

Callahan MK, Rampal R, Harding JJ, et al. Progression of RAS-mutant leukemia during RAF inhibitor treatment. N Engl J Med. 2012 367:2316-21.

Cancer Genome Atlas Network. Comprehensive molecular characterization of human colon and rectal cancer. Nature. 2012 Jul 18;487(7407):330-7. doi: 10.1038/nature11252.

Capecitabine (Xeloda®) Summary of Product Characteristics March 2010

Chapman PB, Hauschild A, Robert C, et al. Improved survival with vemurafenib in melanoma with BRAF V600E mutation. N Engl J Med 2011;364:2507–16.

Chawla N, Butler EN, Lund J, et al. Patterns of colorectal cancer care in Europe, Australia, and New Zealand. J Natl Cancer Inst Monogr. 2013;2013(46):36-61. doi: 10.1093/jncimonographs/lgt009.

Connolly K, Brungs D, Szeto E, et al. Anticancer activity of combination targeted therapy using cetuximab plus vemurafenib for refractory BRAF (V600E)-mutant metastatic colorectal carcinoma. Curr Oncol. 2014 Feb;21(1):e151-4. doi: 10.3747/co.21.1661.

Corcoran RB, Ebi H, Turke AB, et al. EGFR-mediated re-activation of MAPK signaling contributes to insensitivity of BRAF mutant colorectal cancers to RAF inhibition with vemurafenib. Cancer Discov 2012;2:227–35.

Cunningham D, Atkin W, Lenz H, et al. (2010) Colorectal cancer. Lancet 375: 1030-47.

Diamandis M, White N, Yousef G. Personalized medicine: marking a new epoch in cancer patient management. Mol Cancer Res 2010;8:1175-87.

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.

Douillard JY, Oliner KS, Siena S, et al. Panitumumab-FOLFOX4 treatment and RAS mutations in colorectal cancer. N Engl J Med. 2013 Sep 12;369(11):1023-34. doi: 10.1056/NEJMoa1305275.

Douillard JY, Siena S, Cassidy J, et al. Randomized, phase III trial of panitumumab with infusional fluorouracil, leucovorin, and oxaliplatin (FOLFOX4) versus FOLFOX4 alone as first-line treatment in patients with previously untreated metastatic colorectal cancer: The PRIME study. J Clin Oncol. 2010;28:4697-4705.

Downward J. Targeting RAS signalling pathways in cancer therapy. Nat Rev Cancer 2003;3:11−22. Review.

Erbitux® (Cetuximab), Annex I- Summary of Product Characteristics, updated January 27, 2014. Available at: http://www.ema.europa.eu.

Ferlay J, Soerjomataram I, Ervik M, et al. GLOBOCAN 2012 v1.0, Cancer Incidence and Mortality Worldwide: IARC CancerBase No. 11 [Internet]. Lyon, France: International Agency for Research on Cancer; 2013. Available from: http://globocan.iarc.fr, accessed on 04/06/2014.

Fuchs CS, Marshall J, Barrueco J. Randomized, controlled trial of irinotecan plus infusional, bolus, or oral fluoropyrimidines in first-line treatment of metastatic colorectal cancer: Updated results from the BICC-C study. J Clin Oncol 2008;26:689–90.

Fuchs CS, Marshall J, Mitchell E, et al. Randomized, controlled trial of irinotecan plus infusional, bolus, or oral fluoropyrimidines in first-line treatment of metastatic colorectal cancer: Results from the BICC-C study. J Clin Oncol 2007;25:4779–86

Galal KM, Khaled Z, Mourad AM. Role of cetuximab and sorafenib in treatment of metastatic colorectal cancer. Indian J Cancer 2011;48:47–54

Giordano G, Febbaro A, Tomaselli E, et al. Cancer-related CD15/FUT4 Overexpression Decreases Benefit to Agents Targeting EGFR or VEGF Acting as a Novel RAF-MEK-ERK Kinase Downstream Regulator in Metastatic Colorectal Cancer. J Exp Clin Cancer Res 2015;34:108:1−11.

Greenson JK, Bonner JD, Ben-Yzhak O, et al. Phenotype of microsatellite unstable colorectal carcinomas: Well-differentiated and focally mucinous tumors and the absence of dirty necrosis correlate with microsatellite instability. Am J Surg Pathol 2003;27:563- 70.

Guan ZZ, Xu JM, Luo RC, et al. Efficacy and safety of bevacizumab plus chemotherapy in Chinese patients with metastatic colorectal cancer: a randomized phase III ARTIST trial. Chin J Cancer. 2011 Oct;30(10):682-9. doi: 10.5732/cjc.011.10188.

Hales RK, Banchereau J, Ribas A, et al. Assessing oncologic benefit in clinical trials of immunotherapy agents. Ann Oncol 2010;21:1944−51.

Hecht JR, Mitchell E, Chidiac T, et al. A randomized phase IIIB trial of chemotherapy, bevacizumab, and panitumumab compared with chemotherapy and bevacizumab alone for metastatic colorectal cancer. J Clin Oncol 2009;27:672–80.

Houlston RS1; members of COGENT. COGENT (COlorectal cancer GENeTics) revisited. Mutagenesis. 2012 Mar;27(2):143-51. doi: 10.1093/mutage/ger059.

Hurwitz H, Fehrenbacher L, Novotny W, et al. Bevacizumab plus irinotecan, fluorouracil, and leucovorin for metastatic colorectal cancer. N Engl J Med 2004;350:2335–42.

Hurwitz H, Hainsworth J, Swanton C, et al. Targeted Therapy for Gastrointestinal Tumors Based on Molecular Profiles: Early Results From MyPathway, an Open-Label Phase IIa Basket Study in Patients With Advanced Solid Tumors. Poster 653. ASCO GI Jan 2016, San Francisco, USA.

Hurwitz HI, Yi J, Ince W, et al. The clinical benefit of bevacizumab in metastatic colorectal cancer is independent of K-RAS mutation status: analysis of a phase III study of bevacizumab with chemotherapy in previously untreated metastatic colorectal cancer. Oncologist 2009; 14: 22–28.

Kabbinavar FF, Hambleton J, Mass RD et al. Combined analysis of efficacy: the addition of bevacizumab to fluorouracil/leucovorin improves survival for patients with metastatic colorectal cancer. J Clin Oncol. 2005a Jun 1;23(16):3706-12.

Kabbinavar FF, Schulz J, McCleod M et al. Addition of bevacizumab to bolus fluorouracil and leucovorin in first-line metastatic colorectal cancer: results of a randomized phase II trial. J Clin Oncol. 2005b Jun 1;23(16):3697-705.

Kakavand H, Wilmott JS, Menziew AM, et al. PD-L1 expression and tumor-infiltrating lymphocytes define different subsets of MAPK-inhibitor treated melanoma patients. Clin Cancer Res 2015;21:3140−8.

Kaplan R, Maughan T, Crook A et al. Evaluating many treatments and biomarkers in oncology: a new design. J Clin Oncol. 2013 Dec 20;31(36):4562-8.

Karim-Kos HE, de Vries E, Soerjomataram I, et al. Recent trends of cancer in Europe: a combined approach of incidence, survival and mortality for 17 cancer sites since the 1990s. Eur J Cancer. 2008 Jul;44(10):1345-89. doi: 10.1016/j.ejca.2007.12.015.

Karsa LV, Lignini TA, Patnick J, et al. The dimensions of the CRC problem. Best Pract Res Clin Gastroenterol. 2010 Aug;24(4):381-96. doi: 10.1016/j.bpg.2010.06.004.

Kemp Z, Thirlwell C, Sieber O, et al. An update on the genetics of colorectal cancer. Hum Mol Genet. 2004 Oct 1;13 Spec No 2:R177-85.

Koopman M, Simkens L, May A et al. Final results and subgroup analyses of the phase 3 CAIRO3 study: Maintenance treatment with capecitabine and bevacizumab versus observation after induction treatment with chemotherapy and bevacizumab in metastatic colorectal cancer (mCRC). J Clin Oncol 2014 32 (S 3): abstr LBA388.

La Vecchia C, Bosetti C, Lucchini F, et al. Cancer mortality in Europe, 2000-2004, and an overview of trends since 1975. Ann Oncol 2010;21:1323–60.

Le DT, Uram JN, Wang H, et al. PD-1 Blockade in Tumors with Mismatch-Repair Deficiency. N Engl J Med. 2015 Jun 25;372(26):2509-20. doi: 10.1056/NEJMoa1500596.

Lieu C, Bendell J, Powderly JD, et al. Safety and efficacy of MPDL3280A (anti-PDL1) in combination with bevacizumab (bev) and/or chemotherapy (chemo) in patients (pts) with locally advanced or metastatic solid tumors. Ann Oncol 2014;25 (suppl 4; abstr 1049O).

Lievre A, Bachet JB, Le Corre D, et al. KRAS mutation status is predictive of response to cetuximab therapy in colorectal cancer. Cancer Res. 2006;66:3992–95.

Lin YL, Liang YH, Tsai JH, et al. Oxaliplatin-based chemotherapy is more beneficial in KRAS mutant than in KRAS wild-type metastatic colorectal cancer patients. PLoS One. 2014 Feb 4;9(2):e86789. doi: 10.1371/journal.pone.0086789.

Liu I, Mayes PA, Eastman S, et al. The BRAF and MEK inhibitors dabrafenib and trametinib: effects on immune function and ombination with immunomodulatory antibodies targeting PD-1, PD-L1, and CTLA-4. Clin Cancer Res 2015;21:1639−51.

Llosa NJ, Cruise M, Tam A, et al. The vigorous immune microenvironment of microsatellite instable colon cancer is balanced by multiple counter-inhibitory checkpoints. Cancer Discovery 2015:5:43-51:1−18.

Loi S, Dushyanthen S, Beavis PA, et al. RAS/MAPK activation is associated with reduced tumor-infiltrating lymphocytes in triple-negative breast cancer: therapeutic cooperation between MEK and PD-1/PD-L1 immune checkpoint inhibitors. Clin Cancer Res 2016 Mar 15;22(6):1499-509. doi: 10.1158/1078-0432.CCR-15-1125

Manning EA, Ullman JG, Leatherman JM, et al. A vascular endothelial growth factor receptor-2 inhibitor enhances antitumor immunity through an immune-based mechanism. Clin Cancer Res 2007;13:3951–9.

Martín-Martorell P, Roselló S, Rodríguez-Braun E, et al. Biweekly cetuximab and irinotecan in advanced colorectal cancer patients progressing after at least one previous line of chemotherapy: results of a phase II single institution trial. Br J Cancer 2008 Aug 5;99(3):455-8.

McClain KL, Eckstein O. Clinical features and diagnosis of hemophagocytic lymphohistiocytosis. Up to Date [resource on the Internet]. 2014 [updated 29 October 2018; cited: 17 May 2019]. Available from: https://www.uptodate.com/contents/clinical-features-and-diagnosis-of-hemophagocytic-lymphohistiocytosis.

Moorcraft SY, Smyth EC, Cunningham D. The role of personalized medicine in metastatic colorectal cancer: an evolving landscape. Therap Adv Gastroenterol. 2013 Sep;6(5):381-95. doi: 10.1177/1756283X13491797.

Narita Y, Taniguchi H, Komori A, et al. CA19-9 level as a prognostic and predictive factor of bevacizumab efficacy in metastatic colorectal cancer patients undergoing oxaliplatin-based chemotherapy. Cancer Chemother Pharmacol. 2014 Feb;73(2):409-16. doi: 10.1007/s00280-013-2367-7.

National Comprehensive Cancer Network. Colon Cancer (Version 3.2014). http://www.nccn.org/professionals/physician_gls/f_guidelines.asp. Accessed May 8, 2014.

Perjeta® (Pertuzumab) Investigator's Brochure Fifteenth Version, February 2016.

Phan VT, Wu X, Cheng JH, et al. Oncogenic RAS pathway activation promotes resistance to anti-VEGF therapy through G-CSF-induced neutrophil recruitment. Proc Natl Acad Sci USA 2013;110:6079−84.

Prahallad A, Sun C, Huang S, et al. Unresponsiveness of colon cancer to $BRAF^{V600E}$ inhibition through feedback activation of EGFR. Nature 2012;483:100–3.

Primrose J, Falk S, Finch-Jones M et al. Systemic chemotherapy with or without cetuximab in patients with resectable colorectal liver metastasis: the New EPOC randomised controlled trial. Lancet Oncol. 2014 May;15(6):601-11.

Ramanathan RK, Hwang JJ, Zamboni WC, et al. Low overexpression of HER-2/neu in advanced colorectal cancer limits the usefulness of trastuzumab (Herceptin) and irinotecan as therapy. A phase II trial. Cancer Invest. 2004;22(6):858-65.

Ravelli A, Minoia F, Davi S, et al. 2016 classification criteria for macrophage activation syndrome complicating systemic juvenile idiopathic arthritis: a European League Against Rheumatism/American College of Rheumatology/Paediatric Rheumatology International Trials Organisation Collaborative Initiative. Ann Rheum Dis 2016;75:481-9.

Reinacher-Schick A, Schmiegel W. Impact of KRAS status on survival in patients (pts.) with metastatic colorectal cancer (mCRC) undergoing bevacizumab (bev) containing chemotherapy regimen—analysis of the AIO Colorectal Cancer Study Group. Ann Oncol 2010:21(Suppl 8) (Abstr 585PD)

Roberts PJ, Der CJ. Targeting the RAF-MEK-ERK mitogen-activated protein kinase cascade for the treatment of cancer [review]. Oncogene 2007;26:3291−310.

Roland CL, Lynn KD, Toombs JE, et al. Cytokine levels correlate with immune cell infiltration after anti-VEGF therapy in preclinical mouse models of breast cancer. PLOS One 2009;Nov 3;4(11):e7669.

Roth BJ, Krilov L, Adams S, et al. Clinical cancer advances 2012: Annual report on progress against cancer from the American Society of Clinical Oncology. J Clin Oncol. 2013;31:131–61.

Saltz LB, Clarke S, Díaz-Rubio E, et al. Bevacizumab in combination with oxaliplatin-based chemotherapy as first-line therapy in metastatic colorectal cancer: A randomized phase III study. J Clin Oncol 2008;26:2013–19.

Sano M, Fukuda K, Sato T, et al. ERK and p38 MAPK, but not NF-kappaB, are critically involved in reactive oxygen species-mediated induction of IL-6 by angiotensin II in cardiac fibroblasts. Circ Res 2001;89:661−9.

Sartore-Bianchi A, Trusolino L, Martino C, et al. Dual-targeted therapy with trastuzumab and lapatinib in treatment-refractory, KRAS codon 12/13 wild-type, HER2-positive metastatic colorectal cancer (HERACLES): a proof-of-concept, multicentre, open-label, phase 2 trial. Lancet Oncol. 2016 Jun;17(6):738-46. doi: 10.1016/S1470-2045(16)00150-9.

Savari S, Vinnakota K, Zhang Y, et al. Cysteinyl leukotrienes and their receptors: Bridging inflammation and colorectal cancer. World J Gastroenterol. 2014 Jan 28;20(4):968-77.

Schmoll HJ, Van Cutsem E, Stein A, et al. ESMO Consensus Guidelines for management of patients with colon and rectal cancer. a personalized approach to clinical decision making. Ann Oncol. 2012 Oct;23(10):2479-516.

Selcukbiricik F, Erdamar S, Ozkurt CU, et al. The role of K-RAS and B-RAF mutations as biomarkers in metastatic colorectal cancer. J BUON. 2013 Jan-Mar;18(1):116-23.

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.

Seymour M. Conceptual approaches to metastatic disease. Ann Oncol. 2012; 23 (Suppl 10): x77–80.

Shrimali RK, Yu Z, Theoret MR, et al. Antiangiogenic agents can increase lymphocyte infiltration into tumor and enhance the effectiveness of adoptive immunotherapy of cancer. Cancer Res 2010;70:6171–80.

Slamon DJ, Clark GM, Wong SG, Levin WJ, Ullrich A, McGuire WL. Human breast cancer: correlation of relapse and survival with amplification of the HER-2/neu oncogene. Science. 1987 Jan 9;235(4785):177–182.

Slamon DJ, Godolphin W, Jones LA, Holt JA, Wong SG, Keith DE, Levin WJ, Stuart SG, Udove J, Ullrich A. Studies of the HER-2/neu proto-oncogene in human breast and ovarian cancer. Science. 1989 May 12;244(4905):707–712.

Smedt LD, Lemahier J, Palmans S, et al. Microsatellite instable vs stable colon carcinomas: analysis of tumour heterogeneity, inflammation and angiogenesis. Br J Cancer 2015;113:500−9.

Stein A, Bokemeyer C. How to select the optimal treatment for first line metastatic colorectal cancer. World J Gastroenterol. 2014 Jan 28;20(4):899-907. doi: 10.3748/wjg.v20.i4.899.

Stintzing S, Fischer von Weikersthal L, Decker T, et al. FOLFIRI plus cetuximab versus FOLFIRI plus bevacizumab as first-line treatment for patients with metastatic colorectal cancer-subgroup analysis of patients with KRAS: mutated tumours in the randomised German AIO study KRK-0306. Ann Oncol. 2012 Jul;23(7):1693-9. doi: 10.1093/annonc/mdr571.

Strickler JH, Hurwitz HI. Maintenance Therapy for First-Line Metastatic Colorectal Cancer: Activity and Sustainability. Oncologist 2012a; 17:9-10.

Strickler JH, Hurwitz HI. Bevacizumab-based therapies in the first-line treatment of metastatic colorectal cancer. Oncologist. 2012b;17(4):513-24. doi: 10.1634/theoncologist.2012-0003.

Tabernero J, Chan E, Baselga J, et al.VE-BASKET: A Simon 2-stage Adaptive Design, Phase II, Histology-Independent Study in Non-Melanoma Solid Tumors Harboring $BRAF^{V600}$ Mutations: Activity of Vemurafenib With or Without Cetuximab in Colorectal Cancer [poster #3518]. ASCO June 2014, Chicago, United States of America.

Tabernero J, Pfeiffer P, Cervantes A. Administration of cetuximab every 2 weeks in the treatment of metastatic colorectal cancer: an effective, more convenient alternative to weekly administration? Oncologist. 2008 Feb;13(2):113-9. doi: 10.1634/theoncologist.2007-0201.

Tebbutt NC, Wilson K, Gebski VJ, et al. Capecitabine, bevacizumab, and mitomycin in first-line treatment of metastatic colorectal cancer: Results of the Australasian Gastrointestinal Trials Group Randomized Phase III MAX Study. J Clin Oncol 2010;28:3191–98.

Tejpar S, Lenz H-J, Köhne C-H et al. Effect of KRAS and NRAS mutations on treatment outcomes in patients with metastatic colorectal cancer (mCRC) treated first-line with cetuximab plus FOLFOX4: New results from the OPUS study. J Clin Oncol 32, 2014a (suppl 3; abstr LBA444)

Tejpar S, Piessevaux H. Personalized medicine in metastatic colorectal cancer treated with anti-epidermal growth factor receptor agents: A future opportunity? Asia Pac J Clin Oncol. 2014b Mar;10 Suppl 1:2-10. doi: 10.1111/ajco.12176.

Temraz S, Mukherji D, Shamseddine A. Sequencing of treatment in metastatic colorectal cancer: Where to fit the target. World J Gastroenterol. 2014 Feb 28;20(8):1993-2004.

Tol J, Koopman M, Cats A, et al. Chemotherapy, bevacizumab, and cetuximab in metastatic colorectal cancer. N Engl J Med 2009;360:563–72.

Urruticoechea A, Rizwanullah M, Im S-A, et al. PHEREXA: A phase III study of trastuzumab (H) + capecitabine (X) ± pertuzumab (P) for patients (pts) who progressed during/after one line of H-based therapy in the HER2-positive metastatic breast cancer (MBC) setting. Abstract 504. ASCO June 2016, Chicago, USA.

Valtorta E, Martino C, Sartore-Bianchi A, et al. Assessment of a HER2 scoring system for colorectal cancer: results from a validation study. Mod Pathol. 2015 Nov;28(11):1481-91. doi: 10.1038/modpathol.2015.98.

Van Cutsem E, Kohne CH, Hitre E, et al. Cetuximab and chemotherapy as initial treatment for metastatic colorectal cancer. N Engl J Med. 2009;360:1408–17.

Van Cutsem E, Kohne CH, Lang I, et al. Cetuximab plus irinotecan, fluorouracil, and leucovorin as first-line treatment for metastatic colorectal cancer: updated analysis of overall survival according to tumor KRAS and BRAF mutation status. J Clin Oncol 2011; 29: 2011–19.

Van Cutsem E, Nordlinger B, Cervantes A, et al. Advanced colorectal cancer: ESMO Clinical Practice Guidelines for treatment. Ann Oncol. 2010: 21 (Suppl 5): vi93–7.

Van de Velde CJ, Boelens PG, Borras JM, et al. EURECCA colorectal: multidisciplinary management: European consensus conference colon & rectum. Eur J Cancer. 2014 Jan;50(1):1.e1-1.e34. doi: 10.1016/j.ejca.2013.06.048.

Vectibix (Panitumumab), Annex I- Summary of Product Characteristics, updated March 10, 2014. Available at: http://www.ema.europa.eu.

Zelboraf® (Vemurafenib) Investigator's Brochure Eleventh Version, September 2014.

Venook AP, Saltz LB. Biologic agents in the treatment of colorectal cancer: the last decade; the lost decade? Am Soc Clin Oncol Educ Book. 2013. doi: 10.1200/EdBook_AM.2013.33.e121.

Vilar E, Gruber SB. Microsatellite instability in colorectal cancer-the stable evidence. Nat Rev Clin Oncol 2010;7:153-62.

Wolchok JD, Hoos A, O'Day S, et al. Guidelines for the evaluation of immune therapy activity in solid tumors: immune-related response criteria. Clin Can Res 2009;15:7412−20.

Yang H, Higgins B, Kolinsky K, et al. Antitumor activity of BRAF inhibitor vemurafenib in preclinical models of BRAF mutant colorectal cancer. Cancer Res 2012;72:779–89.

Yarden Y, Sliwkowski MX. Untangling the ErbB signalling network. Nat Rev Mol Cell Biol. 2001 Feb;2(2):127-37.

Yuan ZX, Wang XY, Qin QY, et al. The prognostic role of BRAF mutation in metastatic colorectal cancer receiving anti-EGFR monoclonal antibodies: a meta-analysis. PLoS One. 2013 Jun 11;8(6):e65995. doi: 10.1371/journal.pone.0065995

Zhang S, Chen Y, Zhu Z, et al. Differential expression of carbohydrate antigen 19-9 in human colorectal cancer: A comparison with colon and rectal cancers. Mol Clin Oncol. 2013 Nov;1(6):1072-78.

Zhang X, Kerlaria S, Kerstetter J, et al. The functional and prognostic implications of regulatory T cells in colorectal carcinoma. J Gastrointest Oncol 2015;6:307−13.

11. APPENDICES

11.1 APPENDIX 1 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* *Supple-mental 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.

11.2 APPENDIX 2 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	
Haematology and blood chemistry [p]		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
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)
Study medication administration [x]		Every cycle		
Subsequent anti-cancer therapies (see [c])				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
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.

x. Patients in the Experimental Arm will receive: The first six patients in this cohort received 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. Based on results of February 2016 iDMC recommendations, subsequent patients in this cohort will receive 1,600 - 2,400 mg/m^2 5-FU administered via 46-hour IV infusion (IV bolus is not permitted), in combination with LV 400 mg/m^2 administered via 2-hour infusion, on Day 1 of every 2-week cycle. In addition, patients will receive cetuximab 500 mg/m^2 via IV infusion on Day 1 of every 2-week cycle and vemurafenib 960 mg b.i.d. orally. 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 treatment cycles (e.g. ECOG performance status) will be defined by the treatment cycles of concurrently administered bevacizumab.

11.3 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 (approximately every 4 weeks)	(≤ 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]		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 Cycle 1 then every 2 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 (approximately every 4 weeks)	(≤ 30 days after last dose of study treatment)	Every 3 months until May 31, 2019 (see Appendix 19)
Tuberculosis test [o]	x			
HIV, HBV, HCV serology [p]	X			
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*	
Adverse events (including SAEs) [t]		Every cycle	x	x (as applicable)
Study medication administration [u]		Every cycle		

	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 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. If a 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 (control arm) or the treatment cycles of concurrently administered bevacizumab and atezolizumab (experimental arm).

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 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 will be discontinued from the study after completion of the adverse event reporting period. 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, 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 CRF.

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. 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 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. Results from every second cycle only will be recorded in the CRF.

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 urine pregnancy test is positive, it must be confirmed by a serum pregnancy test.

o. Patients with active tuberculosis are not eligible for Cohort 2 and will be excluded from entering the Maintenance Phase of the study. Investigators must confirm absence of active disease in patients with a positive test.

p. 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 2.

q. Up to and including May 31, 2019, tumour assessments will be conducted according to RECIST1.1 for Cohort 2, and additionally according to mRECIST for the experimental arm of Cohort 2. 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. Disease status during maintenance treatment will be determined based on comparison with the tumour assessment done at the end of induction treatment. Up to and including May 31, 2019, tumour assessments will be conducted every 8 weeks from the start of maintenance treatment regardless of treatment cycle delays. After May 31, 2019, disease status will not be collected for the study and tumour assessments may be conducting per local practice. Tumour assessments for Cohort 2 control arm

patients will not be collected for study purposes after disease progression per RECIST 1.1 has been documented or May 31, 2019, whichever occurs first. Tumour assessments for Cohort 2 experimental arm patients will not be collected for study purposes after disease progression per mRECIST has been documented or May 31, 2019, whichever occurs first. 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 or mRECIST (as described above) 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 2 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 5-FU or capecitabine 1,600 – 2,400 mg/m^2 5-FU administered via 46-hour IV infusion (IV bolus is not permitted) and LV 400 mg/m^2 administered via a 2-hour infusion given day 1 every 2 weeks; or 1000 mg/m^2 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. If a 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 (control arm) or concurrently administered bevacizumab and atezolizumab (experimental arm).

11.4 APPENDIX 4 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*	
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, 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 tumour assessment done at the end of induction treatment. Up to and including May 31, 2019, tumour 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.

11.5 APPENDIX 5 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	
Tuberculosis test [o]	x			
HIV, HBV, HCV serology [p]	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
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)
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		

	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
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.

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 treatment 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.

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 urine pregnancy test is positive, it must be confirmed by a serum pregnancy test.

o. Patients with active tuberculosis are not eligible for Cohort 4 and will be excluded from entering the Maintenance Phase of the study. Investigators must confirm absence of active disease in patients with a positive test.

p. 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 4.

q. LVEF must be assessed in all Cohort 4 patients prior to randomization. Only experimental arm patients require subsequent LVEF monitoring which should be conducted every 6 cycles after Cycle 4. In addition, if any experimental arm patient develops clinical signs or symptoms suspicious of cardiac failure they should undergo an LVEF assessment without delaying until the next scheduled assessment (i.e. if indicated prior to the next scheduled assessment). For experimental arm patients who restart cobimetinib following a delay due to asymptomatic or symptomatic LVEF decrease, LVEF must be assessed at 2, 4, 10, and 16 weeks, then every 6 cycles after restarting treatment (see Appendix 16). Evaluation of LVEF must be performed by the same method (ECHO or MUGA) for each patient. It is strongly encouraged that the same laboratory and operator perform ECHO/MUGA scans for each individual patient. The treatment discontinuation visit evaluation of LVEF does not need to be performed at the treatment discontinuation visit if an evaluation has been performed within the last 12 weeks and there are no clinically significant findings and/or changes from baseline.

r. If an ophthalmology exam was done within 12 weeks of the discontinuation visit and was normal, it does not need to be repeated.

s. Up to and including May 31, 2019, tumour assessments will be conducted according to RECIST1.1, and additionally according to mRECIST for patients in the experimental arm. 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. Disease status during maintenance treatment will be determined based on comparison with the tumour assessment done at the end of induction treatment. Up to and including May 31, 2019, tumour assessments will be conducted every 8 weeks from the start of maintenance treatment regardless of treatment cycle delays. After May 31, 2019, disease status will not be collected for the study and tumour assessments may be conducting per local practice. Tumour assessments for control arm patients will not be collected for study purposes after disease progression per RECIST 1.1 has been documented or May 31, 2019, whichever occurs first. Tumour assessments for experimental arm patients will not be collected for study purposes after disease progression per mRECIST has been documented or May 31, 2019, whichever occurs first. 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 or mRECIST (as described above) conducted every 8 weeks until progression or May 31, 2019, whichever comes first.

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

u. 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 on the days indicated, unless otherwise specified (see Appendix 17 and the Laboratory Manual).

v. Patients in the experimental arm of Cohort 4 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.

w. Patients in the experimental arm will receive cobimetinib 60 mg orally once daily 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. Atezolizumab will be administered at a fixed dose of 840 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). 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 treatment cycles (e.g. ECOG performance status) will be defined by the treatment cycles of concurrently administered bevacizumab.

11.6 APPENDIX 6 FOLFOX REGIMENS: INDUCTION TREATMENT PHASE

The choice of FOLFOX regimen administered with bevacizumab in the Induction Treatment Phase is according to the Investigator's discretion. Typical FOLFOX regimens are described below.

FOLFOX-4

- Oxaliplatin: 85 mg/m^2 by 2-hour IV infusion, Day 1 of every 2 week cycle
- Leucovorin: 200 mg/m^2 by 2-hour IV infusion, Day 1 and Day 2 of every 2 week cycle
- 5-FU: 400 mg/m^2 IV bolus loading dose on Day 1 then 600 mg/m^2 by 22-hour IV infusion, Day 1 and Day 2 of every 2 week cycle.

FOLFOX-6

- Oxaliplatin: 100 mg/m^2 by 2-hour IV infusion, Day 1 of every 2 week cycle
- Leucovorin: 400 mg/m^2 by 2-hour IV infusion, Day 1 of every 2 week cycle
- 5-FU: 400 mg/m^2 IV bolus loading dose then 3,000 mg/m^2 by 46-hour IV infusion, Day 1 of every 2 week cycle

modified FOLFOX-6

- Oxaliplatin: 85 mg/m^2 by 2-hour IV infusion on Day 1 of every 2 week cycle
- Leucovorin: 400 mg/m^2 by 2-hour IV infusion on Day 1 of every 2 week cycle
- 5-FU: 400 mg/m^2 IV bolus loading dose on Day 1 then 2,400 by 46-hour IV infusion starting Day 1 of every 2 week cycle

FOLFOX-7

- Oxaliplatin: 130 mg/m^2 by 2-hour IV infusion, Day 1 of every 2 week cycle
- Leucovorin: 400 mg/m^2 by 2-hour IV infusion, Day 1 of every 2 week cycle
- 5-FU: 2,400 mg/m^2 by 46-hour IV infusion, Day 2 of every 2 week cycle.

modified FOLFOX-7

- Oxaliplatin: 85 mg/m^2 by 2-hour IV infusion, Day 1 of every 2 week cycle
- Leucovorin: 200 mg/m^2 by 2-hour IV infusion, Day 1 of every 2 week cycle
- 5-FU: 2,400 mg/m^2 by 46-hour IV infusion, Day 2 of every 2 week cycle.

11.7 APPENDIX 7 CAPECITABINE DOSE CALCULATION BY BODY SURFACE AREA

	Full dose 1000 mg/m^2	Number of 150 mg tablets and/or 500 mg tablets per administration (each administration to be given morning and evening)		Reduced dose (75%) 750 mg/m^2	Reduced dose (50%) 500 mg/m^2
Body Surface Area (m^2)	Dose per administration (mg)	150 mg	500 mg	Dose per administration (mg)	Dose per administration (mg)
≤ 1.26	1150	1	2	800	600
1.27 - 1.38	1300	2	2	1000	600
1.39 - 1.52	1450	3	2	1100	750
1.53 - 1.66	1600	4	2	1200	800
1.67 - 1.78	1750	5	2	1300	800
1.79 - 1.92	1800	2	3	1400	900
1.93 - 2.06	2000	-	4	1500	1000
2.07 - 2.18	2150	1	4	1600	1050
≥ 2.19	2300	2	4	1750	1100

11.8 APPENDIX 8 ECOG PERFORMANCE STATUS

Grade	Description
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light housework or office work
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about > 50% of waking hours
3	Capable of only limited self-care, confined to a bed or chair □ 50% of waking hours
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
5	Dead

11.9 APPENDIX 9 PRE-EXISTING AUTOIMMUNE DISEASES

Patients should be carefully questioned regarding their history of acquired or congenital immune deficiencies or autoimmune disease. Patients with any history of immune deficiencies or autoimmune disease are excluded from participating in the study. Possible exceptions to this exclusion could be patients with a medical history of such entities as atopic disease or childhood arthralgias where the clinical suspicion of autoimmune disease is low. Patients with a history of autoimmune-related hypothyroidism on a stable dose of thyroid replacement hormone may be eligible for this study. In addition, transient autoimmune manifestations of an acute infectious disease that resolved upon treatment of the infectious agent are not excluded (e.g., acute Lyme arthritis). Please contact the Medical Monitor regarding any uncertainty over autoimmune exclusions.

Acute disseminated encephalomyelitis	Dysautonomia	Ord's thyroiditis
Addison's disease	Epidermolysis bullosa acquista	Pemphigus
Ankylosing spondylitis	Gestational pemphigoid	Pernicious anemia
Antiphospholipid antibody syndrome	Giant cell arteritis	Polyarteritis nodusa
Aplastic anemia	Goodpasture's syndrome	Polyarthritis
Autoimmune hemolytic anemia	Graves' disease	Polyglandular autoimmune syndrome
Autoimmune hepatitis	Guillain-Barré syndrome	Primary biliary cirrhosis
Autoimmune hypoparathyroidism	Hashimoto's disease	Psoriasis
Autoimmune hypophysitis	IgA nephropathy	Reiter's syndrome
Autoimmune myocarditis	Inflammatory bowel disease	Rheumatoid arthritis
Autoimmune oophoritis	Interstitial cystitis	Sarcoidosis
Autoimmune orchitis	Kawasaki's disease	Scleroderma
Autoimmune thrombocytopenic purpura	Lambert-Eaton myasthenia syndrome	Sjögren's syndrome
Behcet's disease	Lupus erythematosus	Stiff-Person syndrome
Bullous pemphigold	Lyme disease - chronic	Takayasu's arteritis
Chronic fatigue syndrome	Meniere's syndrome	Ulcerative colitis
Chronic inflammatory demyelinating polyneuropathy	Mooren's ulcer	Vitiligo
Chung-Strauss syndrome	Morphea	Vogt-Kovanagi-Harada disease
Crohn's disease	Multiple sclerosis	Wegener's granulomatosis
Dermatomyositis	Myasthenia gravis	
	Neuromyotonia	
	Opsoclonus myoclonus syndrome	
	Optic neuritis	

11.10 APPENDIX 10 RECIST 1.1

1. MEASURABILITY OF TUMOUR AT BASELINE

1.1 Definitions

At baseline, tumour lesions/lymph nodes will be categorized measurable or non-measurable as follows:

1.1.1 Measurable

Tumour lesions: Must be accurately measured in at least one dimension (*longest* diameter in the plane of measurement is to be recorded) with a *minimum* size of:

- 10 mm by CT scan (CT scan slice thickness no greater than 5 mm).
- 10 mm caliper measurement by clinical exam (lesions which cannot be accurately measured with calipers should be recorded as non-measurable).
- 20 mm by chest X-ray.

Malignant lymph nodes: To be considered pathologically enlarged *and* measurable, a lymph node must be ≥ 15 mm in *short* axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only the *short* axis will be measured and followed.

1.1.2 Non-measurable

All other lesions, including small lesions (longest diameter < 10 mm or pathological lymph nodes with ≥ 10 to < 15 mm short axis) as well as truly non-measurable lesions. Lesions considered truly non-measurable include: leptomeningeal disease, ascites, pleural or pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, abdominal masses/abdominal organomegaly identified by physical exam that is not measurable by reproducible imaging techniques.

1.1.3 Special considerations regarding lesion measurability

Bone lesions, cystic lesions, and lesions previously treated with local therapy require particular comment:

Bone lesions:

- Bone scan, PET scan or plain films are not considered adequate imaging techniques to measure bone lesions. However, these techniques can be used to confirm the presence or disappearance of bone lesions.
- Lytic bone lesions or mixed lytic-blastic lesions, with *identifiable* soft *tissue components*, that can be evaluated by cross sectional imaging techniques such as CT or MRI can be considered as measurable lesions if the soft tissue *component* meets the definition of measurability described above.
- Blastic bone lesions are non-measurable.

Cystic lesions:

- Lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts.
- 'Cystic lesions' thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if noncystic lesions are present in the same patient, these are preferred for selection as target lesions.

Lesions with prior local treatment:

- Tumour lesions situated in a previously irradiated area, or in an area subjected to other loco-regional therapy, are usually not considered measurable unless there has been demonstrated progression in the lesion. Study protocols should detail the conditions under which such lesions would be considered measurable.

1.2 Specifications by methods of measurements

1.2.1 Measurement of lesions

All measurements should be recorded in metric notation, using calipers if clinically assessed. All baseline evaluations should be performed as close as possible to the treatment start and never more than 4 weeks before the beginning of the treatment.

1.2.2 Method of assessment

The same method of assessment and the same technique should be used to characterise each identified and reported lesion at baseline and during follow-up. Imaging based evaluation should always be done rather than clinical examination unless the lesion(s) being followed cannot be imaged but are assessable by clinical exam.

Clinical lesions: Clinical lesions will only be considered measurable when they are superficial and ≥ 10 mm diameter as assessed using calipers (e.g. skin nodules). For the case of skin lesions, documentation by colour photography including a ruler to estimate the size of the lesion is suggested. As noted above, when lesions can be evaluated by both clinical exam and imaging, imaging evaluation should be undertaken since it is more objective and may also be reviewed at the end of the study.

Chest X-ray: Chest CT is preferred over chest X-ray, particularly when progression is an important endpoint, since CT is more sensitive than X-ray, particularly in identifying new lesions. However, lesions on chest X-ray may be considered measurable if they are clearly defined and surrounded by aerated lung.

CT, MRI: CT is the best currently available and reproducible method to measure lesions selected for response assessment. This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. When CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (e.g. for body scans).

Ultrasound: Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement. Ultrasound examinations cannot be reproduced in their entirety

for independent review at a later date and, because they are operator dependent, it cannot be guaranteed that the same technique and measurements will be taken from one assessment to the next. If new lesions are identified by ultrasound in the course of the study, confirmation by CT or MRI is advised. If there is concern about radiation exposure at CT, MRI may be used instead of CT in selected instances.

Endoscopy, laparoscopy: The utilisation of these techniques for objective tumour evaluation is not advised. However, they can be useful to confirm complete pathological response when biopsies are obtained or to determine relapse in trials where recurrence following CR or surgical resection is an endpoint.

Tumour markers: Tumour markers alone cannot be used to assess objective tumour response. If markers are initially above the upper normal limit, however, they must normalise for a patient to be considered in CR. Because tumour markers are disease specific, instructions for their measurement should be incorporated into protocols on a disease specific basis.

Cytology, histology: These techniques can be used to differentiate between PR and CR in rare cases if required by protocol (for example, residual lesions in tumour types such as germ cell tumours, where known residual benign tumours can remain). When effusions are known to be a potential adverse effect of treatment (e.g. with certain taxane compounds or angiogenesis inhibitors), the cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment can be considered if the measurable tumour has met criteria for response or stable disease in order to differentiate between response (or stable disease) and progressive disease.

2. TUMOUR RESPONSE EVALUATION

2.1 Assessment of overall tumour burden and measurable disease

To assess objective response or future progression, it is necessary to estimate the *overall tumour burden at baseline* and use this as a comparator for subsequent measurements. Only patients with measurable disease at baseline should be included in protocols where objective tumour response is the primary endpoint. Measurable disease is defined by the presence of at least one measurable lesion. In studies where the primary endpoint is tumour progression (either time to progression or proportion with progression at a fixed date), the protocol must specify if entry is restricted to those with measurable disease or whether patients having non-measurable disease only are also eligible.

2.2 Baseline documentation of ‘target’ and ‘non-target’ lesions

When more than one measurable lesion is present at baseline all lesions up to a maximum of five lesions total (and a maximum of two lesions per organ) representative of all involved organs should be identified as target lesions and will be recorded and measured at baseline (this means in instances where patients have only one or two organ sites involved a maximum of two and four lesions respectively will be recorded).

Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that lend

themselves to *reproducible repeated measurements*. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion which can be measured reproducibly should be selected.

Lymph nodes merit special mention since they are normal anatomical structures which may be visible by imaging even if not involved by tumour. Pathological nodes which are defined as measurable and may be identified as target lesions must meet the criterion of a short axis of ≥ 15 mm by CT scan. Only the short axis of these nodes will contribute to the baseline sum. The short axis of the node is the diameter normally used by radiologists to judge if a node is involved by solid tumour. Nodal size is normally reported as two dimensions in the plane in which the image is obtained (for CT scan this is almost always the axial plane; for MRI the plane of acquisition may be axial, saggital or coronal). The smaller of these measures is the short axis. For example, an abdominal node which is reported as being 20 mm × 30 mm has a short axis of 20 mm and qualifies as a malignant, measurable node. In this example, 20 mm should be recorded as the node measurement. All other pathological nodes (those with short axis ≥ 10 mm but < 15 mm) should be considered non-target lesions. Nodes that have a short axis < 10 mm are considered non-pathological and should not be recorded or followed.

A *sum of the diameters* (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the *baseline sum diameters*. If lymph nodes are to be included in the sum, then as noted above, only the *short* axis is added into the sum. The baseline sum diameters will be used as reference to further characterise any objective tumour regression in the measurable dimension of the disease.

All other lesions (or sites of disease) including pathological lymph nodes should be identified as *non-target lesions* and should also be recorded at baseline. Measurements are not required and these lesions should be followed as ‘present’, ‘absent’, or in rare cases ‘unequivocal progression’. In addition, it is possible to record multiple non-target lesions involving the same organ as a single item on the case record form (e.g. ‘multiple enlarged pelvic lymph nodes’ or ‘multiple liver metastases’).

2.3 Response criteria

This section provides the definitions of the criteria used to determine objective tumour response for target lesions.

2.3.1 Evaluation of target lesions

Complete Response (CR): Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to < 10 mm.

Partial Response (PR): At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters.

Progressive Disease (PD): At least a 20% increase in the sum of diameters of target lesions, taking as reference the *smallest sum on study* (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (*Note*: the appearance of one or more new lesions is also considered progression).

Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.

2.3.2 Special notes on the assessment of target lesions

Lymph nodes. Lymph nodes identified as target lesions should always have the actual short axis measurement recorded (measured in the same anatomical plane as the baseline examination), even if the nodes regress to below 10 mm on study. This means that when lymph nodes are included as target lesions, the 'sum' of lesions may not be zero even if CR criteria are met, since a normal lymph node is defined as having a short axis of < 10 mm. Case report forms or other data collection methods may therefore be designed to have target nodal lesions recorded in a separate section where, in order to qualify for CR, each node must achieve a short axis < 10 mm. For PR, SD and PD, the actual short axis measurement of the nodes is to be included in the sum of target lesions.

Target lesions that become 'too small to measure'. While on study, all lesions (nodal and non-nodal) recorded at baseline should have their actual measurements recorded at each subsequent evaluation, even when very small (e.g. 2 mm). However, sometimes lesions or lymph nodes which are recorded as target lesions at baseline become so faint on CT scan that the radiologist may not feel comfortable assigning an exact measure and may report the mass being 'too small to measure'. When this occurs it is important that a value be recorded on the case report form. If it is the opinion of the radiologist that the lesion has likely disappeared, the measurement should be recorded as 0 mm. If the lesion is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned (*Note*: It is less likely that this rule will be used for lymph nodes since they usually have a definable size when normal and are frequently surrounded by fat such as in the retroperitoneum; however, if a lymph node is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned in this circumstance as well). This default value is derived from the 5 mm CT slice thickness (but should not be changed with varying CT slice thickness). The measurement of these lesions is potentially non-reproducible, therefore providing this default value will prevent false responses or progressions based upon measurement error. To reiterate, however, if the radiologist is able to provide an actual measure, that should be recorded, even if it is below 5 mm.

Lesions that split or coalesce on treatment. When non-nodal lesions 'fragment', the longest diameters of the fragmented portions should be added together to calculate the target lesion sum. Similarly, as lesions coalesce, a plane between them may be maintained that would aid in obtaining maximal diameter measurements of each individual lesion. If the lesions have truly coalesced such that they are no longer separable, the vector of the longest diameter in this instance should be the maximal longest diameter for the 'coalesced lesion'.

2.3.3 Evaluation of non-target lesions

This section provides the definitions of the criteria used to determine the tumour response for the group of non-target lesions. While some non-target lesions may actually be measurable, they need not be measured and instead should be assessed only *qualitatively* at the time points specified in the protocol.

CR: Disappearance of all non-target lesions and normalisation of tumour marker level. All lymph nodes must be non-pathological in size (< 10 mm short axis).

Non-CR/Non-PD: Persistence of one or more non-target lesion(s) and/or maintenance of tumour marker level above the normal limits.

PD: Unequivocal progression of existing non-target lesions. (Note: the appearance of one or more new lesions is also considered progression).

2.3.4 Special notes on assessment of progression of nontarget disease

The concept of progression of non-target disease requires additional explanation as follows:

When the patient also has measurable disease. In this setting, to achieve 'unequivocal progression' on the basis of the non-target disease, there must be an overall level of substantial worsening in non-target disease such that, even in presence of SD or PR in target disease, the overall tumour burden has increased sufficiently to merit discontinuation of therapy. A modest 'increase' in the size of one or more non-target lesions is usually not sufficient to quality for unequivocal progression status. The designation of overall progression solely on the basis of change in non-target disease in the face of SD or PR of target disease will therefore be extremely rare.

When the patient has only non-measurable disease. This circumstance arises in some Phase III trials when it is not a criterion of study entry to have measurable disease. The same general concepts apply here as noted above, however, in this instance there is no measurable disease assessment to factor into the interpretation of an increase in non-measurable disease burden. Because worsening in non-target disease cannot be easily quantified (by definition: if all lesions are truly non-measurable) a useful test that can be applied when assessing patients for unequivocal progression is to consider if the increase in overall disease burden based on the change in non-measurable disease is comparable in magnitude to the increase that would be required to declare PD for measurable disease: i.e. an increase in tumour burden representing an additional 73% increase in 'volume' (which is equivalent to a 20% increase diameter in a measurable lesion). Examples include an increase in a pleural effusion from 'trace' to 'large', an increase in lymphangitic disease from localised to widespread, or may be described in protocols as 'sufficient to require a change in therapy'. If 'unequivocal progression' is seen, the patient should be considered to have had overall PD at that point. While it would be ideal to have objective criteria to apply to non-measurable disease, the very nature of that disease makes it impossible to do so, therefore the increase must be substantial.

2.3.5 New lesions

The appearance of new malignant lesions denotes disease progression; therefore, some comments on detection of new lesions are important. There are no specific criteria for the identification of new radiographic lesions; however, the finding of a new lesion should be unequivocal: i.e. not attributable to differences in scanning technique, change in imaging modality or findings thought to represent something other than tumour (for example, some 'new' bone lesions may be simply healing or flare of pre-existing lesions). This is particularly important when the patient's baseline lesions show partial or complete response. For example, necrosis of a liver lesion may be reported on a CT scan report as a 'new' cystic lesion, which it is not.

A lesion identified on a follow-up study in an anatomical location that was not scanned at baseline is considered a new lesion and will indicate disease progression. An example of this is the patient who has visceral disease at baseline and while on study has a CT or MRI brain ordered which reveals metastases. The patient's brain metastases are considered to be evidence of PD even if he/she did not have brain imaging at baseline. If a new lesion is equivocal, for example because of its small size, continued therapy and follow-up evaluation will clarify if it represents truly new disease. If repeat scans confirm there is definitely a new lesion, then progression should be declared using the date of the initial scan.

While FDG-PET response assessments need additional study, it is sometimes reasonable to incorporate the use of FDG-PET scanning to complement CT scanning in assessment of progression (particularly possible 'new' disease). New lesions on the basis of FDG-PET imaging can be identified according to the following algorithm:

a. Negative FDG-PET at baseline, with a positive FDG-PET at follow-up is a sign of PD based on a new lesion.
b. No FDG-PET at baseline and a positive FDG-PET at follow-up:
   - If the positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT, this is PD.
   - If the positive FDG-PET at follow-up is not confirmed as a new site of disease on CT, additional follow-up CT scans are needed to determine if there is truly progression occurring at that site (if so, the date of PD will be the date of the initial abnormal FDG-PET scan).
   - If the positive FDG-PET at follow-up corresponds to a pre-existing site of disease on CT that is not progressing on the basis of the anatomic images, this is not PD.

2.4 Evaluation of best overall response

The best overall response is the best response recorded from the start of the study treatment until the end of treatment taking into account any requirement for confirmation. On occasion a response may not be documented until after the end of therapy so protocols should be clear if post-treatment assessments are to be considered in determination of best overall response. Protocols must specify how any new therapy introduced before progression will affect best response designation. The patient's best overall response assignment will depend on the findings of both target and non-target disease and will also take into consideration the appearance of new lesions. Furthermore, depending on the nature of the study and the protocol requirements, it may also require confirmatory measurement. Specifically, in non-randomised trials where response is the primary endpoint, confirmation of PR or CR is needed to deem either one the 'best overall response'. This is described further below.

2.4.1 Time point response

It is assumed that at each protocol specified time point, a response assessment occurs. Table A provides a summary of the overall response status calculation at each time point for patients who have measurable disease at baseline.

Table A: Time point response: patients with target (± non-target) disease.

Target lesions	Non-Target lesions	New Lesions	Overall response
CR	CR	No	CR
CR	Non-CR/non-PD	No	PR
CR	Not evaluated	No	PR
PR	Non-PD or not all evaluated	No	PR
SD	Non-PD or not all evaluated	No	SD
Not all evaluated	Non-PD	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

When patients have non-measurable (therefore non-target) disease only, Table B is to be used.

Table B: Time point response: patients with non-target disease only.

Non-Target lesions	New Lesions	Overall response
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD [a]
Not all evaluated	No	NE
Unequivocal PD	Yes or No	PD
Any	Yes	PD

a. "Non-CR/non-PD" is preferred over 'stable disease' for non-target disease since SD is increasingly used as endpoint for assessment of efficacy in some trials so to assign this category when no lesions can be measured is not advised

2.4.2 Missing assessments and inevaluable designation

When no imaging/measurement is done at all at a particular time point, the patient is not evaluable (NE) at that time point. If only a subset of lesion measurements are made at an assessment, usually the case is also considered NE at that time point, unless a convincing argument can be made that the contribution of the individual missing lesion(s) would not change the assigned time point response. This would be most likely to happen in the case of PD. For example, if a patient had a baseline sum of 50 mm with three measured lesions and at follow-up only two lesions were assessed, but those gave a sum of 80 mm, the patient will have achieved PD status, regardless of the contribution of the missing lesion.

2.4.3 Best overall response: all time points

The best overall response is determined once all the data for the patient is known.

Best response determination in trials where confirmation of complete or partial response IS NOT required: Best response in these trials is defined as the best response across all time points (for example, a patient who has SD at first assessment, PR at second assessment,

and PD on last assessment has a best overall response of PR). When SD is believed to be best response, it must also meet the protocol specified minimum time from baseline. If the minimum time is not met when SD is otherwise the best time point response, the patient's best response depends on the subsequent assessments. For example, a patient who has SD at first assessment, PD at second and does not meet minimum duration for SD, will have a best response of PD. The same patient lost to follow-up after the first SD assessment would be considered inevaluable.

Best response determination in trials where confirmation of complete or partial response IS required: Complete or partial responses may be claimed only if the criteria for each are met at a subsequent time point as specified in the protocol (generally 4 weeks later). In this circumstance, the best overall response can be interpreted as in Table C.

Table C: Best overall response when confirmation of CR and PR required

Overall response First time point	Overall response Subsequent time point	Best overall response
CR	CR	CR
CR	PR	SD, PD or PR [a]
CR	SD	SD provided minimum criteria for SD duration met, otherwise PD
CR	PD	SD provided minimum criteria for SD duration met, otherwise PD
CR	NE	SD provided minimum criteria for SD duration met, otherwise NE
PR	CR	PR
PR	PR	PR
PR	SD	SD
PR	PD	SD provided minimum criteria for SD duration met, otherwise PD
PR	NE	SD provided minimum criteria for SD duration met, otherwise NE
NE	NE	NE

a. If a CR is truly met at first time point, then any disease seen at a subsequent time point, even disease meeting PR criteria relative to baseline, makes the disease PD at that time point (since disease must have reappeared after CR). Best response would depend on whether minimum duration for SD was met. However, sometimes 'CR' may be claimed when subsequent scans suggest small lesions were likely still present and in fact the patient had PR, not CR at the first time point. Under these circumstances, the original CR should be changed to PR and the best response is PR.

2.4.4 Special notes on response assessment

When nodal disease is included in the sum of target lesions and the nodes decrease to 'normal' size (< 10 mm), they may still have a measurement reported on scans. This measurement should be recorded even though the nodes are normal in order not to overstate progression should it be based on increase in size of the nodes. As noted earlier, this means that patients with CR may not have a total sum of 'zero' on the case report form (CRF).

In trials where confirmation of response is required, repeated 'NE' time point assessments may complicate best response determination. The analysis plan for the trial must address how missing data/assessments will be addressed in determination of response and progression. For example, in most trials it is reasonable to consider a patient with time point responses of PR-NE-PR as a confirmed response.

Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as 'symptomatic deterioration'. Every effort should be made to document objective progression even after discontinuation of treatment. Symptomatic deterioration is not a descriptor of an objective response: it is a reason for stopping study therapy. The objective response status of such patients is to be determined by evaluation of target and non-target disease as shown in Table A, Table B, and Table C.

Conditions that define 'early progression, early death and inevaluability' are study specific and should be clearly described in each protocol (depending on treatment duration, treatment periodicity).

In some circumstances it may be difficult to distinguish residual disease from normal tissue. When the evaluation of complete response depends upon this determination, it is recommended that the residual lesion be investigated (fine needle aspirate/biopsy) before assigning a status of complete response. FDG-PET may be used to upgrade a response to a CR in a manner similar to a biopsy in cases where a residual radiographic abnormality is thought to represent fibrosis or scarring. The use of FDG-PET in this circumstance should be prospectively described in the protocol and supported by disease specific medical literature for the indication. However, it must be acknowledged that both approaches may lead to false positive CR due to limitations of FDG-PET and biopsy resolution/sensitivity.

For equivocal findings of progression (e.g. very small and uncertain new lesions; cystic changes or necrosis in existing lesions), treatment may continue until the next scheduled assessment. If at the next scheduled assessment, progression is confirmed, the date of progression should be the earlier date when progression was suspected.

2.5 Frequency of tumour re-evaluation

Frequency of tumour re-evaluation while on treatment should be protocol specific and adapted to the type and schedule of treatment. However, in the context of Phase II studies where the beneficial effect of therapy is not known, follow-up every 6–8 weeks (timed to coincide with the end of a cycle) is reasonable. Smaller or greater time intervals than these could be justified in specific regimens or circumstances. The protocol should specify which organ sites are to be evaluated at baseline (usually those most likely to be involved with metastatic disease for the tumour type under study) and how often evaluations are repeated. Normally, all target and non-target sites are evaluated at each assessment. In selected circumstances certain non-target organs may be evaluated less frequently. For example, bone scans may need to be repeated only when complete response is identified in target disease or when progression in bone is suspected.

After the end of the treatment, the need for repetitive tumour evaluations depends on whether the trial has as a goal the response rate or the time to an event (progression/death).

If ‘time to an event’ (e.g. time to progression, disease-free survival, progression-free survival) is the main endpoint of the study, then routine scheduled re-evaluation of protocol specified sites of disease is warranted. In randomised comparative trials in particular, the scheduled assessments should be performed as identified on a calendar schedule (for example: every 6–8 weeks on treatment or every 3–4 months after treatment) and should not be affected by delays in therapy, drug holidays or any other events that might lead to imbalance in a treatment arm in the timing of disease assessment.

2.6 Confirmatory measurement/duration of response

2.6.1 Confirmation

In non-randomised trials where response is the primary endpoint, confirmation of PR and CR is required to ensure responses identified are not the result of measurement error. This will also permit appropriate interpretation of results in the context of historical data where response has traditionally required confirmation in such trials. However, in all other circumstances, i.e. in randomised trials (Phase II or III) or studies where stable disease or progression are the primary endpoints, confirmation of response is not required since it will not add value to the interpretation of trial results. However, elimination of the requirement for response confirmation may increase the importance of central review to protect against bias, in particular in studies which are not blinded.

In the case of SD, measurements must have met the SD criteria at least once after study entry at a minimum interval (in general not less than 6–8 weeks) that is defined in the study protocol.

2.6.2 Duration of overall response

The duration of overall response is measured from the time measurement criteria are first met for CR/PR (whichever is first recorded) until the first date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded on study).

The duration of overall complete response is measured from the time measurement criteria are first met for CR until the first date that recurrent disease is objectively documented.

2.6.3 Duration of stable disease

Stable disease is measured from the start of the treatment (in randomised trials, from date of randomisation) until the criteria for progression are met, taking as reference the smallest sum on study (if the baseline sum is the smallest, this is the reference for calculation of PD).

The clinical relevance of the duration of stable disease varies in different studies and diseases. If the proportion of patients achieving stable disease for a minimum period of time is an endpoint of importance in a particular trial, the protocol should specify the minimal time interval required between two measurements for determination of stable disease.

REFERENCES:

Eisenhauer EA, et al. New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1). *Eur J Cancer*. 2009 Jan;45(2):228-47.

11.11 APPENDIX 11 MODIFIED RECIST (MRECIST)

Conventional response criteria may not be adequate to characterize the anti-tumour activity of immunotherapeutic agents like atezolizumab, which can produce delayed responses that may be preceded by initial apparent radiological progression, including the appearance of new lesions. Therefore, modified response criteria have been developed that account for the possible appearance of new lesions and allow radiological progression to be confirmed at a subsequent assessment. In this protocol, patients will be permitted to continue study treatment even after modified RECIST criteria for progressive disease are met if the risk/benefit ratio is judged to be favourable.

Modified RECIST is derived from RECIST, Version 1.1 conventions[1-3] and immune-related response criteria[2] (irRC).

Table A: Modified RECIST and RECIST, Version 1.1: Summary of Changes

	RECIST v1.1	Modified RECIST
New lesions after baseline	Define progression	New measurable lesions are added into the total tumour burden and followed
Non-target lesions	May contribute to the designation of overall progression	Contribute only in the assessment of a complete response
Radiographic progression	First instance of ≥ 20% increase in the sum of diameters or unequivocal progression in non-target disease	Determined only on the basis of measurable disease; may be confirmed by a consecutive assessment ≥ 4 weeks from the date first documented

1. DEFINITIONS OF MEASURABLE/NON-MEASURABLE LESIONS

All measurable and non-measurable lesions should be assessed at Screening and at the protocol-specified tumour assessment timepoints. Additional assessments may be performed, as clinically indicated for suspicion of progression. The Investigator will evaluate response to treatment using modified RECIST.

1.1 Measurable lesions

Tumour Lesions. Tumour lesions must be accurately measured in at least one dimension (longest diameter in the plane of measurement is to be recorded) with a minimum size as follows:

- 10 mm by computed tomography (CT) or magnetic resonance imaging (MRI) scan (CT/MRI scan slice thickness/interval no greater than 5 mm)
- 10-mm caliper measurement by clinical examination (lesions that cannot be accurately measured with calipers should be recorded as non-measurable)

Malignant Lymph Nodes. To be considered pathologically enlarged and measurable, a lymph node must be ≥ 15 mm in the short axis when assessed by CT scan (CT scan slice

thickness recommended to be no greater than 5 mm). At baseline and follow-up, only the short axis will be measured and followed.

1.2 Non-measurable lesions

Non-measurable tumour lesions encompass small lesions (longest diameter < 10 mm or pathological lymph nodes with short axis ≥ 10 but < 15 mm), as well as truly non-measurable lesions. Lesions considered truly non-measurable include leptomeningeal disease, ascites, pleural or pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, peritoneal spread, and abdominal mass/abdominal organomegaly identified by physical examination that is not measurable by reproducible imaging techniques.

2 SPECIAL CONSIDERATIONS REGARDING LESION MEASURABILITY

Bone lesions, cystic lesions, and lesions previously treated with local therapy require particular comment, as outlined below.

2.1 Bone lesions

Bone scan, positron emission tomography (PET) scan, or plain films are not considered adequate imaging techniques for measuring bone lesions. However, these techniques can be used to confirm the presence or disappearance of bone lesions.

Lytic bone lesions or mixed lytic-blastic lesions, with identifiable soft tissue components, that can be evaluated by cross-sectional imaging techniques such as CT or MRI can be considered as measurable lesions if the soft tissue component meets the definition of measurability described above.

Blastic bone lesions are non-measurable.

2.2 Cystic lesions

Lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts.

Cystic lesions thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same patient, these are preferred for selection as target lesions.

2.3 Lesions with prior local treatment

Tumour lesions situated in a previously irradiated area or in an area subjected to other loco-regional therapy are usually not considered measurable unless there has been demonstrated progression in the lesion. Study protocols should detail the conditions under which such lesions would be considered measurable.

3 TUMOUR RESPONSE EVALUATION

3.1 Definitions of target/non-target lesions

3.1.1 Target Lesions

When more than one measurable lesion is present at baseline, all lesions up to a maximum of five lesions total (and a maximum of two lesions per organ) representative of all involved organs should be identified as target lesions and will be recorded and measured at baseline. This means that, for instances in which patients have only one or two organ sites involved, a maximum of two lesions (one site) and four lesions (two sites), respectively, will be recorded. Other lesions (albeit measurable) in those organs will be recorded as non-measurable lesions (even if the size is > 10 mm by CT scan).

Target lesions should be selected on the basis of their size (lesions with the longest diameter) and be representative of all involved organs, but in addition, should lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement, in which circumstance, the next largest lesion that can be measured reproducibly should be selected.

Lymph nodes merit special mention since they are normal anatomical structures that may be visible by imaging even if not involved by tumour. As noted above, pathological nodes that are defined as measurable and may be identified as target lesions must meet the criterion of a short axis of ≥ 15 mm by CT scan. Only the short axis of these nodes will contribute to the baseline sum. The short axis of the node is the diameter normally used by radiologists to judge if a node is involved by solid tumour. Nodal size is normally reported as two dimensions in the plane in which the image is obtained (for CT, this is almost always the axial plane; for MRI, the plane of acquisition may be axial, sagittal, or coronal). The smaller of these measures is the short axis. For example, an abdominal node that is reported as being 20 mm x 30 mm has a short axis of 20 mm and qualifies as a malignant, measurable node. In this example, 20 mm should be recorded as the node measurement. All other pathological nodes (those with short axis ≥ 10 mm but <15 mm) should be considered non-target lesions. Nodes that have a short axis of < 10 mm are considered non-pathological and should not be recorded or followed.

Lesions irradiated within 3 weeks prior to Cycle 1, Day 1 may not be counted as target lesions.

3.1.2 Non-Target Lesions

All other lesions (or sites of disease), including pathological lymph nodes, should be identified as non-target lesions and should also be recorded at baseline. Measurements are not required.

It is possible to record multiple non-target lesions involving the same organ as a single item on the Case Report Form (CRF) (e.g., “multiple enlarged pelvic lymph nodes” or “multiple liver metastases”).

After baseline, changes in non-target lesions will contribute only in the assessment of complete response (i.e., a complete response is attained only with the complete

disappearance of all tumour lesions, including non-target lesions) and will not be used to assess progressive disease.

3.2 Calculation of sum of the diameters

A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated as a measure of tumour burden.

The sum of the diameters is calculated at baseline and at each tumour assessment for the purpose of classification of tumour responses.

Sum of the Diameters at Baseline: The sum of the diameters for all target lesions identified at baseline prior to treatment on Day 1.

Sum of the Diameters at Tumour Assessment: For every on-study tumour assessment collected per protocol or as clinically indicated, the sum of the diameters at tumour assessment will be calculated using tumour imaging scans. All target lesions and all new measurable lesions that have emerged after baseline will contribute to the sum of the diameters at tumour assessment. Hence, each net percentage change in tumour burden per assessment with use of modified RECIST accounts for the size and growth kinetics of both old and new lesions as they appear.

3.3 Response criteria

3.3.1 Evaluation of Target Lesions

Complete Response (CR): Disappearance of all target lesions. Lymph nodes that shrink to < 10 mm short axis are considered normal.

Partial Response (PR): At least a 30% decrease in the sum of the diameters of all target and all new measurable lesions, taking as reference the baseline sum of diameters, in the absence of CR.

Note: The appearance of new measurable lesions is factored into the overall tumour burden but *does not automatically qualify as progressive disease* until the sum of the diameters increases by ≥ 20% when compared with the sum of the diameters at nadir.

Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum of the diameters while on study.

Progressive Disease (PD): At least a 20% increase in the sum of diameters of all target and all new measurable lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm.

3.3.2 Impact of New Lesions on Modified RECIST

New lesions alone do not qualify as progressive disease. However, their contribution to total tumour burden is included in the sum of the diameters, which is used to determine the overall modified RECIST tumour response.

4 EVALUATION OF BEST OVERALL RESPONSE USING MODIFIED RECIST

4.1 Timepoint response

It is assumed that at each protocol-specified timepoint, a response assessment occurs. Table B provides a summary of the overall response status calculation at each timepoint for patients who have measurable disease at baseline.

4.2 Missing assessments and inevaluable designation

When no imaging/measurement is done at all at a particular timepoint, the patient is not evaluable (NE) at that timepoint. If only a subset of lesion measurements are made at an assessment, usually the case is also considered NE at that timepoint, unless a convincing argument can be made that the contribution of the individual missing lesion(s) would not change the assigned time point response. This would be most likely to happen in the case of PD. For example, if a patient had a baseline sum of 50 mm with three measured lesions and at follow-up only two lesions were assessed but those gave a sum of 80 mm, the patient will have achieved PD status, regardless of the contribution of the missing lesion.

Table B: Modified RECIST Timepoint Response Definitions

% Change in Sum of the Diameters (Including Measurable New Lesions when Present)	Target Lesion Definition	Non-Target Lesion Definition	New Measurable Lesions	New Unmeasurable Lesions	Overall Modified RECIST Timepoint Response
−100% [a]	CR	CR	No	No	CR
−100% a	CR	Non-CR or not all evaluated	No	No	PR
≤ −30%	PR	Any	Yes or No	Yes or No	PR
> −30% to < +20%	SD	Any	Yes or No	Yes or No	SD
Not all evaluated	Not evaluated	Any	Yes or No	Yes or No	NE
≥ +20%	PD	Any	Yes or No	Yes or No	PD

a. When lymph nodes are included as target lesions, the % change in the sum of the diameters may not be 100% even if complete response criteria are met since a normal lymph node is defined as having a short axis of < 10 mm. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to < 10 mm in order to meet the definition of CR.

4.3 Best overall response: all timepoints

The best overall response is determined once all the data for the patient are known.

The best overall response according to modified RECIST is interpreted as below:

a. **CR:** Complete disappearance of all tumour lesions (target and non-target) and no new measurable or unmeasurable lesions, confirmed by a consecutive assessment ≥ 4 weeks from the date first documented. All lymph nodes short axes must be < 10 mm.

b. **PR:** Decrease in the sum of the diameters of all target and all new measurable lesions ≥ 30% relative to baseline, in the absence of CR, confirmed by a consecutive assessment ≥ 4 weeks from the date first documented.

c. **SD:** Criteria for CR, PR, and PD are not met.

d. **PD:** Increase in the sum of the diameters of all target and all new measurable lesions ≥ 20% relative to the nadir, which may be confirmed by a consecutive assessment ≥ 4 weeks from the date first documented as follows:

   The confirmatory assessment shows an additional measurable increase in tumour burden as measured by the sum of the diameters of all target and all new measurable lesions.

This protocol allows patients to continue to receive study treatment even after confirmed radiographic PD per modified RECIST, and patients may achieve a best overall response of PR or CR based on tumour regression achieved at any time prior to study treatment discontinuation.

REFERENCES:

1. Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer 2009;45:228−47.
2. Wolchok JD, Hoos A, O'Day S, et al. Guidelines for the evaluation of immune therapy activity in solid tumors: immune-related response criteria. Clin Can Res 2009;15:7412−20.
3. Topalian SL, Hodi FS, Brahmer JR, et al. Safety, activity, and immune correlates of anti−PD-1 antibody in cancer. N Engl J Med 2012;366:2443−54.

11.12 APPENDIX 12 MEDICATIONS AFFECTING QT INTERVALS

Albuterol	Doxepin	Lithium	Quinidine
Alfuzosin	Droperidol	Mesoridazine	Ranolazine
Amantadine	Ephedrine	Metaproterenol	Risperidone
Amiodarone	Epinephrine	Methadone	Ritodrine
Amitriptyline	Erythromycin	Methylphenidate	Roxithromycin
Amphetamine	Felbamate	Mexiletine	Salmeterol
Arsenic trioxide	Fenfluramine	Midodrine	Sertindole
Astemizole	Flecainide	Moexipril	Sertraline
Atazanavir	Fluconazole	Moxifloxacin	Sibutramine
Atomoxetine	Fluoxetine	Nicardipine	Sibutramine
Azithromycin	Foscarnet	Nilotinib	Solifenacin
Bepridil	Fosphenytoin	Norepinephrine	Sotalol
Chloral hydrate	Galantamine	Nortriptyline	Sparfloxacin
Chloroquine	Gatifloxacin	Octreotide	Sunitinib
Chlorpromazine	Gemifloxacin	Ofloxacin	Tacrolimus
Ciprofloxacin	Granisetron	Ondansetron	Tamoxifen
Cisapride	Halofantrine	Oxytocin	Telithromycin
Citalopram	Haloperidol	Paliperidone	Terbutaline
Clarithromycin	Ibutilide	Paroxetine	Terfenadine
Clomipramine	Imipramine	Pentamidine	Thioridazine
Clozapine	Indapamide	Perflutren lipid microspheres	Tizanidine
Cocaine	Isoproterenol	Phentermine	Tolterodine
Desipramine	Isradipine	Phenylephrine	Trimethoprim-Sulfa
Dexmethylphenidate	Itraconazole	Phenylpropanolamine	Trimipramine
Disopyramide	Ketoconazole	Pimozide	Vardenafil
Dobutamine	Lapatinib	Probucol	Venlafaxine
Dofetilide	Levafloxacin	Procainamide	Voriconazole
Dolasetron	Levalbuterol	Protriptyline	Ziprasidone
Domperidone	Levomethadyl	Pseudoephedrine	
Dopamine	Lisdexamfetamine	Quetiapine	

11.13 APPENDIX 13 AGENTS METABOLISED BY CYP1A2, CYP2C9 AND CYP3A4

Substrate		
CYP1A2 [a]	**CYP2C9 [a]**	**CYP3A4 [b]**
amitriptyline caffeine clomipramine clozapine cyclobenzaprine estradiol fluvoxamine haloperidol imipramine N-DeMe mexilletine naproxen olanzapine ondansetron phenacetin acetaminophen propranolol riluzole ropivacaine tacrine theophylline tizanidine verapamil (R) warfarin zileuton zolmitriptan	NSAIDs: diclofenac ibuprofen lornoxicam meloxicam S-naproxen norpiroxicam suprofen Oral Hypoglycemic: tolbutamide glipizide glyburide glibenclamide/glyburide glipizide glimepiride nateglinide rosiglitazone Angiotensin II Blockers: losartan irbesartan Miscellaneous: amitriptyline celecoxib fluoxetine fluvastatin phenytoin-4-OH2 tamoxifen torsemide S-warfarin	Macrolide antibiotics: clarithromycin erythromycin telithromycin Anti-arrhythmics: quinidine 3OH Benzodiazepines: alprazolam diazepam 3OH midazolam triazolam Immune Modulators: cyclosporine tacrolimus (FK506) HIV Antivirals: indinavir nelfinavir ritonavir saquinavir Prokinetic: cisapride Antihistamines: astemizole chlorpheniramine terfenadine Calcium Channel Blockers: amlodipine diltiazem felodipine lercanidipine nifedipine2 nisoldipine nitrendipine verapamil HMG CoA Reductase Inhibitors: atorvastatin cerivastatin lovastatin simvastatin Steroid 6beta-OH: estradiol hydrocortisone progesterone testosterone

Substrate		
CYP1A2 [a]	**CYP2C9 [a]**	**CYP3A4 [b]**
		Miscellaneous: alfentanyl aprepitant aripiprazole buspirone cafergot caffeine cilostazol cocaine codeine-N demethylation dapsone dexamethasone dextromethorphan docetaxel domperidone eplerenone fentanyl finasteride gleevec haloperidol irinotecan lidocaine methadone nateglinide ondansetron pimozide propranolol quetiapine quinine risperidone salmeterol sildenafil sirolimus tamoxifen taxol terfenadine trazodone vincristine zaleplon ziprasidone zolpidem
a. Exposure of these drugs may be increased following vemurafenib treatment. b. Exposure of these drugs may be decreased following vemurafenib treatment.		

The above lists of medications are not necessarily comprehensive. The Investigator should consult the prescribing information for any concomitant medication not listed, as well as the following website: http://medicine.iupui.edu/clinpharm/ddis/table.aspx.

11.14 APPENDIX 14 CETUXIMAB PACKAGE INSERT

Please refer to the below European Medicines Agency hyperlink:

http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000558/WC500029119.pdf

11.15 APPENDIX 15 CARDIAC TOXICITY MANAGEMENT AND REPORTING CONVENTIONS WITH TRASTUZUMAB AND PERTUZUMAB

Pertuzumab and trastuzumab should be discontinued in any Cohort 3 experimental arm patient who develops clinical signs and symptoms suggesting CHF, with the diagnosis confirmed by a suggestive chest X-ray and a drop in LVEF by ECHO or MUGA. CHF should be treated and monitored according to standard medical practice. At the present time, there are inadequate data available to assess the prognostic significance of asymptomatic drops of LVEF. However, to ensure patient safety, pertuzumab and trastuzumab must be discontinued in all patients for whom a drop of LVEF to a value lower than 40% is documented and confirmed with a repeat assessment within 3 weeks of the first assessment, using the same assessment method.

For Cohort 3 experimental arm patients whose LVEF drops to values lower than 45%, the decision to stop or continue study treatment is based on the algorithm shown in Figure 3. 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.

Cohort 3 experimental arm patients for whom study treatment was permanently discontinued because of a drop in LVEF should continue to have LVEF assessments repeated as clinically indicated, with a maximum interval between LVEF assessments of 6 weeks, until the LVEF values return to ≥ 50% or for 2 years, whichever occurs first.

All patient management decisions will be made by the investigator based on local LVEF assessments. LVEF assessment results must be available before or on the day of the next scheduled trastuzumab administration, and a decision to give or hold that dose must be made based on the algorithm in Figure 3. In addition, any patient who develops clinical signs or symptoms suspicious of cardiac failure at any time during the study should undergo an LVEF assessment immediately.

Note: Anemia can occur in patients receiving treatment with capecitabine. Because anemia might place a strain on the myocardium, transfusion should be considered for Cohort 3 experimental arm patients whose hemoglobin levels fall during study treatment, particularly if the anemia is symptomatic. Transfusion of packed red blood cells is preferred over transfusion of whole blood so as to minimise the fluid load.

Appropriate methods for AE and AE of special interest reporting of left ventricular systolic dysfunction/heart failure in Cohort 3 experimental arm patients are shown in Table 1 of this appendix.

Figure 3: Trastuzumab/Pertuzumab Dose Management for Left Ventricular Dysfunction

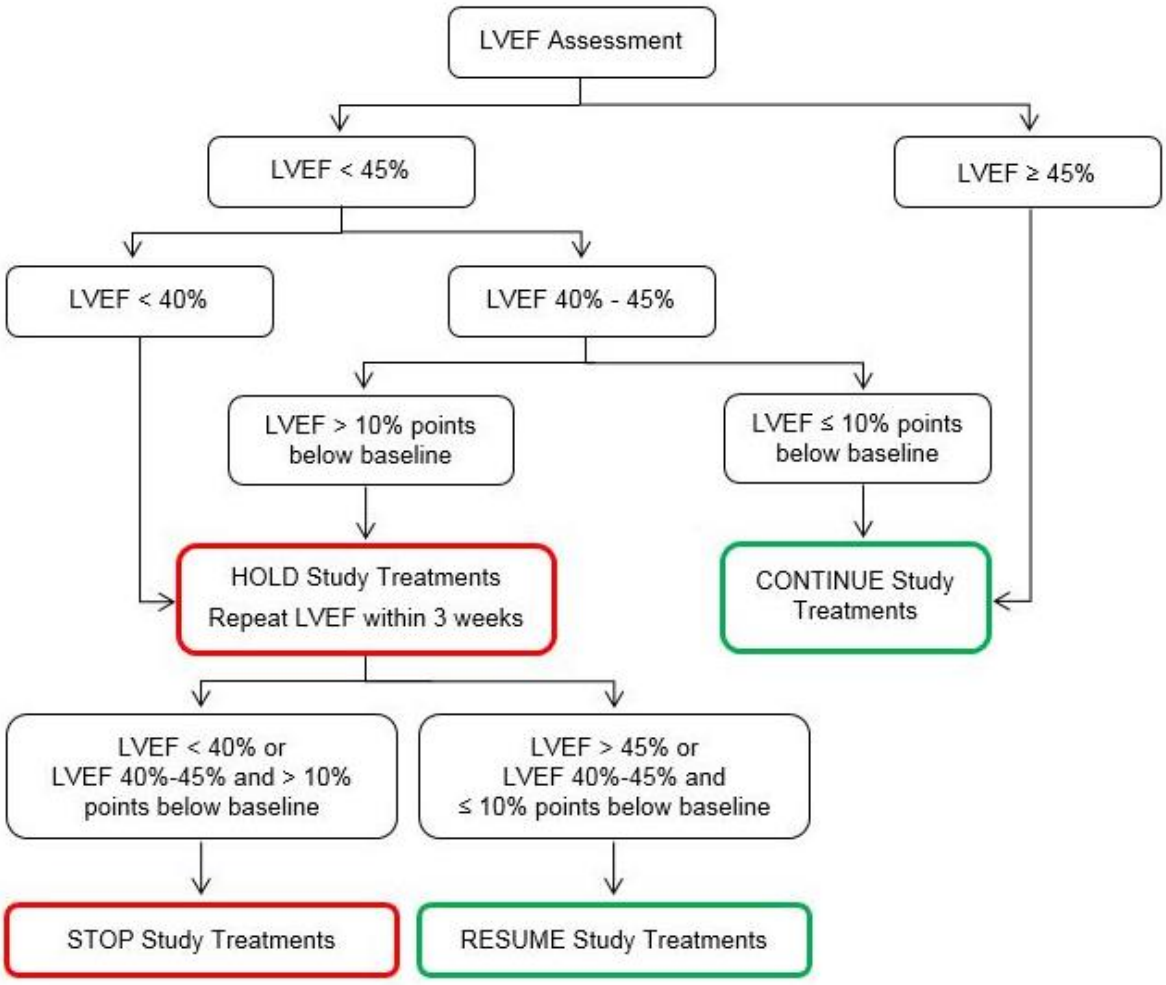


Table 1: Reporting Conventions for Left Ventricular Systolic Dysfunction/Heart Failure

Observation	How to Report	Term to be Reported	Grading
Asymptomatic decline in LVEF < 10%-points from baseline or to an LVEF ≥ 50%	No additional reporting required, LVEF results to be reported on eCRF	N/A	N/A
Asymptomatic decline in LVEF [a] 10%-points from baseline to an LVEF < 50%	AE (eCRF)	"Ejection fraction decreased" [a]	NCI CTCAE for "ejection fraction decreased"
Asymptomatic decline in LVEF [a] requiring treatment or leading to discontinuation of pertuzumab and trastuzumab	AE (eCRF) and non-serious AESI (reported on an SAE form)	"Ejection fraction decreased" [a]	NCI CTCAE for "ejection fraction decreased"
Heart failure / CHF (symptomatic LVSD) [b]	AE (eCRF) and SAE (SAE form)	"Heart failure"	NCI CTCAE for "heart failure" and NYHA Class

AE: adverse event; eCRF: electronic case report form; LVEF: left ventricular ejection fraction; LVSD: left ventricular systolic dysfunction; NYHA: New York Heart Association; NCI CTCAE: National Cancer Institute Common Terminology Criteria for Adverse Events; SAE: serious adverse event.

a. Report the status "asymptomatic" and the left ventricular ejection fraction value in the comments field as appropriate.
b. Any symptomatic left ventricular systolic dysfunction event must be reported as "heart failure".

11.16 APPENDIX 16 GUIDELINES FOR THE MANAGEMENT OF ADVERSE EVENTS WITH COBIMETINIB AND ATEZOLIZUMAB

General guidance for cobimetinib and atezolizumab dose management and AEs in Cohort 4 are provided in Table 1 and 2 respectively. Guidelines for the management of specific AEs are provided in Tables 3 to 11.

Table 1: Cohort 4 General Guidance for Cobimetinib and Atezolizumab Dose Management

General Guidance for Cobimetinib and Atezolizumab	
General guidance for dose modifications and treatment delays and discontinuation	• There will be no dose modifications for atezolizumab. • If atezolizumab is withheld and corticosteroids are initiated for an atezolizumab-related toxicity, corticosteroids must be tapered over ≥ 1 month to ≤ 10 mg/day oral prednisone or equivalent before atezolizumab can be resumed [a,b]. • The dose of cobimetinib can be reduced by 20 mg (one dose level) up to two times (i.e. from 60 mg to 40 mg and then from 40 mg to 20 mg). If further dose reduction is indicated after two dose reductions, the patient must discontinue cobimetinib but may continue treatment with atezolizumab if approved by the Medical Monitor. • If cobimetinib is withheld for > 21 days because of toxicity, the patient should be discontinued from study treatment, unless resumption of treatment is approved by the Medical Monitor after discussion with the investigator.

a. Atezolizumab may be withheld for a period of time beyond 12 weeks to allow for corticosteroids to be reduced to ≤ 10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be agreed upon by the investigator and the Medical Monitor.

b. Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-related event. Patients can be re-challenged with atezolizumab only after approval has been documented by both the investigator (or an appropriate delegate) and the Medical Monitor.

Table 2: Guidance for the Management of General Adverse Events with Cobimetinib and Atezolizumab

Event	Action to Be Taken
Grade 3 or 4 or intolerable Grade 2 treatment-related toxicities not described in Tables 3 to 11	• Withhold all study treatment. • If event resolves to ≤ Grade 1 within 21 days, resume atezolizumab at a fixed dose. If event resolves to ≤ Grade 1 within > 21 days but ≤ 12 weeks, atezolizumab may be resumed at a fixed dose with approval of the Medical Monitor. If the event has not resolved to ≤ Grade 1 within 12 weeks, atezolizumab must be permanently discontinued [a,b,c]. • If event resolves to ≤ Grade 1 within 21 days, resume cobimetinib with dose reduced by one level. If event resolves to ≤ Grade 1 within > 21 days but ≤ 28 days, cobimetinib may be resumed with dose reduced by one level with approval from the Medical Monitor. If the event has not resolved to ≤ Grade 1 in 28 days, cobimetinib must be permanently discontinued.

a. If corticosteroids have been initiated, they must be tapered over ≥ 1 month to ≤ 10 mg/day oral prednisone or equivalent before atezolizumab can be resumed.

b. Atezolizumab may be withheld for a period of time beyond 12 weeks to allow for corticosteroids to be reduced to ≤ 10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be agreed upon by the investigator and the Medical Monitor.

c. Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-related event. Patients can be rechallenged with atezolizumab only after approval has been documented by both the investigator (or an appropriate delegate) and the Medical Monitor.

Table 3: Guidance for Management of Infusion-related Reactions, Hypersensitivity and Anaphylaxis with Cobimetinib and Atezolizumab

Event	Action to Be Taken
Infusion-related reactions and hypersensitivity reactions	• Guidelines for management of Infusion-related reactions are provided in the Atezolizumab Investigator's Brochure. • For severe hypersensitivity reactions, permanently discontinue all study treatment.
Anaphylaxis and anaphylaxis precautions	**Equipment needed:** Tourniquet Oxygen Epinephrine for subcutaneous, IV, and/or endotracheal use in accordance with standard practice Antihistamines Corticosteroids IV infusion solutions, tubing, catheters, tape **Procedures:** In the event of a suspected anaphylactic reaction during study drug infusion, the following procedures should be performed: 1. Stop the drug infusion. 2. Apply a tourniquet proximal to the injection site to slow systemic absorption of study drug. Do not obstruct arterial flow in the limb. 3. Maintain adequate airway. 4. Administer antihistamines, epinephrine, or other medications as required by patient status and directed by physician in charge. 5. Continue to observed the patient and document observations.

Table 4: Guidance for the Management of Gastrointestinal Toxicity with Cobimetinib and Atezolizumab

Event	Action to Be Taken
Gastrointestinal events: general guidance	• All events of diarrhea or colitis should be thoroughly evaluated for more common etiologies other than drug induced effects. • For events of significant duration or severity or associated with signs of systemic inflammation or acute phase reactants, check for immune-related colitis. • Administer anti-diarrheal agents and other maximal supportive care per institutional guidelines such as: at the first report of watery diarrhea or loose stool, initiate maximal anti-diarrheal supportive care (Lomotil and loperamide). • Suggested regimen: o Loperamide: Initiate dose with 4 mg, then 4 mg/6 hr around the clock, alternating with Lomotil. o Lomotil (diphenoxylate and atropine): 2 tablets (diphenoxylate 5 mg, atropine 0.05 mg) every 6 hrs around the clock o Continue Lomotil and loperamide until no loose stools for 24 hours. o If Grade ≤ 2 diarrhea persists after 48 hr total treatment with Lomotil and loperamide, consider second-line agents (e.g., octreotide, budesonide, tincture of opium). • Oral supplementation: o Initiate oral supplementation of potassium and/or magnesium if serum levels are < LLN. o Consider oral rehydration therapy (e.g., Pedialyte®) for Grade ≥ 1 diarrhea or vomiting. • Dietary modifications: o Stop all lactose-containing products and eat small meals. o The BRAT (banana, rice, apples, toast) diet, without fiber (other vegetables and fruits), may be helpful. o Encourage adequate hydration with salt-containing liquids, such as broth or Gatorade.

Event	Action to Be Taken
Diarrhea, Grade 2 (intolerable) or Grade 3	• Withhold atezolizumab and cobimetinib. • Initiate supportive care and monitor patient closely. • Discontinue medications that may exacerbate colitis (e.g. NSAIDS) while investigating etiology. • Investigate etiology, referring patient to GI specialist for evaluation of possible colitis, including biopsy if appropriate. • If event resolves to ≤ Grade 1 within 21 days, resume atezolizumab at fixed dose. If event resolves to ≤ Grade 1 within > 21 days but ≤ 12 weeks, atezolizumab may be resumed at fixed dose with approval of the Medical Monitor. If the event has not resolved to ≤ Grade 1 within 12 weeks, atezolizumab must be permanently discontinued [a,b,c]. • If event resolves to ≤ Grade 1 within 21 days, resume cobimetinib with dose reduced by one level. If event resolves to ≤ Grade 1 within > 21 days but ≤ 28 days, cobimetinib may be resumed with dose reduced by one level with approval from the Medical Monitor. If the event has not resolved to ≤ Grade 1 within 28 days, cobimetinib must be permanently discontinued.
Diarrhea, Grade 4	• Permanently discontinue atezolizumab and cobimetinib, and contact Medical Monitor [c]. • Initiate supportive care and monitor patient closely. • Discontinue medications that may exacerbate colitis (e.g., NSAIDS) while investigating etiology. • Rule out bowel perforation. • Investigate etiology, referring patient to GI specialist for evaluation of possible colitis, including biopsy if appropriate.
Colitis, Grade 1	• Continue atezolizumab and cobimetinib. • Initiate supportive care and monitor patient closely. • Discontinue medications that may exacerbate colitis (e.g., NSAIDS). • Refer patient to gastrointestinal specialist for evaluation and confirmatory biopsy if symptoms persist for > 7 days.

Event	Action to Be Taken
Colitis, Grade 2	• Withhold atezolizumab and cobimetinib. • Initiate supportive care and monitor patient closely. • Discontinue medications that may exacerbate colitis (e.g., NSAIDS). • Refer patient to gastrointestinal specialist for evaluation and confirmatory biopsy. • For recurrent events or events that persist > 5 days, initiate treatment with 1−2 mg/kg/day oral prednisone or equivalent. • If event resolves to ≤ Grade 1 within 21 days, resume atezolizumab at fixed dose. If event resolves to ≤ Grade 1 within > 21 days but ≤ 12 weeks, atezolizumab may be resumed at fixed dose with approval of the Medical Monitor. If the event has not resolved to ≤ Grade 1 within 12 weeks, atezolizumab must be permanently discontinued [a,b,c]. • If event resolves to ≤ Grade 1 within 21 days, resume cobimetinib with dose reduced by one level. If event resolves to ≤ Grade 1 within > 21 days but ≤ 28 days, cobimetinib may be resumed with dose reduced by one level with approval from the Medical Monitor. If the event has not resolved to ≤ Grade 1 within 28 days, cobimetinib must be permanently discontinued.
Colitis, Grade 3	• Withhold atezolizumab and cobimetinib. • Initiate supportive care and monitor patient closely. • Discontinue medications that may exacerbate colitis (e.g., NSAIDS). • Refer patient to gastrointestinal specialist for evaluation and confirmatory biopsy. • Initiate treatment with 1−2 mg/kg/day IV methylprednisolone or equivalent and convert to 1−2 mg/kg/day oral prednisone or equivalent upon improvement. • If event resolves to ≤ Grade 1 within 21 days, resume atezolizumab at fixed dose. If event resolves to ≤ Grade 1 within > 21 days but ≤ 12 weeks, atezolizumab may be resumed at fixed dose with approval of the Medical Monitor. If the event has not resolved to ≤ Grade 1 within 12 weeks, atezolizumab must be permanently discontinued [a,b,c]. • If event resolves to ≤ Grade 1 within 21 days, resume cobimetinib with dose reduced by one level. If event resolves to ≤ Grade 1 within > 21 days but ≤ 28 days, cobimetinib may be resumed with dose reduced by one level with approval from the Medical Monitor. If the event has not resolved to ≤ Grade 1 within 28 days, cobimetinib must be permanently discontinued.

Event	Action to Be Taken
Colitis, Grade 4	• Permanently discontinue atezolizumab and cobimetinib, and contact Medical Monitor [c]. • Initiate supportive care and monitor patient closely. • Discontinue medications that may exacerbate colitis (e.g., NSAIDS). • Refer patient to gastrointestinal specialist for evaluation and confirmatory biopsy. • Initiate treatment with 1−2 mg/kg/day IV methylprednisolone or equivalent and convert to 1−2 mg/kg/day oral prednisone or equivalent upon improvement. • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month.

GI = gastrointestinal; IV = intravenous; NSAID = non-steroidal anti-inflammatory drug.

a. If corticosteroids have been initiated, they must be tapered over ≥ 1 month to ≤ 10 mg/day oral prednisone or equivalent before atezolizumab can be resumed.

b. Atezolizumab may be withheld for a period of time beyond 12 weeks to allow for corticosteroids to be reduced to ≤ 10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be agreed upon by the investigator and the Medical Monitor.

c. Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-related event. Patients can be rechallenged with atezolizumab only after approval has been documented by both the investigator (or an appropriate delegate) and the Medical Monitor.

Table 5: Guidance for the Management of Dermatologic Toxicity with Cobimetinib and Atezolizumab

Event	Action to Be Taken
Dermatologic toxicity	
General guidance	• A dermatologist should evaluate persistent and/or severe rash or pruritus. A biopsy should be considered unless contraindicated.
Dermatologic event, Grade 1/2	• Continue atezolizumab and cobimetinib. • Initiate supportive care (e.g., antihistamines, topical corticosteroids). If event does not improve, consider treatment with higher-potency topical corticosteroids. • For grade 2 rash, consider referral to dermatologist. **Acneiform rash:** • Consider topical corticosteroids (e.g., hydrocortisone 2.5%, alclometasone) and oral antibiotics (minocycline, doxycycline, or antibiotics covering skin flora) as clinically indicated.
Dermatologic event, Grade 3	• Withhold atezolizumab and cobimetinib. • Refer patient to dermatologist. A biopsy should be performed if appropriate. • Consider initiating treatment with 10 mg/day oral prednisone or equivalent, increasing dose to 1−2 mg/kg/day if event does not improve within 48−72 hours. • If event resolves to ≤ Grade 2 within 21 days, resume atezolizumab at fixed dose. If event resolves to ≤ Grade 2 within > 21 days but ≤ 12 weeks, atezolizumab may be resumed at fixed dose with approval of the Medical Monitor. If the event has not resolved to ≤ Grade 2 within 12 weeks, atezolizumab and cobimetinib must be permanently discontinued [a,b]. • Permanently discontinue atezolizumab and cobimetinib and contact Medical Monitor if event does not resolve to ≤ Grade 1 within 12 weeks [a,b,c]. • If event resolves to ≤ Grade 2 within 21 days, resume cobimetinib with dose reduced by one level. If event resolves to ≤ Grade 2 within > 21 days but ≤ 28 days, cobimetinib may be resumed with dose reduced by one level with approval from the Medical Monitor. If the event has not resolved to ≤ Grade 2 within 28 days, cobimetinib must be permanently discontinued. **Acneiform rash:** • Consider continuation of topical corticosteroids (e.g., 2.5% alclometasone) and oral antibiotics (e.g., minocycline, doxycycline or antibiotics covering skin flora) when restarting cobimetinib.
Dermatologic event, Grade 4	• Permanently discontinue atezolizumab and cobimetinib, and contact Medical Monitor [c].

a. If corticosteroids have been initiated, they must be tapered over ≥ 1 month to ≤ 10 mg/day oral prednisone or equivalent before atezolizumab can be resumed.

b. Atezolizumab may be withheld for a period of time beyond 12 weeks to allow for corticosteroids to be reduced to ≤ 10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be agreed upon by the investigator and the Medical Monitor.

c. Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-related event. Patients can be rechallenged with atezolizumab only after approval has been documented by both the investigator (or an appropriate delegate) and the Medical Monitor.

Table 6: Guidance for the Management of Elevations in ALT, AST, and/or Bilirubin with Cobimetinib and Atezolizumab

Event	Action to Be Taken
Elevations in ALT, AST, and/or bilirubin	
AST/ALT > ULN to ≤ 3 × ULN with total bilirubin < 2 × ULN (Grade 1)	• Continue atezolizumab and cobimetinib. • Continue with the standard monitoring plan (i.e. LFTs every 4 weeks before dosing).
AST/ALT > 3 × baseline values to < 5 × ULN with total bilirubin < 2 × ULN (Grade 2)	• Continue all study treatment. • Monitor LFTs at least weekly. • Consider referral to a hepatologist and liver biopsy. • For suspected immune related events of > 5 days duration o Consider withholding atezolizumab [c]. Note that patient may continue on cobimetinib alone if approved by Medical Monitor. o Consider administering 1−2 mg/kg/day oral prednisone or equivalent followed by ≥ 1 month taper o If event resolves to ≤ Grade 1 within 21 days resume atezolizumab at fixed dose. If event resolves to ≤ Grade 1 within > 21 days but ≤ 12 weeks atezolizumab may be resumed at fixed dose with approval of the Medical Monitor [a,b]. o Atezolizumab and cobimetinib must be permanently discontinued if event does not resolve to ≤ Grade 1 within 12 weeks [a,b,c].
AST/ALT > 5 × baseline values to < 10 × ULN with total bilirubin < 2 × ULN (Grade 3)	• Continue all study treatment. • Monitor LFTs at least weekly. • Consider referral to a hepatologist and liver biopsy. • For suspected immune related events o Withhold atezolizumab and cobimetinib. o Consider administering 1−2 mg/kg/day oral prednisone or equivalent followed by ≥ 1 month taper o If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month. o Approval to re-initiate atezolizumab and cobimetinib if delayed > 21 days must be obtained from the Medical Monitor. o Atezolizumab and cobimetinib must be permanently discontinued if event does not resolve to ≤ Grade 1 or better within 12 weeks [a,b,c].

Event	Action to Be Taken
AST/ALT > 3 × ULN with bilirubin > 2 × ULN	• Withhold atezolizumab and cobimetinib. • Consult hepatologist and consider liver biopsy. • Consider administering 1−2 mg/kg/day oral prednisone or equivalent followed by ≥ 1 month taper (for possible autoimmune hepatitis). • If LFTs do not decrease within 48 hr after initiation of systemic steroids, consider adding an immunosuppressive agent (e.g., mycophenolate or TNF-α antagonist). • Monitor LFTs every 48−72 hr until decreasing and then follow weekly. • Restart atezolizumab at fixed dose and cobimetinib at 1 dose reduction after discussion with medical monitor if AST/ALT < 3 × ULN with bilirubin < 2 × ULN and steroid dose < 10 mg oral prednisone equivalent per day [a,b,c]. • Permanently discontinue atezolizumab and cobimetinib for life-threatening hepatic events, and contact the Medical Monitor.
AST/ALT > 10 × ULN	• Permanently discontinue atezolizumab and cobimetinib [c]. • Consult hepatologist and consider liver biopsy. • Consider administering 1−2 mg/kg/day oral prednisone or equivalent (for possible autoimmune hepatitis). If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month. • If LFTs do not decrease within 48 hr after initiation of systemic steroids, addition of an alternative immunosuppressive agent (e.g., mycophenolate or TNF-α antagonist) or dose escalation of corticosteroids may be considered. • Monitor LFTs every 48−72 hr until decreasing and then follow weekly.

ULN = upper limit of normal.

a. If corticosteroids have been initiated, they must be tapered over ≥ 1 month to ≤ 10 mg/day oral prednisone or equivalent before atezolizumab can be resumed.

b. Atezolizumab may be withheld for a period of time beyond 12 weeks to allow for corticosteroids to be reduced to ≤ 10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be agreed upon by the investigator and the Medical Monitor.

c. Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-related event. Patients can be rechallenged with atezolizumab only after approval has been documented by both the investigator (or an appropriate delegate) and the Medical Monitor.

Table 7: Guidance for the Management of Pulmonary Toxicity with Cobimetinib and Atezolizumab

Event	Action to Be Taken
Pulmonary events	
General Guidance	Mild-to-moderate events of pneumonitis have been reported with atezolizumab and cobimetinib. All pulmonary events should be thoroughly evaluated for other commonly reported etiologies such as pneumonia/infection, lymphangitic carcinomatosis, pulmonary embolism, heart failure, chronic obstructive pulmonary disease, or pulmonary hypertension. For events concerning for pneumonitis, consider comprehensive infectious evaluation including viral etiologies.
Pneumonitis, grade 1 (asymptomatic)	• Continue atezolizumab and cobimetinib. • Re-evaluate on serial imaging. • Consider patient referral to pulmonary specialist. • For recurrent pneumonitis, treat as Grade 3 or 4 event.
Pneumonitis, grade 2	• Withhold atezolizumab and cobimetinib. • Refer patient to pulmonary and infectious disease specialists and consider bronchoscopy or BAL. • If bronchoscopy is consistent with immune-related etiology, initiate treatment with 1−2 mg/kg/day oral prednisone or equivalent. • Resume atezolizumab and cobimetinib if event resolves to ≤ Grade 1 within 21 days. If event resolves to ≤ Grade 1 within > 21 days but ≤ 12 weeks, atezolizumab and cobimetinib may be resumed with approval of the Medical Monitor[a,b]. • Contact Medical Monitor if event does not resolve to ≤ Grade 1 within 12 weeks. Atezolizumab and cobimetinib must be permanently discontinued if event does not resolve to ≤ Grade 1 within 12 weeks [a,b,c]. • For recurrent events, treat as a Grade 3 or 4 event.
Pneumonitis, grade 3/4	• Permanently discontinue atezolizumab and cobimetinib [c]. • Refer patient to pulmonary and infectious disease specialists and consider bronchoscopy or BAL. • If bronchoscopy is consistent with immune-related etiology, initiate treatment with 1−2 mg/kg/day oral prednisone or equivalent. • If pulmonary event does not improve within 48 hr or worsens, consider adding an immunosuppressive agent (e.g., infliximab, cyclophosphamide, IV Ig, or mycophenolate mofetil). • If event resolves to ≤ Grade 1, taper corticosteroids over ≥ 1 month.

BAL = bronchoscopic alveolar lavage.

a. If corticosteroids have been initiated, they must be tapered over ≥ 1 month to ≤ 10 mg/day oral prednisone or equivalent before atezolizumab can be resumed.

b. Atezolizumab may be withheld for a period of time beyond 12 weeks to allow for corticosteroids to be reduced to ≤ 10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be agreed upon by the investigator and the Medical Monitor.

c. Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-related event. Patients can be rechallenged with atezolizumab only after approval has been documented by both the investigator (or appropriate delegate) and the Medical Monitor.

Table 8: Guidance for the Management of Ocular Toxicity with Cobimetinib and Atezolizumab

Event	Action to Be Taken
Ocular toxicity	
General guidance	• An ophthalmologist should evaluate visual complaints. • Uveitis or episcleritis and other immune-mediated ocular disease may be associated with atezolizumab and may be treated with topical corticosteroid eye drops. Atezolizumab should be permanently discontinued for immune-related ocular event that is unresponsive to local immunosuppressive therapy. • Serous retinopathy is associated with cobimetinib. In clinical trials, most events were Grade 1 (asymptomatic) or 2 (symptomatic). Most events in clinical trials resolved or improved to asymptomatic grade 1 following dose interruption or reduction. If serous retinopathy is diagnosed, cobimetinib should be withheld until visual symptoms improve to ≤ Grade 1. Serous retinopathy can be managed with treatment interruption, dose reduction or with treatment discontinuation. • Retinal vein occlusion (RVO) has been reported in patients treated with MEK inhibitors other than cobimetinib.
Serous retinopathy Severity grade assessment based on NCI CTCAE v4 "Eye Disorders − Other" scale [a,b,c,d]	**Serous retinopathy, Grade 1 [a] or 2 [b] (tolerable):** • Continue cobimetinib and atezolizumab without dose change. • Continue ophthalmology follow-up as clinically indicated. **Serous retinopathy, Grade 2 [b] (intolerable) or 3/4 [c,d]:** • Interrupt cobimetinib until ≤ Grade 1. • Continue atezolizumab as clinically indicated following approval from the Medical Monitor. • Consult ophthalmology and undergo complete ophthalmologic examination, which includes visual acuity testing, intra-ocular pressure measurements, slit lamp ophthalmoscopy, indirect ophthalmoscopy, visual field, and OCT. Consider a fluorescein angiogram and/or indocyanine green angiogram, if clinically indicated. • Cobimetinib should be dose reduced by 1 dose level when restarting. • Consider permanent discontinuation of cobimetinib if serous retinopathy recurs despite 2 dose level reductions. Atezolizumab may be continued if approved by the Medical Monitor.
Potential immune-related ocular toxicity (e.g., uveitis, iritis, episcleritis, or retinitis)	• Follow guidelines provided in the Atezolizumab Investigator's Brochure. • Continue cobimetinib as clinically indicated. If atezolizumab has been discontinued, approval to continue cobimetinib must be obtained from the Medical Monitor.
Retinal vein occlusion (any grade)	• If RVO (any grade) is diagnosed, cobimetinib dosing should be permanently discontinued and RVO treated per institutional guidelines. • Continue atezolizumab if approval obtained from the Medical Monitor.

ADL = activities of daily living; NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events; RVO = retinal vein occlusion; OCT = optical coherence tomography.

a. Grade 1: Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
b. Grade 2: Moderate; minimal, local or noninvasive intervention indicated; limiting age appropriate instrumental ADL.
c. Grade 3: Severe or medically significant but not immediately sight threatening; hospitalization or prolongation of existing hospitalization indicated; disabling; limiting self-care ADL.
d. Grade 4: Sight-threatening consequences; urgent intervention indicated; blindness (20/200 or worse) in the affected eye.

Table 9: Guidance for the Management of LVEF Decreases with Cobimetinib and Atezolizumab

Left Ventricular Ejection Fraction (LVEF) Decrease from Baseline				
Patient	**LVEF value**	**Recommended action with cobimetinib and atezolizumab**	**LVEF value following treatment break**	**Recommended cobimetinib daily dose**
Asymptomatic	≥ 50% (or 40%–49% and < 10% absolute decrease from BL)	Continue atezolizumab and cobimetinib at current dose	N/A	N/A
	< 40% (or 40%–49% and ≥ 10% absolute decrease from BL)	Interrupt cobimetinib treatment for 2 weeks Continue atezolizumab as clinically indicated with approval of the Medical Monitor	< 10% absolute decrease from BL	First occurrence: 40 mg [a]
				Second occurrence: 20 mg [a]
				Third occurrence: permanent discontinuation
			< 40% (or ≥ 10% absolute decrease from BL)	Permanent discontinuation
Symptomatic	N/A	Interrupt cobimetinib treatment. Consult Medical Monitor for approval to withhold cobimetinib for 4 weeks and appropriate management of atezolizumab. Medical Monitor approval is required to continue atezolizumab while cobimetinib is withheld. If atezolizumab is withheld, re-initiation must be discussed with the Medical Monitor. Cardiology consultation is strongly recommended.	Asymptomatic and < 10% absolute decrease from BL	First occurrence: 40 mg [a]
				Second occurrence: 20 mg [a]
				Third occurrence: Permanent discontinuation
			Asymptomatic and < 40% (or ≥ 10% absolute decrease from BL)	Permanent discontinuation
			Symptomatic regardless of LVEF	Permanent discontinuation

BL = baseline; LVEF = left ventricular ejection fraction; N/A = not applicable.

a. Patients who restart cobimetinib following a treatment delay due to LVEF decrease, LVEF must be assessed at 2, 4, 10, and 16 weeks, then every 6 cycles after restarting treatment.

Table 10: Guidance for the Management of Rhabdomyolysis or Creatine Phosphokinase Elevation with Cobimetinib and Atezolizumab

Event	Action to Be Taken
Rhabdomyolysis or CPK elevation	
General guidance	• Rule out cardiac cause (check ECG, serum cardiac troponin, and CPK-isoforms M and B fraction) and rule out rhabdomyolysis (clinical examination; serum creatinine, potassium, calcium, phosphorus, uric acid, and albumin; and urine myoglobin). • Assess patient for any history of strenuous physical activity, blunt trauma, or recent IM injections.
For Grade ≤ 3 CPK elevations that are asymptomatic and deemed not clinically significant	• Cobimetinib and atezolizumab dosing does not need to be modified or interrupted to manage asymptomatic ≤ Grade 3 creatine phosphokinase (CPK) elevations. • Recheck CPK at least once a week.
For Grade 4 CPK elevations that are asymptomatic and deemed not clinically significant	• Interrupt cobimetinib and atezolizumab treatment. • If improved to ≤ Grade 3 within 21 days restart cobimetinib at a dose reduced by 20 mg, if clinically indicated. If improved to ≤ Grade 3 within > 21 days but ≤ 4 weeks, restart cobimetinib at a dose reduced by 20 mg, if clinically indicated and with approval from the Medical Monitor. • If CPK elevations do not improve to ≤ Grade 3 within 4 weeks following dose interruption, cobimetinib must be permanently discontinued. • Resumption of atezolizumab may be considered at the same time as cobimetinib in patients who are deriving benefit.
Rhabdomyolysis or symptomatic CPK elevations	• Interrupt cobimetinib and atezolizumab treatment. • If severity is improved by at least one grade and symptoms resolve within 21 days, restart cobimetinib at a dose reduced by 20 mg, if clinically indicated. If severity is improved by at least one grade and symptoms resolve > 21 days but ≤ 4 weeks, restart cobimetinib at a dose reduced by 20 mg, if clinically indicated and with approval from the Medical Monitor. • If rhabdomyolysis or symptomatic CPK elevations do not improve within 4 weeks, cobimetinib must be permanently discontinued. • Resumption of atezolizumab may be considered at the same time as cobimetinib in patients who are deriving benefit.

CPK = creatine phosphokinase.

Table 11: Guidance for the Management of Haemorrhage with Cobimetinib and Atezolizumab

Event	Action to Be Taken
Haemorrhage	
Grade 3 haemorrhage	• Interrupt cobimetinib treatment. There are no data on the effectiveness of cobimetinib dose modification for hemorrhage events. Clinical judgment should be applied when considering restarting cobimetinib. • Continue atezolizumab treatment with approval from the Medical Monitor.
Grade 4 haemorrhage or any grade cerebral haemorrhage	• Interrupt cobimetinib treatment. Permanently discontinue cobimetinib for hemorrhage events attributed to cobimetinib. • Continue atezolizumab treatment with approval from the Medical Monitor.

11.17 APPENDIX 17 BIOMARKER ASSESSMENTS

11.17.1 Archival Primary Tumour Block from Initial Diagnosis

For all patients (including those enrolled in the Supplemental Biomarker Program), biomarker assessments determining cohort assignment and stratification will be conducted on archival tumour tissue (FFPET) block from primary tumour used for their initial CRC diagnoses that was obtained as part of standard clinical practice. The primary tumour specimen was selected for biomarker assessment for consistency and comparability reasons, as they are the only samples collected for all study patients. If the tumour block is not available, ≥ 20 slides cut from the primary tumour sample will be accepted as an alternative.

After a patient has provided informed consent to participate in the study, but before they can be enrolled in the study, their sample must be shipped to the designated laboratory with the corresponding pathology report and receipt of shipment must be confirmed by the designated laboratory. Patients without confirmed receipt of their primary tumour sample (either the block or ≥ 20 slides) at the designated laboratory are not eligible for the study. Tumour blocks from patients who are not enrolled in the study and remainders of tumour blocks from patients who are enrolled in the study will be returned to the study site.

Biomarker results to determine cohort assignment (see Figure 4) will be available to IxRS during the Induction Treatment Phase.

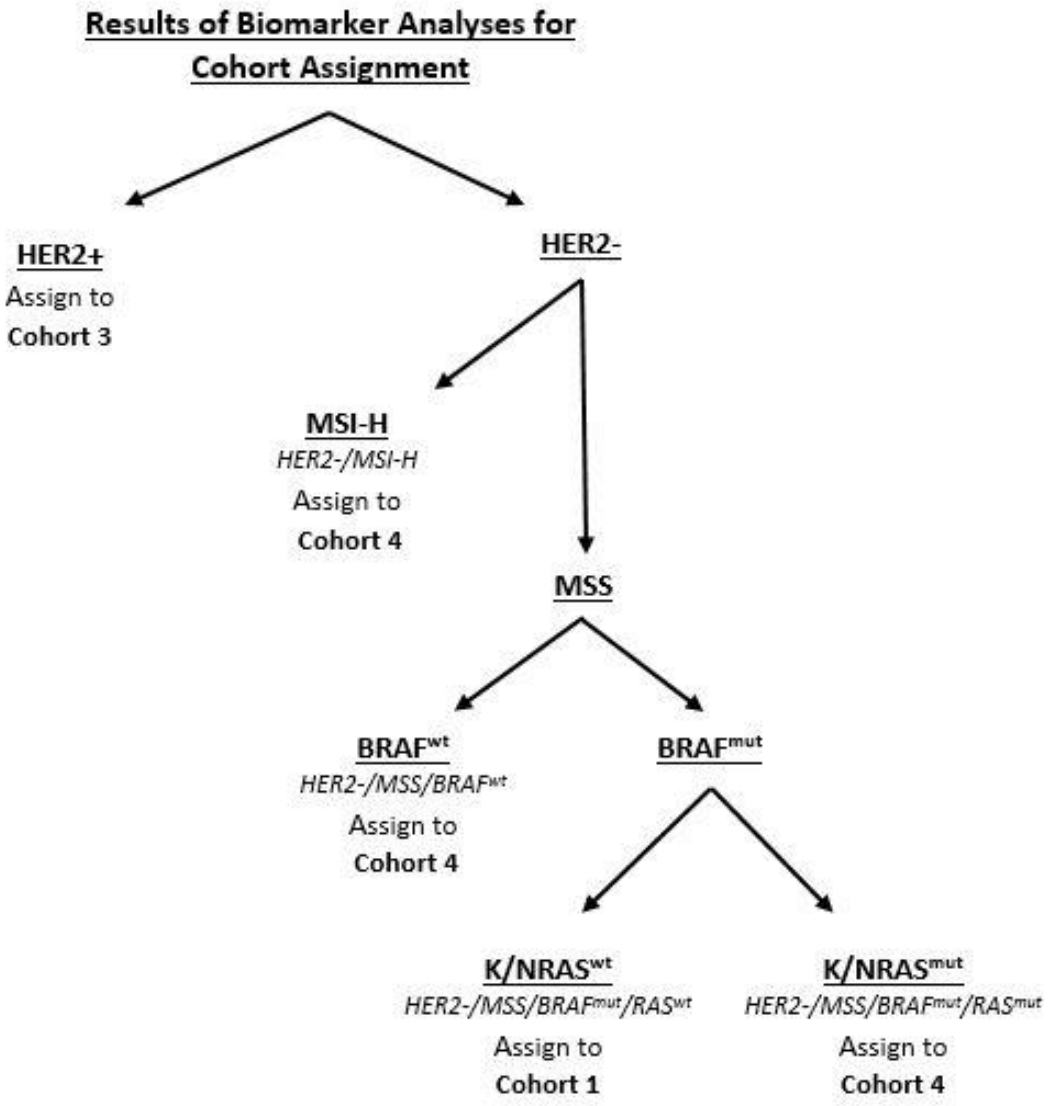
Next generation sequencing may be performed by Foundation Medicine. If performed by Foundation Medicine, the Investigator can obtain results from the samples collected at the time of disease progression in the form of an NGS report, which is available upon request directly from Foundation Medicine. The Investigator may share and discuss the results with the patient, unless the patient chooses otherwise. The Foundation Medicine NGS assay has not been cleared or approved by health authorities. The NGS report is generated for research purposes and is not provided for the purposes of guiding future treatment decisions.

11.17.2 Biomarker Testing for Cohort Assignment

Tumour (non-inherited) DNA will be isolated from archival tumour blocks for NGS on tumour related genes. Results from this analysis on the following biomarkers only will guide maintenance treatment cohort assignment (shown in Figure 4):

a. HER2: gene copy numbers ≥ 5 will be considered as amplified and HER2+ for the purposes of cohort assignment. Amplified samples will be reflex tested by HER2 IHC/FISH. HER2 overexpression by IHC is a stratification variable in Cohort 3 randomization (IHC0/IHC1+/IHC2+ vs. IHC3+).
b. MSI: microsatellite stability determined as stable (MSS) or unstable (MSI-H)
c. BRAF: determined as either mutated ($BRAF^{mut}$) or wild-type ($BRAF^{wt}$)
d. KRAS and NRAS: activating RAS gene mutations.

Figure 4: Biomarker-based Cohort Assignment Decision Tree



BRAF: v-raf murine sarcoma viral oncogene homolog B1; HER2: human epidermal growth factor receptor; K/NRAS: neuroblastoma/Kirsten rat sarcoma viral oncogene homolog; MSI-H: high microsatellite instability; MSS: microsatellite stable

Patients with an adequate tumour sample but without biomarker results available for cohort assignment due to lack of determinant test outcome (e.g. due to technical issues) may still be included in the study depending on the addition of future cohorts. Patients who are not eligible for their assigned cohort will undergo a Study Treatment Discontinuation Visit and enter the Post-Treatment Follow-up Phase.

11.17.3 Biomarker Stratification Variables

Randomisation in Cohorts 3 and 4 will be stratified by biomarkers.

Randomisation in Cohort 3 will be stratified by IHC result (IHC0/IHC1+/IHC2+ vs. IHC3+) in addition to patient response after induction treatment (CR/PR vs. SD).

Randomisation in Cohort 4 will be stratified by microsatellite stability (MSI-H vs. MSS) and RAS status (wild-type KRAS and NRAS vs. mutant KRAS and/or NRAS) in addition to region (EU vs. rest of world) and patient response after induction treatment (CR/PR vs. SD).

11.17.4 Core Biopsy of Metastases

Prior to May 2018, a core tumour biopsy of metastases at baseline was optional for all patients. Since May 2018, these samples are not being collected.

Additional core tumour biopsies of metastases were required from patients participating in the Supplemental Biomarker Program (see Appendix 18) post-induction (but before start of maintenance) and at progression. The Supplemental Biomarker Program was closed in May 2018 and no further samples are being collected.

Baseline metastatic tumour samples and Supplemental Biomarker Program samples obtained prior to the May 2018 discontinuation of collection may still be used for exploratory biomarker analyses.

11.17.5 Stool Sample

Stool samples were collected from all Supplemental Biomarker Program Participants at screening (prior to start of induction treatment), at completion of induction treatment (prior to start of maintenance treatment) and at disease progression (see Appendix 18). The Supplemental Biomarker Program was closed in May 2018 and no further samples are being collected. Sample collected up to this timepoint may still be used for exploratory biomarker analyses.

11.17.6 Exploratory Biomarker Outcome Measures

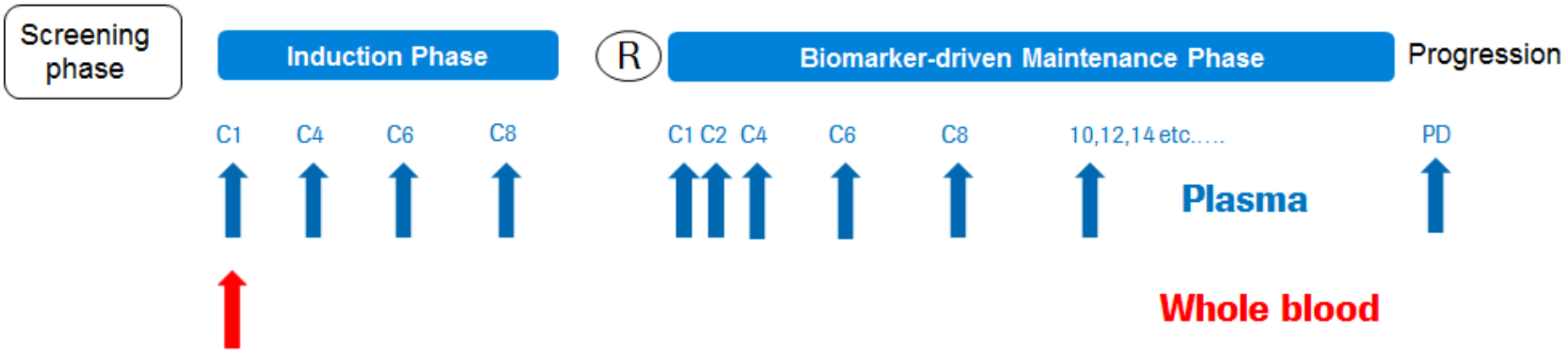
The exploratory biomarker outcome measures for this study include molecular markers, marker profiles, microbiome results and efficacy and/or safety outcomes. Efficacy outcomes considered for this analysis may include ORR, PFS and OS, as appropriate.

Non-inherited (somatic) biomarkers and biomarker profiles will be assessed using multiple technologies including but not limited to IHC and RNA/DNA sequencing methods (e.g. polymerase chain reaction, NGS). These tests will be conducted on material that includes proteins, DNA and RNA obtained from tumour tissue, peripheral blood and stool.

Profiling of inherited (germline) markers obtained from peripheral blood may be performed in countries where allowed by federal law.

11.17.7 Whole Blood and Plasma Biomarker Assessments

Figure 5: Blood Biomarker Sample Collections



Whole blood (unless genomic analysis not allowed per federal regulations) and plasma testing will be performed for all study patients. All samples during treatment should be taken within 48 hours before study treatment administration on Day 1 of cycle, unless otherwise specified.

Please refer to the study's **Laboratory Manual** for further information including sample quality requirements, sample preparation methods, shipping and handling.

11.18 APPENDIX 18 SUPPLEMENTAL BIOMARKER PROGRAM

As of May 2018, the Supplemental Biomarker Program is closed (no further samples collected) and collection of the optional baseline tumour sample has ended. Baseline metastatic tumour samples and Supplemental Biomarker Program samples collected up to this time point may still be used for exploratory biomarker analyses.

Prior to May 2018, selected study sites participating in the Supplemental Biomarker Program collected samples from patients enrolled at these sites who had provided separate informed consent to participate in the program.

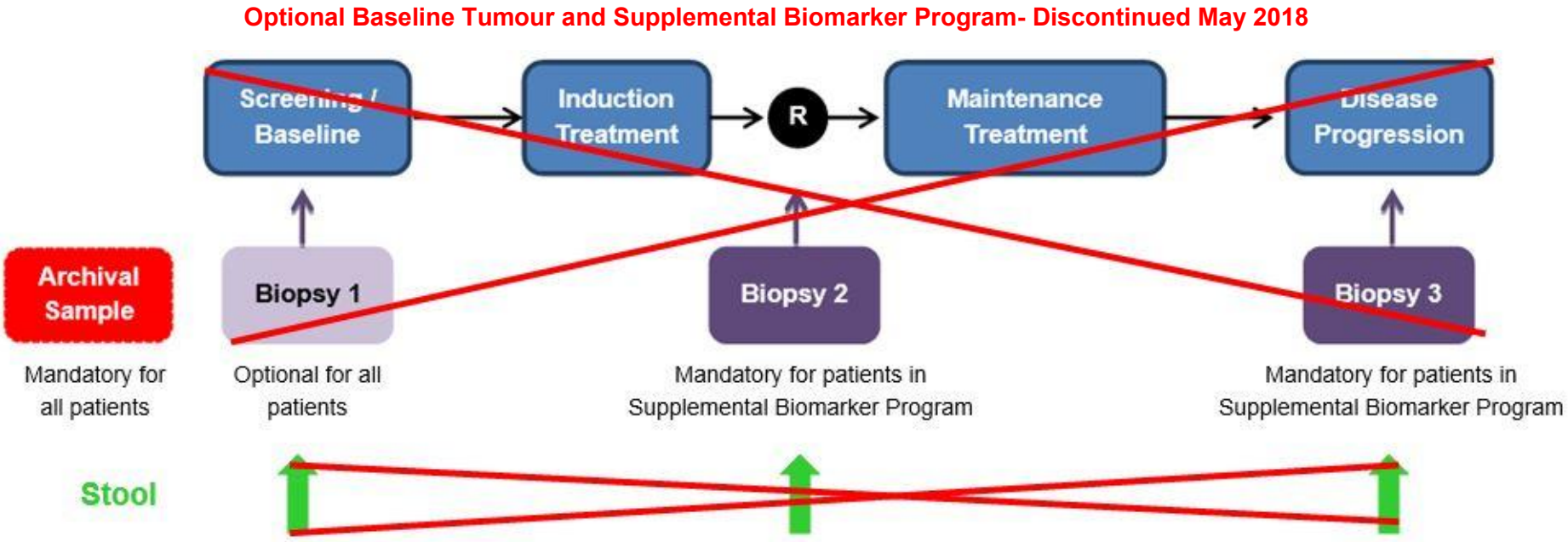
Participation in the program involved obtaining additional metastatic tumour tissue biopsies and stool samples at the following time points as shown in Figure 6:

a. Stool: mandatory at screening (prior to initiation of induction treatment)
b. Metastatic tumour tissue: mandatory if clinically feasible at completion of study induction treatment, prior to initiation of study maintenance treatment
c. Stool: mandatory at completion of study induction treatment, prior to initiation of study maintenance treatment
d. Metastatic tumour tissue: mandatory if clinically feasible at disease progression during the Induction or Maintenance Treatment Phases
e. Stool: mandatory at disease progression during induction or maintenance treatment study phases. Sample may be collected at the time of the Study Treatment Discontinuation Visit.

Samples were submitted to the designated laboratory for inclusion in the exploratory biomarker analyses described in Appendix 17.

Please refer to the study's **Laboratory Manual** for further information including sample quality requirements, sample preparation methods, shipping and handling.

Figure 6: Mandatory and Supplemental Biomarker Program Tumour and Stool Sampling



Archival Tumour Sample: **Mandatory for all patients**: Assessment of biomarkers for cohort assignment will be based on archival primary tumour samples for all patients. Prior to performing any screening procedures, the Investigator must ensure that adequate archival tissue from a potential participant's primary tumour is available. The sample must be shipped to the Sponsor's designated laboratory and sample receipt confirmed by the laboratory before study enrolment. If the tumour block is not available, ≥ 20 slides cut from the primary tumour sample will be accepted as an alternative.

Tumour Biopsy 1: Collection of the optional sample discontinued May 2018.

Tumour Biopsy 2: Supplemental Biomarker Program sample collection discontinued May 2018.

Tumour Biopsy 3: Supplemental Biomarker Program sample collection discontinued May 2018.

Stool Samples: Supplemental Biomarker Program sample collection discontinued May 2018.

11.19 APPENDIX 19 PATIENT MANAGEMENT AND DATA COLLECTION AFTER MAY 31, 2019

Table 1: Management of Patients in Post-Treatment Follow-up Phase on or before May 31, 2019

Patients Not Randomized in Maintenance Treatment Phase	Patients in Cohorts 1 and 4	Patients in Cohorts 2 and 3
Patients 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).	Patients will be followed until the end of the study according to the applicable Schedule of Assessments. Disease status (for patients who have not yet progressed) will not be collected after May 31, 2019. Disease assessments may be conducted according to local practice after this time.	Patients who have completed the adverse event reporting period and, if applicable, 7 month post-treatment pregnancy test (see protocol Section 5.3.1) prior to May 31, 2019: 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). Female Cohort 3 experimental arm patients of child-bearing potential must remain in the study until the 7 month post-treatment pregnancy test has been conducted. Patients who have not yet completed the adverse event reporting period as of May 31, 2019: will remain in the study until completion of the adverse event reporting period and, if applicable, 7 month post-treatment pregnancy test (see protocol Section 5.3.1). Deaths unrelated to AEs (e.g. death due to disease progression) occurring during the safety follow-up period should be reported as described in protocol Section 5.3.5.8. Disease status (for patients who have not yet progressed) and subsequent anti-cancer therapies will not be collected for the study after May 31, 2019.

Note: All patients must complete the Study Treatment Discontinuation Visit prior to entering the Post-Treatment Follow-up Phase.

Table 2: Management of Patients Still Receiving Maintenance Treatment on May 31, 2019

Patients in Cohorts 1 and 4	Patients in Cohorts 2 and 3
Patients will be followed until the end of the study according to the applicable Schedule of Assessments. Disease status will not be collected for the study following May 31, 2019. Disease assessments may be conducted according to local practice after this time.	Patients will be followed according to the applicable Schedule of Assessments until study treatment discontinuation. Disease status will not be collected for the study following May 31, 2019. Disease assessments may be conducted according to local practice after this time. Following study treatment discontinuation, patients will complete the Study Treatment Discontinuation visit and the applicable adverse event reporting period (see protocol Section 5.3.1). Deaths unrelated to AEs (e.g. death due to disease progression) occurring during the safety follow-up period should be reported as described in protocol Section 5.3.5.8. Anti-cancer therapies administered after study treatment discontinuation will not be collected for the study following May 31, 2019. Patients will be discontinued from the study upon completion of the applicable adverse event reporting period; however, if the patient was treated in the Cohort 3 experimental arm and is a female of child-bearing potential, they must remain in The Post-Treatment Follow-up period until the 7 month post-treatment pregnancy test has been conducted.