Official Title: A Phase III, Open-Label, Multicenter, Three-Arm, Randomized Study to Investigate the Efficacy and Safety of Cobimetinib Plus Atezolizumab and Atezolizumab Monotherapy vs. Regorafenib in Patients With Previously Treated Unresectable Locally Advanced or Metastatic Colorectal Adenocarcinoma

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STATISTICAL ANALYSIS PLAN

TITLE:	**A PHASE III, OPEN-LABEL, MULTICENTER, THREE-ARM, RANDOMIZED STUDY TO INVESTIGATE THE EFFICACY AND SAFETY OF COBIMETINIB PLUS ATEZOLIZUMAB AND ATEZOLIZUMAB MONOTHERAPY VS. REGORAFENIB IN PATIENTS WITH PREVIOUSLY TREATED UNRESECTABLE LOCALLY ADVANCED OR METASTATIC COLORECTAL ADENOCARCINOMA**
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VERSION NUMBER:	2
IND NUMBER:	130,091
EUDRACT NUMBER:	2016-000202-11
SPONSOR:	F. Hoffmann-La Roche Ltd
PLAN PREPARED BY:	███ , Ph.D
DATE FINAL:	02 March 2017
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STATISTICAL ANALYSIS PLAN APPROVAL

Name	Reason for Signing	Date and Time (UTC)
██████	Company Signatory	27-Nov-2017 21:56:09

CONFIDENTIAL

STATISTICAL ANALYSIS PLAN AMENDMENT
RATIONALE for Version 2

The Statistical Analysis Plan (SAP) has been amended mainly due to the change in the order of hierarchical testing for efficacy endpoints, overall survival (OS), progression-free survival (PFS) and objective response rate (ORR).

GO30182 was designed and powered to evaluate the primary endpoint, OS in two comparisons: Arm A (cobimetinib plus atezolizumab) versus Arm C (regorafenib), and Arm B (atezolizumab) versus Arm C.

However, the original procedure to control type 1 error proposed in the SAP Version 1 (v1) consisted of OS as well as two secondary endpoints, PFS and ORR, in the hierarchical testing order of: OS, PFS and ORR in the comparison of Arm A vs. Arm C, followed by OS, PFS and ORR in the comparison of Arm B vs. Arm C.

Therefore, in order to adequately test the primary endpoint (OS) in both comparisons, while maintaining appropriate type 1 error control, the SAP is revised to keep only the primary comparisons in the hierarchical testing procedure (OS in Arm A versus Arm C, followed by OS in Arm B versus Arm C). Analysis of all secondary endpoints including PFS and ORR will be performed and will be submitted to health authorities according to the methodologies stated in the protocol and SAP.

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1.   BACKGROUND

This Statistical Analysis Plan (SAP) provides details of the planned analyses and statistical methods for Study GO30182 (IMblaze370): A Phase III, open-label, multicenter, three-arm, randomized study to investigate the efficacy and safety of cobimetinib plus atezolizumab and atezolizumab monotherapy versus regorafenib in patients with previously treated unresectable locally advanced or metastatic colorectal adenocarcinoma. The background for the study can be found in the study protocol.

It is anticipated that positive results from Study GO30182 will support the submission of filing applications globally for the use of cobimetinib plus atezolizumab for the treatment of patients with chemotherapy-refractory, unresectable, locally advanced or metastatic colorectal cancer. For purposes of registration, the analyses outlined in this SAP will supersede those specified in the protocol.

2.   STUDY DESIGN

This is a Phase III, multicenter, open-label, three-arm, randomized study in patients with unresectable locally advanced or metastatic colorectal cancer (mCRC) who have received at least two prior regimens of cytotoxic chemotherapy for metastatic disease. The study compares regorafenib, a standard-of-care therapy in this setting, with cobimetinib plus atezolizumab and atezolizumab monotherapy.

This study will be conducted globally, and approximately 360 patients will be randomized in a 2:1:1 ratio to one of the following treatments:

- Arm A: cobimetinib 60 mg orally on Days 1–21 plus atezolizumab 840 mg intravenous (IV) on Day 1 and Day 15 in a 28-day cycle (n=approximately 180), or

- Arm B: atezolizumab monotherapy 1200 mg IV on Day 1 in a 21-day cycle (n=approximately 90), or

- Arm C: regorafenib 160 mg orally on Days 1–21 in a 28-day cycle (n=approximately 90).

Stratification factors are extended RAS mutation status of the tumor and time since diagnosis of first metastasis (< 18 months vs. ≥ 18 months). Permuted-block randomization will be applied to ensure a balanced assignment to each treatment arm. Randomization and stratification will be managed through an interactive voice/web response system (IxRS).

At least 50% of patients with extended RAS-mutant tumors (refer to Protocol Section 4.5.7.1 for definition) will be enrolled in each arm. Enrollment of patients with microsatellite (MSI)-high status (see Protocol Section 4.5.7.1 for definition) will be limited to approximately 5% to reflect the natural prevalence in mCRC (Goldstein et al. 2014). Figure 1 illustrates the study schema.

Figure 1 Study Schema
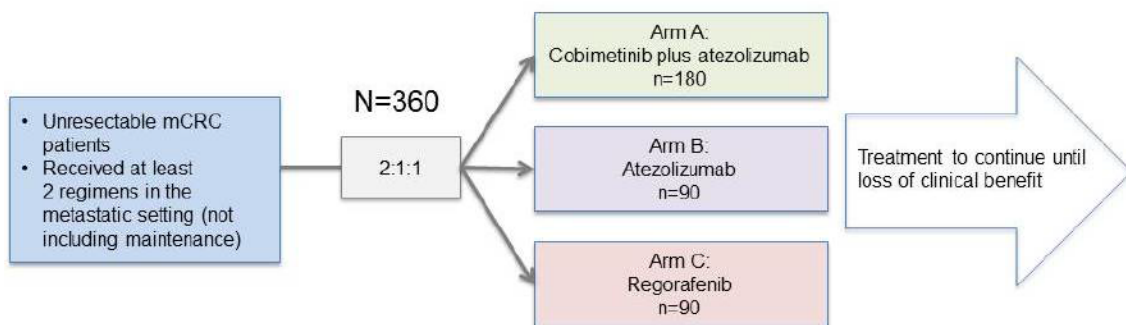
Stratified by tumor extended RAS status and time since diagnosis of first metastasis
MSI-H capped at approximately 5%
At least 180 patients with extended RAS-mutant tumors to be enrolled

mCRC=metastatic colorectal cancer; MSI-H=microsatellite high.

Patients will undergo tumor assessments at baseline and every 8 weeks (±7 days), regardless of any dose delays or treatment cycle, until documented investigator-determined progressive disease, loss of clinical benefit, withdrawal of consent, death, or study termination by the Sponsor, whichever occurs first. Tumor response will be evaluated according to Response Evaluation Criteria in Solid Tumors Version1.1 (RECIST v1.1). Any evaluable and measurable disease must be documented at screening and re-assessed at each subsequent tumor evaluation.

Treatment will continue until the patient has disease progression according to RECIST v1.1, unacceptable toxicity, death, patient or physician decision to withdraw, or pregnancy, whichever occurs first. Patients in all treatment arms are allowed to receive study treatment beyond disease progression if certain conditions are met (see Protocol Section 4.3.2.4).

After completion of study treatment, patients may receive any subsequent line of therapy as directed by their treating physician.

Patients who discontinue treatment for reasons other than disease progression (e.g., toxicity) will continue scheduled tumor assessments until disease progression, withdrawal of consent, study termination by Sponsor, or death, whichever occurs first. In the absence of disease progression, tumor assessments should continue regardless of whether patients start a new anti-cancer therapy, unless consent is withdrawn. All patients will be followed for survival unless consent is withdrawn.

The primary efficacy endpoint is overall survival (OS), which is defined as the time (in months) between the date of randomization and the date of death due to any cause. Patients who have not died at the time of analysis will be censored at the date when they were last known to be alive.

The analysis of the primary endpoint of OS will occur after a total of approximately 235 deaths have occurred.

The secondary endpoints include investigator-assessed progression-free survival (PFS), objective response rate (ORR), and duration of response (DOR) per RECIST v1.1. The analyses of PFS, ORR, and DOR will take place at the time of final analysis of OS.

2.1   PROTOCOL SYNOPSIS

The Protocol Synopsis is included in Appendix 1. For additional details, see the study schedule of assessments in Appendix 2.

2.2   OUTCOME MEASURES

2.2.1   Primary Efficacy Endpoint

The primary efficacy endpoint for this study is OS, defined as the time (in months) from randomization to death from any cause.

2.2.2   Secondary Efficacy Endpoints

Secondary efficacy outcome measures for this study are as follows:

- Progression free survival, defined as the time between the date of randomization and the date of first documented disease progression or death, whichever occurs first. Disease progression will be determined based on investigator assessment with the use of RECIST v1.1.

- ORR, defined as the proportion of patients with an objective response, either a confirmed complete response (CR) or confirmed partial response (PR) observed on two assessment ≥ 28 days apart with the use of RECIST v1.1 as determined by the investigator.

- DOR, defined for patients with an objective response as the time from the first documented objective response to documented disease progression with the use of RECIST v1.1 as determined by the investigator or death from any cause, whichever occurs first.

- Impact on functioning as measured by changes from baseline on the five-item physical functioning sub-scale of the patient–completed European Organization for Research and Treatment of Cancer Quality of Life Core 30 questionnaire (EORTC QLQ-C30).

- Impact on health–related quality of life (HRQoL) as measured by changes from baseline on the two-item global health status/quality of life sub-scale of the EORTC QLQ-C30.

2.2.3   Exploratory Analyses Endpoints

Exploratory analyses endpoints for this study are as follows:

- OS rate at fixed timepoints (e.g., 6, 12, 18, 24 months), defined as the proportion of patients alive at fixed timepoints after randomization estimated using Kaplan-Meier methodology

- PFS rate at fixed time points (e.g., 3, 6, 9, 12 months), defined as the proportion of patients alive and without disease progression as assessed by the investigator in accordance with RECIST v1.1 at fixed time points after randomization estimated using Kaplan-Meier methodology

- Time to response (TTR), defined as the time from randomization to the first occurrence of a CR or PR as determined by the investigator with the use of RECIST v1.1

- Utility scores of the Euro QoL5 Dimensions (EQ-5D-3L) for use in health economic models

Exploratory biomarker endpoints for this study are as follows:

- The following molecular characteristics in tumor samples during pretreatment, on treatment, and at disease progression:

    Genetic profile, including but not limited to somatic mutations and MSI status or mutation load as identified through next-generation sequencing (NGS) or other genetic analysis

    Immune contextures, such as programmed death–ligand 1 (PD-L1), CD8 T cells or major histocompatibility complex expression, as identified by immunohistochemistry (IHC) and gene signature profiling

    CRC molecular subtyping as defined by genetic and RNA and protein profiles

- The relationship between circulating tumor biomarker (including but not limited to carcinoembryonic antigen, tumor-associated mutations in cell-free DNA) and measures of efficacy

2.2.4 Patient-Reported Outcomes Objectives

The additional patient-reported outcome objective of the study is to assess treatment impact and disease symptoms from the sub-scales of the EORTC QLQ-C30 questionnaire that assess diarrhea, constipation, lack of appetite, fatigue, and two additional items from the EORTC item bank that assess bloating and abdominal pain associated with cobimetinib plus atezolizumab compared with regorafenib in patients with metastatic mCRC.

2.2.5 Pharmacokinetic Efficacy Outcome Measures

The pharmacokinetic (PK) outcome measures for this study are the following:

- Plasma concentration of cobimetinib in Arm A

- Serum concentration of atezolizumab in both the atezolizumab + cobimetinib arm (Arm A) and the monotherapy atezolizumab arm (Arm B)

2.2.6 Safety Outcome Measures

The safety outcome measures for this study are the following:

- Incidence, nature, and severity of adverse events (AEs) graded in accordance with the National Cancer Institute Common Terminology Criteria in Adverse Events, Version 4.0 (NCI CTCAE v4.0)

- Changes in vital signs, physical findings, and clinical laboratory results during the course of study
- Incidence of anti-therapeutic antibody (ATA) response to atezolizumab and potential correlation with PK, safety, and efficacy parameters

2.3 DETERMINATION OF SAMPLE SIZE

The study will randomize approximately 360 patients, including a minimum of 180 patients with extended RAS-mutant mCRC (assuming a prevalence of at least 50%), to cobimetinib plus atezolizumab (Arm A), atezolizumab monotherapy (Arm B), and regorafenib (Arm C) with the randomization ratio of 2:1:1, respectively.

The type 1 error (α) for the analysis of the primary endpoint of OS in the comparison of Arm A versus Arm C (the control arm) is 0.05 (2-sided). If OS is statistically significant in the comparison of Arm A versus Arm C, then the OS comparison of Arm B versus Arm C will be tested at a 2-sided α-level of 0.05.

The overview of the type 1 error (α) control is shown in Figure 2.

Figure 2 Overview of Hierarchical Testing Sequence for Type 1 Error [a] Control (2-Sided)

Arm A versus Arm C		Arm B versus Arm C
Overall Survival (OS)	⇨	Overall Survival (OS)
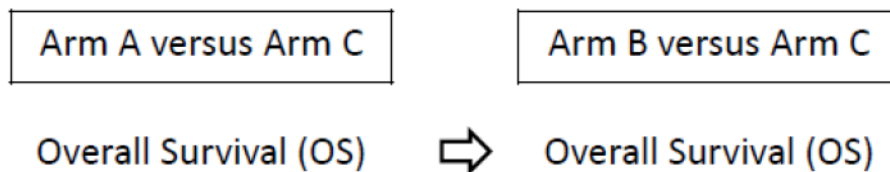
OS = overall survival
[a] OS will be tested at a 2-sided significance level $\alpha = 0.05$ only if the result of previous testing is positive (i.e., statistically significant). .

The sample size of this study is determined on the basis of the number of events required to demonstrate efficacy with regard to OS in both comparisons (Arm A vs. Arm C and Arm B vs. Arm C).

The estimate of the number of events required to demonstrate efficacy with regard to OS is based on the following assumptions:

- Two-sided significance level of 0.05
- Arm A versus Arm C: 87% power to detect an hazard ratio (HR) of 0.61, corresponding to an improvement in median OS from 6.4 months in Arm C to 10.5 months in Arm A
- Arm B versus Arm C: 80% power to detect an HR of 0.61, corresponding to an improvement in median OS from 6.4 months in Arm C to 10.5 months in Arm B
- No interim analysis for OS

- Dropout rate of 10% in 24 months
- Hierarchical testing of Arm A versus Arm C followed by Arm B versus Arm C to control the overall α level of 5%

With these assumptions, approximately 360 patients in total will be randomized into this study, with approximately 270 patients for the comparison of Arm A versus Arm C and approximately 180 patients for the comparison of Arm B versus Arm C. The OS final analysis will be conducted when there are approximately 235 deaths occurring from all three arms. At this time, it is expected that approximately 178 deaths for the comparison of Arm A versus Arm C and approximately 127 deaths for the comparison of Arm B versus Arm C will have occurred.

The number of events corresponds to a minimum detectable difference in HR of approximately 0.73 for the Arm A versus Arm C comparison and approximately 0.71 for the Arm B versus Arm C comparison.

2.4   ANALYSIS TIMING

2.4.1   Primary Analysis Timing

No interim analyses are planned for the efficacy endpoints. The OS final analysis for the primary comparisons of Arm A versus Arm C and Arm B versus Arm C will be conducted when there are a total of approximately 235 OS events from the study, which is expected to occur approximately 23 months after the first patient is randomized, based on the study assumptions and the projected accrual rate. The number of events, the event ratio, the minimum detectable difference (MDD), and the power for each comparison are summarized in Table 1.

Table 1   Analysis for Overall Survival for Primary Comparisons (Arm A vs. Arm C and Arm B vs. Arm C)

	OS Final Analysis	
	Arm A vs. Arm C	Arm B vs. Arm C
Events (event ratio)	178 (66%)	127 (71%)
MDD in HR	0.73	0.71
Power	87%	80%

FPI=first patient in; HR=hazard ratio; MDD=minimum detectable difference; OS=overall survival; event ratio=number of events / number of patients randomized.
Note: OS final analysis to occur approximately 23 months from FPI.

2.4.2   Analysis Timing for Experimental Arm Comparison

If both of the primary comparisons (i.e., Arm A vs. Arm C and Arm B vs. Arm C) are statistically significant for OS, then OS between the experimental arms (i.e., Arm A vs. Arm B) will be compared at the time of the primary analysis. At this time, a total of approximately 165 OS events are expected from Arms A and B, corresponding to an

MDD in HR of 0.72. The operating characteristics for selected target HRs comparing Arm A with Arm B is presented in Table 2.

Table 2 Operating Characteristics for the Comparison of Arm A versus Arm B with Approximately 165 Overall Survival Events

Target HR	Power	95% CI [a]
0.61	85%	(0.44, 0.84)
0.67	69%	(0.48, 0.93)
0.75	42%	(0.54, 1.04)

FPI = first patient in; HR = hazard ratio; mOS = median overall survival.
[a] 95% CI when the target HR is observed.

3. STUDY CONDUCT

3.1 RANDOMIZATION ISSUES

Randomization to arms A, B, and C will occur in a 2:1:1 ratio, respectively, using a permuted-block randomization method. Randomization will be stratified by the following factors:

- Extended RAS mutation status of the tumor (yes vs. no)
- Time since diagnosis of first metastasis (<18 months vs. ≥ 18 months)

3.2 DATA MONITORING

An Internal Monitoring Committee (IMC) will be used to evaluate safety during the study on a periodic basis until the primary analysis. For details of the IMC, refer to the IMC Charter (Appendix 4).

4. STATISTICAL METHODS

The analyses described in this SAP will supersede those specified in Protocol GO30182 for the purpose of a regulatory filing.

4.1 ANALYSIS POPULATIONS

4.1.1 Efficacy Analysis Population

The randomized population or intent-to-treat (ITT) population is defined as all randomized patients, whether or not the patient received the assigned treatment.

4.1.2 Pharmacokinetic-Evaluable Population

The pharmacokinetic-evaluable population is defined as all patients who received any dose of study medication and who have at least one post-baseline PK sample available.

4.1.3 Safety Population

Safety analyses will be performed on all randomized patients who received any amount of any component of protocol treatment, with patients grouped as follows:

- Cobimetinib + atezolizumab arm (Arm A): patients who received any amount of cobimetinib

- Atezolizumab arm (Arm B): patients who received any amount of atezolizumab without any amount of cobimetinib

- Regorafenib arm (Arm C): patients who received any amount of regorafenib without any amount of either atezolizumab or cobimetinib.

4.2 ANALYSIS OF STUDY CONDUCT

Study enrollment, major protocol deviations including major deviations of inclusion/exclusion criteria, and reasons for study termination will be summarized overall and by treatment arm for the ITT population. Study treatment administration and reasons for discontinuation from study treatment will be summarized for the Safety population.

4.3 ANALYSIS OF TREATMENT GROUP COMPARABILITY

Demographic characteristics, such as age, race/ethnicity, baseline disease characteristics (e.g., Eastern Cooperative Oncology Group [ECOG] performance status), and stratification factors will be summarized by treatment arms for the ITT population. Descriptive statistics (mean, median, standard deviation, and range) will be presented for continuous data, and frequencies and percentages will be presented for categorical data.

Baseline values are the last available data obtained prior to the patient receiving the first dose of any component of study treatment on Cycle 1, Day 1.

4.4 EFFICACY ANALYSIS

Patients will be grouped for efficacy analyses according to the treatment assigned at randomization, whether or not the assigned treatment was received.

4.4.1 Primary Efficacy Endpoint

The primary efficacy endpoint is OS. Overall survival is defined as the time between the date of randomization and the date of death due to any cause. Data for patients who are not reported as having died at the time of analysis will be censored at the date they were last known to be alive. Data for patients who do not have post-baseline information will be censored at the date of randomization plus 1 day.

Comparisons with respect to OS for each of the two comparisons between treatment arms will be tested based on a stratified log-rank test in the ITT populations in the analysis at the two-sided level of significance as described in Section 2.3. The stratification factors will be those used for randomization (i.e., extended RAS

mutation status (yes vs. no) and time since diagnosis of first metastasis [$<$18 months vs. $\geq$18 months]), and will be obtained from the IxRS.

The null and alternative hypotheses can be phrased in terms of the survival functions $S_E(t)$ and $S_C(t)$, where $S_E(t)$ represents the survival function for experimental arm (either Arm A or Arm B) and $S_C(t)$ represents the survival function for Arm C:

$$H_0: \ S_E(t) = S_C(t) \text{ versus } H_1: \ S_E(t) \neq S_C(t)$$

The HR (λ_E/λ_C, where λ_E represents the hazard of death in experimental arm [either Arm A or Arm B] and λ_C represents the hazard of death in Arm C, comparing the treatment effect between the two treatment arms) will be estimated using a stratified Cox regression model with the same stratification variables used for the stratified log-rank test, and the 95% CI will be provided. Results from an unstratified analysis will also be provided.

Kaplan-Meier methodology will be used to estimate median OS and to construct survival curves for each treatment arm for a visual description of the difference among arms. The Brookmeyer-Crowley methodology will be used to construct the 95% CI for the median OS (Brookmeyer and Crowley 1982).

4.4.2 <u>Secondary Efficacy Endpoints</u>
4.4.2.1 **Progression-Free Survival**
PFS is defined as the time between the date of randomization and the date of first documented disease progression or death, whichever occurs first. Disease progression will be determined on the basis of investigator assessment using RECIST v1.1. Data for patients who are alive and have not experienced disease progression at the time of analysis will be censored at the date of last tumor assessment. Data from patients with no post-baseline tumor assessment will be censored at the randomization date plus 1 day. PFS will be analyzed using the same methods as described in Section 4.4.1.

4.4.2.2 **Objective Response Rate**
ORR is defined as the proportion of patients who had a confirmed objective response of CR or PR assessed by the investigator according to the RECIST v1.1. The analysis population for ORR will be all randomized patients with measurable disease at baseline (i.e., patients with at least one measureable lesion according to RECIST v1.1 based on investigator assessment). An estimate of ORR and its 95% CI will be calculated using the Clopper-Pearson method for each treatment arm.

Treatment difference in ORR will be tested using the stratified Cochrane-Mantel-Haenszel test, stratified by the same factors used in the OS analysis, and a 95% Hauck-Anderson CI will be calculated for the difference in ORR between treatment arms.

4.4.2.3 Duration of Response

DOR is defined as the period measured from the date of the first occurrence of a CR or PR (whichever status is recorded first) until the first date that progressive disease or death is documented. Disease progression will be determined on the basis of investigator assessment with use of RECIST v1.1. DOR will be assessed in patients who have an objective response during the study as determined by the investigator with use of RECIST v1.1. Patients who have not progressed and who have not died by the date of data cutoff for analysis will be censored at the time of last tumor assessment date. Median DOR will be estimated using the Kaplan-Meier method, and the 95% CI will be calculated using the method of Brookmeyer and Crowley (1982). DOR analysis is performed on the basis of a non-randomized subset of patients (i.e., patients who achieve an objective response); therefore, formal hypothesis testing will not be performed for this endpoint. Comparisons between treatment arms will be made using the unstratified log-rank test for descriptive purposes only.

4.4.2.4 Patient-Reported Outcomes

Data from the EORTC QLQ-C30 questionnaire and two additional items from the EORTC Item Bank will be scored according to the EORTC scoring manual (Fayers et al. 2001).

The primary analysis population for evaluation of patient-reported outcome (PRO) assessments will include patients in a modified ITT population with a baseline PRO assessment and at least one post-baseline PRO assessment.

Data from the physical function scale and the global health status/quality of life sub-scale of the EORTC QLQ-C30 will be analyzed as time to clinically meaningful deterioration, which will be compared as secondary efficacy endpoints among treatment groups with use of the log rank test (2-sided). Confirmed clinically meaningful deterioration will be defined as a $\geq$ 10-point decrease (on a transformed 0 to 100 score) from baseline on the physical function score or the global status/quality of life scores that must be held for at least two consecutive assessments or an initial $\geq$ 10-point decrease from baseline followed by death within 4 weeks of the last assessment. Data for patients who do not achieve a 10-point decrease will be censored at the last time PRO data are available. The HR will be estimated using a stratified Cox proportional hazards model and its 95% CI will be provided.

Summary statistics (mean, standard deviation, median, and range) of absolute scores and mean changes from baseline will be calculated for all items and subscales of the EORTC QLQ-C30 and the two additional items from the EORTC Item Bank at each assessment timepoint for each arm while patients are receiving treatment. The mean (and 95% CI) and median of the absolute scores and the changes from baseline to each follow-up point will be reported for categorical and continuous variables, and the proportion of patients selecting each response option will be reported for the two additional items from the EORTC Item Bank. Previously published minimally important

differences (of 10 points) will be used to identify meaningful change from baseline within each treatment group on the functional and disease or treatment–related symptoms scales (Osoba et al. 1998; Cocks et al. 2011). Additional sensitivity analyses may be conducted.

A longitudinal analysis for the physical functioning and global health status/HRQoL subscales may be conducted to estimate the effect difference on PRO-repeated responses over a selected period of time and between the treatment arms, and mixed models on a set of covariates (baseline domain score, patient demographic, and clinical variables) may be conducted.

In the event of incomplete data, for all questionnaire subscales, if more than 50% of the constituent items are completed, a prorated score will be computed consistent with the scoring manuals and validation papers. For subscales with less than 50% of the items completed at a given timepoint, the subscale will be considered as missing. PRO completion, compliance rates, and reasons for missing data will be summarized at each timepoint by treatment arm.

Exploratory descriptive analyses will be conducted using post-treatment data.

4.4.3   Exploratory Efficacy Endpoints
4.4.3.1   Overall Survival/Progression-Free Survival Rate at Fixed Timepoints
The OS and PFS rates at fixed timepoints (e.g., 6, 12, 18, 24 months) after randomization in ITT populations will be estimated for each treatment arm using Kaplan-Meier methodology, along with 95% CI calculated with the standard error derived from Greenwood's formula. The 95% CI for the difference in OS rates between the two treatment arms will be estimated using the normal approximation method, with standard errors computed by use of Greenwood's method.

4.4.3.2   Time to Response
TTR is defined for patients with an objective response as the time from randomization to the first occurrence of a CR or PR as determined by the investigator using the RECIST v1.1. TTR will be summarized for descriptive purposes. The mean, standard error, median, and range of TTR will be provided. No formal treatment comparisons will be performed.

4.4.3.3   Health Economic Analyses
Health economic data, as assessed by the EQ-5D-5L, will be evaluated for patients with a baseline assessment and at least one post-baseline EQ-5D-5L assessment that generates a score. Scores at baseline and change-from-baseline scores for each timepoint will be quantified using descriptive statistics. Patients without post-baseline assessments will be excluded from this analysis. A single summary index from the

EQ-5D-5L health states will be utilized in this study for economic modeling. These results will not be reported in the Clinical Study Report (CSR).

4.4.4 Evaluation of Each Drug's Contribution to The Combination

If both of the primary comparisons (i.e., Arm A vs. Arm C and Arm B vs. Arm C) for OS are statistically significant, OS as well as other secondary and exploratory endpoints will be compared between experimental arms (i.e., Arm A vs. Arm B) using the same methods described in Sections 4.4.1, 4.4.2, and 4.4.3. The clinical benefit associated with adding cobimetinib to atezolizumab will be evaluated with the focus on clinically meaningful improvement rather than statistical significance.

If the OS comparison for Arm A versus Arm C is statistically significant but the OS comparison for Arm B versus Arm C is not, atezolizumab's contribution to the treatment effect in Arm A will be evaluated for all study endpoints. The evaluation of clinical benefit by adding atezolizumab to the combination will use descriptive statistics (e.g., point estimate and confidence intervals) without hypothesis testing.

4.4.5 Sensitivity Analyses

4.4.5.1 Loss to Follow-Up for Overall Survival Analyses

The impact of loss to follow-up on OS will be assessed depending on the number of patients who are determined to be lost to follow-up. If $>10\%$ of patients are lost to follow-up for OS in either treatment arm, a sensitivity analysis will be performed for the comparisons between two treatment arms (i.e., Arm A vs. Arm C, Arm B vs. Arm C) in which patients who are lost to follow-up will be considered as having died at the last date they were known to be alive plus 1 day.

4.4.5.2 Missing Tumor Assessment

The impact of missing scheduled tumor assessments on PFS will be assessed depending on the number of patients who missed assessments scheduled immediately prior to the date of disease progression per RECIST v1.1 or the data cutoff. If $>5\%$ of patients missed two or more assessments scheduled immediately prior to the date of disease progression per RECIST v1.1 or death in any treatment arm, the following sensitivity analysis will be performed:

- Patients who missed two or more scheduled assessments immediately prior to the date of disease progression per RECIST v1.1 or death will be censored at the last tumor assessment prior to the missed visits.

Statistical methodologies analogous to those used in the analysis of PFS as specified in Section 4.4.2 will be used for this sensitivity analysis.

4.4.6 Subgroup Analyses

The consistency of OS and PFS results will be examined in subgroups defined by demographic and baseline characteristics and stratification factors. Summaries of OS and PFS, including the unstratified HR estimated from a Cox proportional hazards model

and Kaplan-Meier estimates of median OS and PFS, will be produced separately for each level of the subgroup for the comparisons between two treatment arms and displayed in a Forest plot (Lewis and Clarke 2001). Kaplan-Meier plots of OS and PFS will also be produced for selected subgroups.

Summaries of ORR by subgroup will also be provided.

The subgroups to be considered include but are not limited to the following:

- Age ($\leq$65 years, $>$65 years) at randomization
- Race (non-White, White)
- Sex (female, male)
- Region (North America, Europe, Asia, Australia)
- Extended RAS mutation status (no, yes)
- MSI status (high, standard)
- PD-L1 status (high, low)
- Time since diagnosis of first metastasis ($<$18 months, $\geq$18 months)
- ECOG performance status at randomization (0, 1)
- Location of the tumor in the colon (left colon, right colon)
- Liver metastases (no, yes)
- Previous treatment of any anti-epidermal growth factor receptor monoclonal antibodies (no, yes)
- Previous treatment of any anti-vascular endothelial growth factor therapies (no, yes)
- Number of previous treatment lines (3, $>$3)

4.5   PHARMACOKINETIC AND PHARMACODYNAMIC ANALYSES

PK samples will be collected in this study as outlined in Appendix 3. Cobimetinib and atezolizumab maximum and minimum concentration data (C_{max} and C_{min}, respectively) will be tabulated and summarized (mean, standard deviation, median, range, coefficient of variation, geometric mean, and geometric mean coefficient of variation, as appropriate.

Additional PK analyses will be conducted, as appropriate, based on the availability of data.

Exploratory biomarker analyses will be performed in an effort to understand the association of these markers with study drug response, including efficacy and/or AEs. The blood and tumor biomarkers include but are not limited to mutational load by NGS, PD-L1 and CD8 as defined by IHC, or other methods. Additional pharmacodynamic analyses will be conducted as appropriate.

4.6 SAFETY ANALYSES

Unless specified otherwise, the safety analyses described below will be conducted for the safety population with patients grouped according to whether study treatment was received. Specifically, the treatment arm for safety analyses will be defined as follows:

- Cobimetinib + atezolizumab arm: patients who received any amount of cobimetinib

- Atezolizumab arm: patients who received any amount of atezolizumab without any amount of cobimetinib

- Regorafenib arm: patients who received any amount of regorafenib without any amount of either atezolizumab or cobimetinib

If a patient did not receive any amount of atezolizumab, cobimetinib, or regorafenib, the patient will not be included in the safety analyses.

4.6.1 Exposure of Study Medication

Study drug exposure, including treatment duration, number of cycles, and dose intensity, will be summarized for each treatment arm with descriptive statistics.

4.6.2 Adverse Events

Verbatim description of AEs will be mapped to MedDRA thesaurus terms and graded according to NCI CTCAE v4.0. All AEs that occur during or after the first study drug dose will be summarized by treatment arm and NCI CTCAE grade. In addition, serious adverse events (SAE), severe AEs (Grades 3, 4, and 5), AEs of special interest, and AEs leading to study drug discontinuation or interruption will be summarized accordingly. Multiple occurrences of the same event will be counted once at the maximum severity. The proportion of patients who experience at least one AE will be reported by toxicity term and treatment arm.

Listings of AEs will include all AEs with an onset that occurred on or after the first study drug treatment up to the data cutoff date.

Deaths reported during the study treatment period and those reported during the follow-up period after treatment discontinuation will be summarized by treatment arm.

4.6.3 Laboratory Data

Laboratory data will be summarized over time including change from baseline by treatment arm. Values outside the normal ranges will be summarized. Additionally, selected laboratory data will be classified in accordance with NCI CTCAE v4.0and will be summarized by grade and treatment arm. Highest NCI CTCAE grade post-baseline will also be reported, and shift tables from baseline to worst value during the study post-baseline will be presented.

4.6.4 <u>Vital Signs</u>

Changes in selected vital signs will be summarized by treatment arm and by change over time including change from baseline.

ECOG performance status will also be summarized over time.

4.7 IMMUNOGENICITY ANALYSES

The number and percentage of patients with positive serum antibodies to atezolizumab at baseline and postbaseline during the study period will be summarized. Adverse events occurring in patients with positive serum antibodies to atezolizumab will be reviewed. The relationship of the immunogenicity response with pharmacokinetics, safety, and efficacy may also be evaluated when appropriate.

ATA sampling timepoints are provided in Appendix 3.

4.8 MISSING DATA

Please refer to Sections 4.4.1 and 4.4.2 for methods of handling missing data for the primary and secondary efficacy endpoints.

4.9 EXPLORATORY ANALYSES

Exploratory efficacy endpoints defined in the protocol other than the analyses specified in Section 4.4.3 are outside of the scope of this SAP and will not be included in the CSR.

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Appendix 1
Protocol Synopsis

PROTOCOL SYNOPSIS

TITLE: A Phase III, open-label, multicenter, three-arm, randomized study to investigate the efficacy and safety of cobimetinib plus atezolizumab and atezolizumab monotherapy vs. regorafenib in patients with previously treated unresectable locally advanced or metastatic colorectal adenocarcinoma

PROTOCOL NUMBER: GO30182

VERSION NUMBER: 4

EUDRACT NUMBER: 2016-000202-11

IND NUMBER: 130,091

TEST PRODUCT: Cobimetinib (RO5514041); atezolizumab (RO5541267)

PHASE: III

INDICATION: Previously treated unresectable locally advanced or metastatic colorectal adenocarcinoma

SPONSOR: F. Hoffmann-La Roche Ltd

Objectives and Endpoints

Primary Efficacy Objective

The primary efficacy objective for this study is to evaluate the efficacy of cobimetinib plus atezolizumab compared to regorafenib (standard of care) in patients with previously treated, unresectable locally advanced or metastatic colorectal cancer (CRC) on the basis of overall survival (OS). Atezolizumab monotherapy will also be evaluated compared to regorafenib on the basis of OS.

Secondary Efficacy Objectives

The secondary efficacy objectives include:

- Investigator-assessed progression-free survival per Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 of patients in the cobimetinib plus atezolizumab arm and the atezolizumab monotherapy arm compared to the regorafenib arm.

- Investigator-assessed objective response rate per RECIST v1.1 of patients in the cobimetinib plus atezolizumab arm and atezolizumab monotherapy arm compared to the regorafenib arm

- Duration of response of patients in the cobimetinib plus atezolizumab arm and atezolizumab monotherapy arm compared to the regorafenib arm

- Impact on functioning as measured by changes from baseline on the five-item physical functioning sub-scale of the patient–completed European Organization for Research and Treatment of Cancer Quality of Life Core 30 questionnaire (EORTC QLQ-C30)

- Impact on health–related quality of life as measured by changes from baseline on the two-item global health status/quality of life sub-scale of the EORTC QLQ-C30

Appendix 1
Protocol Synopsis (cont.)

Safety Objective

The safety objective for this study is to evaluate the safety profile and adverse events encountered by patients in the cobimetinib plus atezolizumab arm and atezolizumab monotherapy arm compared to the regorafenib arm.

Pharmacokinetic Objective

The PK objective for this study is to characterize the cobimetinib and atezolizumab PK profiles on the basis of the following:

- Plasma concentration of cobimetinib at timepoints specified in Appendix 2

- Serum concentration of atezolizumab in both the cobimetinib plus atezolizumab arm and the monotherapy atezolizumab arm at timepoints specified in Appendix 2

Immunogenicity Objective

The immunogenicity objective for this study is to evaluate the immune response to atezolizumab on the basis of the following endpoint:

- Incidence of anti-therapeutic antibodies (ATAs) during the study relative to the prevalence of ATAs at baseline in both the cobimetinib plus atezolizumab arm and the atezolizumab monotherapy arm.

The exploratory immunogenicity objective for this study is to evaluate potential effects of ATAs on efficacy, safety, or pharmacokinetics.

Biomarker Objectives

The exploratory biomarker objectives for this study are as follows:

- To assess the following molecular characteristics in tumor samples during pretreatment, on treatment, and at progression:

  - Genetic profile including but not limited to somatic mutations and microsatellite (MSI) status or mutation load as identified through next-generation sequencing or other genetic analysis.

  - Immune contextures, such as programmed death-ligand 1 (PD-L1), CD8 T cells or major histocompatibility complex expression, as identified by immunohistochemistry and gene signature profiling

  - CRC molecular subtyping as defined by genetic and RNA and protein profiles

- To evaluate the relationship between circulating tumor biomarkers (including but not limited to carcinoembryonic antigen [CEA], tumor-associated mutations in cell-free DNA) and measures of efficacy

Patient-Reported Outcomes Objectives

The additional patient-reported outcome objective of the study is to assess treatment impact and disease symptoms from the sub-scales of the EORTC QLQ-C30 that assess diarrhea, constipation, lack of appetite, fatigue, and two additional items from the EORTC item bank that assess bloating and abdominal pain associated with cobimetinib plus atezolizumab compared with regorafenib in patients with metastatic CRC (mCRC).

Pharmacoeconomic Objectives

In addition, a study objective is to obtain general measures of health as measured by the EuroQoL 5 Dimensions questionnaire for health economic modeling of cobimetinib plus

atezolizumab or atezolizumab monotherapy compared with regorafenib in patients with mCRC. This information is not intended to be included in the clinical study report.

Study Design

Description of Study

This is a Phase III, multicenter, open-label, three-arm, randomized study in patients with unresectable locally advanced or metastatic CRC who have received at least two prior regimens of cytotoxic chemotherapy for metastatic disease. The study compares regorafenib, a standard of care therapy in this setting, to cobimetinib plus atezolizumab and atezolizumab monotherapy.

The primary objective of the study is to evaluate the efficacy of cobimetinib plus atezolizumab compared to regorafenib in patients with unresectable locally advanced or metastatic CRC who have received at least two prior regimens of chemotherapy in the metastatic setting.
The efficacy of atezolizumab monotherapy compared to regorafenib in the same patient population will also be evaluated as a primary objective.

This study will be conducted globally and approximately 360 patients will be randomized in a 2:1:1 ratio to receive:

- Arm A: cobimetinib 60 mg orally on Days 1–21 plus atezolizumab 840 mg intravenous (IV) on Day 1 and Day 15 in a 28-day cycle (n ≈ 180), or

- Arm B: atezolizumab monotherapy 1200 mg IV on Day 1 in a 21-day cycle (n ≈ 90), or

- Arm C: regorafenib 160 mg orally on Days 1–21 in a 28-day cycle (n ≈ 90).

At least 50% patients with extended RAS-mutant tumors will be enrolled in each arm. Enrollment of patients with MSI-high status will be limited to approximately 5% to reflect the natural prevalence in mCRC.

Stratification factors are extended RAS mutation status of the tumor and time since diagnosis of first metastasis (<18 months vs. ≥ 18 months). Permuted-block randomization will be applied to ensure a balanced assignment to each treatment arm. Randomization and stratification will be managed through an interactive voice/web response system.

The Sponsor will monitor the enrollment for each region (North America, Europe, and Pacific/Asia). To ensure balanced global enrollment, the Sponsor may institute temporary limitations on enrollment in certain regions in the event of disproportionate accrual of patients.

After signing informed consent, patients will undergo screening procedures that include testing the tumor for extended RAS mutation status and MSI status (local tests accepted but confirmatory centralized testing required); laboratory tests (e.g., hematology, chemistries, liver function tests); left-ventricular function evaluation (echocardiogram or multigated acquisition scan); contrast-enhanced computed tomography scan or magnetic resonance imaging of the chest, abdomen, and pelvis; and ophthalmologic assessments.

All eligible patients will be randomized to treatment in either Arm A (cobimetinib plus atezolizumab), Arm B (atezolizumab monotherapy) or Arm C (regorafenib).

All patients will be closely monitored for safety and tolerability during all cycles of therapy, at the treatment discontinuation visit, and during the follow-up period. The National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) Version 4.0 will be used to characterize the toxicity profile of the study treatments on all patients. Patients will be assessed for adverse events according to the schedule of assessments and as necessary throughout the study.

Tumor response will be evaluated according to RECIST v1.1. Any evaluable and measurable disease must be documented at screening and re-assessed at each subsequent tumor evaluation. Investigators will assess tumor response at 8-week intervals, regardless of any dose delays or treatment cycle.

Treatment will continue until the patient has disease progression according to RECIST v1.1, unacceptable toxicity, death, patient or physician decision to withdraw, or pregnancy, whichever occurs first. A rising CEA level alone is not considered disease progression. No crossover will

be allowed. Patients are allowed to receive study treatment beyond disease progression if certain conditions are met.

After discontinuation of study treatment, patients may receive any subsequent line therapy as directed by their treating physician.

Patients who discontinue treatment for reasons other than disease progression (e.g., toxicity) will continue scheduled tumor assessments until disease progression, withdrawal of consent, study termination by Sponsor, or death, whichever occurs first. In the absence of disease progression, tumor assessments should continue regardless of whether patients start a new anti-cancer therapy, unless consent is withdrawn. All patients will be followed for survival unless consent is withdrawn.

Number of Patients

Approximately 360 patients with unresectable locally advanced or metastatic CRC who have received at least two different chemotherapy regimens for metastatic disease will be enrolled in this study.

Target Population

Inclusion Criteria

Patients must meet the following criteria for study entry:

Disease-specific inclusion criteria:

- Histologically confirmed adenocarcinoma originating from the colon or rectum (Stage IV American Joint Committee on Cancer 7th edition)

- Experienced disease progression on at least two prior systemic chemotherapy regimens for mCRC

    1. Prior systemic cytotoxic chemotherapy must include ALL of the following agents:

        a) Fluoropyrimidines

        b) Irinotecan

        c) Oxaliplatin

    2. Patients who have received prior anti-angiogenic therapy (e.g., bevacizumab) and/or anti-epidermal growth factor receptor therapy (e.g., cetuximab) are eligible.

    3. Patients must have had documented disease progression within 3 months of the last systemic therapy administration.

    4. Patients who were intolerant to prior systemic chemotherapy regimens are eligible if there is documented evidence of clinically significant intolerance despite adequate supportive measures.

    5. For patients who had disease recurrence within 6 months of completing adjuvant chemotherapy, the adjuvant regimen can be considered as one chemotherapy regimen for metastatic disease.

General inclusion criteria:

- Signed Informed Consent Form
- Age $\geq$ 18 years
- In the investigator's judgment, patient is able to comply with the requirements and assessments of the study protocol
- Eastern Cooperative Oncology Group performance status of 0 or 1

Appendix 1
Protocol Synopsis (cont.)

- Anticipated life expectancy ≥ 3 months
- Able to comply with the requirements and assessments of the study protocol
- Adequate hematologic and end organ function, defined by the following laboratory results obtained within 14 days prior to first dose of study drug treatment:

    1. Hemoglobin ≥ 9 g/dL, platelet count $\geq 100,000/mm^3$, ANC $\geq 1500/mm^3$

    2. Creatinine clearance ≥ 30 mL/min

    3. Amylase and lipase $\leq 1.5 \times$ the upper limit of normal (ULN)

    4. Serum bilirubin $\leq 1.5\times$ ULN; patients with known Gilbert's disease may have a bilirubin $\leq 3.0x$ ULN

    5. AST, ALT, and alkaline phosphatase (ALP) $\leq 2.5 \times$ ULN with the following exceptions:

        a) Patients with documented liver metastases: AST and/or ALT $\leq 5 \times$ ULN

        b) Patients with documented liver or bone metastases: ALP $\leq 5 \times$ ULN

    6. INR and PTT $\leq 1.5 \times$ ULN. Patients who are on therapeutic doses of anti-coagulants are eligible if they are on a stable dose of anti-coagulant for 28 days with stable INR and PTT values.

- Women of childbearing potential must agree to appropriately use an effective form of contraception (failure rate of $< 1\%$ per year) during the treatment period, *within 5* months after the last dose of *atezolizumab, and within 3 months after the last dose of cobimetinib and regorafenib.*

    1. A woman of childbearing potential is defined as a sexually mature woman without prior oophorectomy or hysterectomy who have had menses within the last 12 months.

    2. A woman is not considered to be of childbearing potential if she has become amenorrheic for > 12 months and has a follicle-stimulating hormone level ≥ 40 IU/L.

- Men must agree not to donate sperm or have intercourse with a female partner without using appropriate barrier contraception during the treatment period and for 3 months after the last dose of *either cobimetinib or regorafenib.*
- Available and adequate baseline tumor tissue sample (archival or newly obtained biopsy)

Exclusion Criteria
Patients who meet any of the following criteria will be excluded from study entry:
Cancer-related exclusion criteria:

- After the approximate 5% cap for MSI-high patients is reached, only MSI-stable patients will be eligible.
- Once the 50% cap for wild-type RAS has been reached, only extended RAS-mutant patients will be eligible.
- Major surgery or radiotherapy within 21 days prior to Cycle 1 Day 1 or anticipation of needing such procedure while receiving study treatment.
- Treatment with any anti-cancer agent within 14 days prior to Cycle 1 Day 1
- Uncontrolled tumor-related pain. Patients requiring narcotic pain medication must be on a stable regimen at study entry.

Appendix 1
Protocol Synopsis (cont.)

1. Symptomatic lesions (e.g., bone metastases or metastases causing nerve impingement) amenable to palliative radiotherapy should be treated prior to start of study treatment.

2. Asymptomatic metastatic lesions whose further growth would likely cause functional deficits or intractable pain (e.g., epidural metastasis that is not presently associated with spinal cord compression) should be considered for loco-regional therapy if appropriate prior to the start of study treatment.

- Uncontrolled pleural effusion, pericardial effusion or ascites requiring repeated drainage more than once every 28 days. Indwelling drainage catheters (e.g., PleurX®) are allowed.

- Active or untreated CNS metastases are excluded. Patients with treated and asymptomatic CNS metastases are eligible, if they meet all of the following:

  1. Evaluable or measurable disease outside the CNS

  2. No metastases to midbrain, pons, medulla or within 10 mm of the optic nerves and chiasm

  3. No history or evidence of intracranial hemorrhage or spinal cord hemorrhage

  4. No evidence of clinically significant vasogenic edema

  5. Not on corticosteroids for ≥ 2 weeks; anti-convulsants at a stable dose are allowed.

  6. No evidence of clinical and radiographic disease progression in the CNS for ≥ 3 weeks after radiotherapy or surgery.

- Exclusion criteria related to study medication:

  1. Any cancer immunotherapy including CD137 agonists, anti–programmed death-1, anti–PD-L1, or anti-CTLA4

  2. Any MEK or ERK inhibitor

  3. Regorafenib

- Patients with active malignancy (other than CRC) or a prior malignancy within the past 3 years are excluded. Patients with completely resected cutaneous melanoma (early stage), basal cell carcinoma, cutaneous squamous cell carcinoma, cervical carcinoma in-situ, breast carcinoma in-situ, and localized prostate cancer are eligible.

Exclusion criteria based on organ function or medical history:

Cardiovascular:

- Unstable angina, new onset angina within last 3 months, myocardial infarction within last 6 months and current congestive heart failure New York Heart Association Class II or higher.

- Left ventricular ejection fraction below institutional lower limit of normal or below 50%, whichever is lower.

- Poorly controlled hypertension, defined as a blood pressure consistently above 150/90 mmHg despite optimal medical management.

Infections:

- HIV infection

- Active tuberculosis infection

- Severe infections within 2 weeks prior to Cycle 1 Day 1

- Signs or symptoms of significant infection within 2 weeks prior to Cycle 1 Day 1

- Received oral or IV antibiotics within 2 weeks prior to Cycle 1 Day 1

  Patients receiving prophylactic antibiotics (e.g., for prevention of urinary tract infection or chronic obstructive pulmonary disease) are eligible

- Active or chronic viral hepatitis B or C infection

  1. Patients with hepatitis B virus (HBV) infection are eligible if test for hepatitis B surface antigen and HBV DNA are negative

  2. Patients with hepatitis C virus (HCV) infection are eligible if polymerase chain reaction test for HCV RNA is negative.

Ocular:

- History of 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:

  1. Uncontrolled glaucoma with intra ocular pressure $\geq$ 21 mmHg

  2. Uncontrolled hypercholesterolemia > 300 mg/dL or 7.75 mmol/L

  3. Uncontrolled hypertriglyceridemia > 300 mg/dL or 3.42 mmol/L

  4. Fasting hyperglycemia > 160 mg/dL or 8.9 mmol/L

Autoimmune conditions and immunomodulatory drugs:

- History of autoimmune disease except for the following:

  1. Patients with autoimmune hypothyroidism on a stable dose of thyroid replacement hormone are eligible.

  2. Patients with controlled type 1 diabetes mellitus on a stable dose of insulin regimen are eligible.

- Patients with eczema, psoriasis, lichen simplex chronicus, or vitiligo with dermatologic manifestations only (e.g., patients with psoriatic arthritis) are permitted provided that they meet the following conditions:

  Patients with psoriasis must have a baseline ophthalmologic exam to rule out ocular manifestations

  Rash must cover less than 10% of body surface area

  Disease is well controlled at baseline and only requiring low–potency topical steroids (e.g., hydrocortisone 2.5%, hydrocortisone butyrate 0.1%, flucinolone 0.01%, desonide 0.05%, aclometasone dipropionate 0.05%)

  No acute exacerbations of underlying condition within the last 12 months (not requiring PUVA [psoralen plus ultraviolet A radiation], methotrexate, retinoids, biologic agents, oral calcineurin inhibitors, or high-potency or oral steroids)

- History of idiopathic pulmonary fibrosis, organizing pneumonia, bronchiolitis obliterans, drug-induced pneumonitis, or idiopathic pneumonitis

  Patients with radiation pneumonitis within the radiation field are eligible.

- History of organ transplantation including allogeneic bone marrow transplantation

Other medical conditions or medications:

- Any hemorrhage or bleeding event CTCAE Grade 3 or higher within 28 days of Cycle 1 Day 1

Appendix 1
Protocol Synopsis (cont.)

- History of stroke, reversible ischemic neurological defect, or transient ischemic attack within 6 months prior to Day 1

- Proteinuria > 3.5 g/24 hours

- Serum albumin < 2.5 g/dL

- Foods, supplements or drugs that are potent CYP3A4 enzyme inducer or inhibitors are prohibited at least 7 days prior to Cycle 1 Day 1 and during study treatment. These include St. John's wort or hyperforin (potent CYP3A4 enzyme inducer) and grapefruit juice (potent cytochrome P450 CYP3A4 enzyme inhibitor).

General exclusion criteria:

- Inability to swallow medications

- Malabsorption condition that would alter the absorption of orally administered medications

- Pregnant, lactating, breastfeeding, or intending to become pregnant during the study

- History of severe hypersensitivity reactions to components of:

  1. Cobimetinib formulation

  2. Regorafenib formulation

  3. Atezolizumab formulation

- Administration of a live, attenuated vaccine within 4 weeks before randomization or anticipation of a live attenuated vaccine will be required during the study

- Any anti-cancer therapy, including chemotherapy, or hormonal therapy within 2 weeks prior to initiation of study treatment

- Treatment with systemic immunostimulatory agents (including but not limited to interferons, IL-2) within 4 weeks or 5 half-lives of the drug, whichever is shorter, prior to Cycle 1 Day 1

- Treatment with systemic immunosuppressive medications (including but not limited to prednisone, cyclophosphamide, azathioprine, methotrexate, thalidomide, and anti-tumor necrosis factor agents) within 2 weeks prior to Cycle 1 Day 1

End of Study

The OS final analysis will be conducted when there are approximately 178 deaths for the comparison of Arm A versus Arm C and approximately 127 deaths for the comparison of Arm B versus Arm C. This is expected to occur approximately 21 months after the first patient is randomized.

The end of this study is defined as the date when the last patient, last visit (LPLV) occurs or the date at which the last data point required for statistical analysis (i.e., OS) or safety follow-up is received from the last patient, whichever occurs later.

Length of Study

LPLV is expected to occur 3 years after the first patient is enrolled. The study will end at any time if the Sponsor decides to end the trial.

Investigational Medicinal Products and Non-Investigational Medicinal Products

The investigational medicinal products (IMPs) for this study are cobimetinib and atezolizumab. Regorafenib is an approved treatment for mCRC and is considered a standard of care in this disease setting and administered in this study at the same dose that was used in the pivotal clinical trials and the approved and marketed dose for this indication. In this study, regorafenib is considered a non-investigational medicinal product, unless depending on local classification, regorafenib is deemed an IMP. If considered an IMP, then appropriate information on formulation, packaging, handling, and administration will be provided.

Appendix 1
Protocol Synopsis (cont.)

Test Products (Investigational Drugs)

Patients randomized to cobimetinib will receive 60 mg (three tablets of 20 mg each) orally once daily for Days 1–21 of a 28-day cycle. This 4-week period is considered a treatment cycle.

Atezolizumab dose and schedule will depend on the treatment arm:

- Arm A: cobimetinib plus atezolizumab 840 mg IV every 2 weeks
- Arm B: atezolizumab 1200 mg IV every 3 weeks as monotherapy

Comparator

Patients randomized to Arm C: regorafenib, will receive 160 mg (four tablets of 40 mg each) of regorafenib to be taken orally once daily on Days 1–21 of a 28-day cycle. This 4-week period is considered a treatment cycle.

Other Non-Investigational Medicinal Products

The following therapies are permitted in the study:

- Hormonal therapy with gonadotropin–releasing hormone agonists or antagonists for prostate cancer
- Oral contraceptives
- Hormone-replacement therapy
- Prophylactic or therapeutic anticoagulation therapy (such as low-molecular weight heparin or warfarin at a stable dose level)
- Palliative radiotherapy (e.g., treatment of known bone metastases) provided it does not interfere with assessment of tumor target lesions

  It is not required to withhold atezolizumab during palliative radiotherapy.
- Inactive influenza vaccinations during influenza season ONLY
- Megastrol administered as an appetite stimulant
- Inhaled corticosteroids for chronic obstructive pulmonary disease
- Mineralocorticoids (e.g., fludrocortisone)

Anti-emetics and anti-diarrheal medications should not be administered prophylactically before initial treatment with study drugs. At the discretion of the investigator, prophylactic anti-emetic and anti-diarrheal medication(s) may be used per standard clinical practice before subsequent doses of study drugs. Hematopoietic growth factors should not be administered prophylactically before initial treatment with study drugs. Hematopoietic growth factors may be administered according to local guidelines if indicated during the course of the study.

In general, investigators should manage a patient's care with supportive therapies as clinically indicated, as per local standards. Patients who experience infusion-associated symptoms may be treated symptomatically with acetaminophen, ibuprofen, diphenhydramine, and/or famotidine or another H2 receptor antagonist as per standard practice (for sites outside the United States, equivalent medications may be substituted per local practice). Serious infusion–associated events manifested by dyspnea, 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).

Statistical Methods

Primary Analysis

The primary efficacy endpoint is OS, which is defined as the time (in months) between the date of randomization and the date of death due to any cause. Patients who have not died at the time of analysis will be censored at the date when they were last known to be alive.

Appendix 1
Protocol Synopsis (cont.)

Comparisons with respect to OS between two treatment arms (i.e., Arm A vs. Arm C, Arm B vs. Arm C) will be tested based on a stratified log-rank test. The stratification factors will be extended RAS mutation status of the tumor and time since diagnosis of first metastasis (<18 months and ≥ 18 months).

Each comparison will be tested at a 2-sided significance level of 0.05 within the intent-to-treat (ITT) population:

- Test to reject the null hypothesis of no difference in OS between either experimental arm (i.e., Arm A or Arm B) and the control arm (Arm C) in the ITT population. If the 2–sided p-value corresponding to the stratified log-rank test is less than 0.05, the null hypothesis will be rejected.

The hazard ratio (HR) for OS will be estimated using a stratified Cox model. Two-sided 95% CIs for the HR will be provided. The stratified analyses will incorporate extended RAS mutation status and time since diagnosis of first metastasis as stratification factors. Results from an unstratified log-rank test and the unstratified HR will also be presented. Kaplan-Meier methodology will be used to estimate median OS for each treatment arm, and the Kaplan-Meier curves will be provided. The Brookmeyer-Crowley methodology will be used to construct the 95% CI for the median OS for each treatment arm.

The comparison between the two experimental arms (Arm A vs. Arm B) will be conducted for descriptive purposes.

Determination of Sample Size

The study will randomize approximately 360 patients, including a minimum of 180 patients with extended RAS-mutant mCRC (assuming a prevalence of at least 50%), to cobimetinib plus atezolizumab (Arm A), atezolizumab monotherapy (Arm B), and regorafenib (Arm C) with the randomization ratio of 2:1:1, respectively.

The type 1 error (α) for the analysis of the primary endpoint of OS in the comparison of cobimetinib plus atezolizumab (Arm A) against the control arm of regorafenib (Arm C) is 0.05 (2-sided). If OS in the comparison of Arm A against Arm C is statistically significant, then the OS in the comparison of Arm B against Arm C will be tested at a 2-sided α level of 0.05.

The sample size of this study is determined on the basis of the number of events required to demonstrate efficacy with regard to OS in both comparisons (Arm A vs. Arm C and Arm B vs. Arm C).

The estimate of the number of events required to demonstrate efficacy with regard to OS is based on the following assumptions:

- Two-sided significance level of 0.05
- Arm A versus Arm C: 87% power to detect an HR of 0.61, corresponding to an improvement in median OS from 6.4 months in Arm C to 10.5 months in Arm A
- Arm B versus Arm C: 80% power to detect an HR of 0.61, corresponding to an improvement in median OS from 6.4 months in Arm C to 10.5 months in Arm B
- No interim analysis for OS
- Dropout rate of 10% in 24 months
- Hierarchical testing of Arm A versus Arm C followed by Arm B versus Arm C to control the overall α level of 5%

With these assumptions, approximately 360 patients in total will be randomized into this study, with approximately 270 patients for the comparison of Arm A versus Arm C and approximately 180 patients for the comparison of Arm B versus Arm C. The OS final analysis will be conducted when there are approximately 178 deaths for the comparison of Arm A versus Arm C and approximately 127 deaths for the comparison of Arm B versus Arm C. This is expected to occur approximately 22 months after the first patient is randomized. If 178th event from Arms A

and C occurs after 127th event from Arms B and C, the OS final analysis will be conducted after 178th event from Arms A and C has occurred.

This number of events corresponds to a minimum detectable difference in HR of approximately 0.73 for the Arm A versus Arm C comparison and approximately 0.71 for the Arm B versus Arm C comparison.

Appendix 2
Schedule of Assessments

Arm A: Cobimetinib Plus Atezolizumab Schedule of Assessments (28-Day Cycle)

	Screening[a]	Cycle 1		Cycle 2		Cycle 3 +		Treatment Discontinuation[b]	ATA Visit	Survival FU[c]
Day	-35 to 1	1	15	1	15	1	15	< 30 d after last dose	120 d after last dose	q3m
Informed consent[d]	x									
Demographics	x									
Medical and CRC history	x									
Vital signs[e,f]	x	x	x	x	x	x	x			
ECOG PS	x	x		x		x				
Weight	x	x		x		x				
Height	x									
Complete physical examination	x									
Limited physical examination		x[g]		x		x				
Hematology[h]	x	x		x		x				
Coagulation (INR and aPTT)	x									
PK sample for cobimetinib	See Appendix 2 *of the study protocol*									
PK and ATA sample for atezolizumab	See Appendix 2 *of the study protocol*								x	
Serum samples for auto antibody tests		x								
Optional WGS		x								
Chemistry[i]	x	x		x		x				
CEA		x		x		x		x		
ECHO/MUGA	x			x		*x*[j]				
Tumor *assessments*[k]	x	Scans will be done every 8 weeks								
Serology[l]	x									

Appendix 2
Schedule of Assessments (cont.)

Arm A: Cobimetinib Plus Atezolizumab Schedule of Assessments (cont.)

	Screening[a]	Cycle 1		Cycle 2		Cycle 3 +		Treatment Discontinuation[b]	ATA Visit	Survival FU[c]
Day	-35 to 1	1	15	1	15	1	15	< 30 d after last dose	120 d after last dose	q3m
Thyroid function	x	x		x		x^m				
Ophthalmologic $exam^n$	x			x		x^n		x		
Pregnancy $test^o$	x	x		x		x				
Adverse events	x^p	x	x	x	x	x	x	x^q		x
Tumor $biopsy^r$	x		x					x		
Concomitant medications	x	x		x		x		x		
EORTC QLQ-C30 EQ-5D-$5L^s$		x		x		x		x		x^s
Survival and anti-cancer therapy follow-up										x
Biomarker blood samples		x		x		x		x		
Atezolizumab $administration^t$		x	x	x	x	x	x			
Cobimetinib $administration^u$		x		x		x				

ATA = anti-therapeutic antibody; C3 = Cycle 3; C4 = Cycle 4; CEA = carcinoembryonic antigen; CRC = colorectal cancer; d = day; ECHO = echocardiogram; ECOG PS = Eastern Cooperative Oncology Group Performance Status; EORTC QLQ-C30 = European Organization for Research and Treatment of Cancer Quality of Life-C30 questionnaire; EQ-5D-5L = EuroQoL 5 Dimensions; FU = follow-up; MUGA = multigated acquisition scan; PK = pharmacokinetic; q3m = every 3 months; WGS = whole genome sequencing.

[a] Results of standard of care tests or examinations performed prior to obtaining informed consent and within 35 days prior to Day 1 may be used; such tests do not need to be repeated for screening

[b] Patients who discontinue study drug will return to the clinic for a treatment discontinuation visit.

[c] Required follow-up information will be collected via telephone calls and/or clinic visits every 3 months until death, withdrawal of consent, the patient is lost to follow-up, or study termination by the Sponsor, whichever occurs first.

[d] Informed consent must be documented before and study-specific screening procedure is performed and may be obtained up to 35 days before initiation of study treatment.

Appendix 2
Schedule of Assessments (cont.)

Arm A: Cobimetinib Plus Atezolizumab Schedule of Assessments (cont.)

e Includes respiratory rate, heart rate, temperature, and systolic and diastolic blood pressure while the patient is in a seated position. Record abnormalities observed at baseline on the General Medical History and Baseline Conditions eCRF. At subsequent visits record new or worsened clinically significant abnormalities on the Adverse Event eCRF

f *Vital signs will be measured and recorded at the following timepoints: within 60 minutes prior to infusion and during and after infusion if clinically indicated.*

g If physical examinations are assessed within 7 days of the Cycle 1 Day 1 visit, they do not have to be repeated at Day 1.

h Hematology (CBC, hemoglobin, hematocrit, WBC count with differential [neutrophils, eosinophils, lymphocytes], and platelet count) $\pm$ *3 days*.

i Serum chemistry (glucose, BUN or urea, creatinine, sodium, potassium, magnesium, calcium, phosphorus, total bilirubin, ALT, AST, ALP, CPK, lipase, amylase [albumin and LDH at screening only]) $\pm$ *3 days*.

j All patients will undergo evaluation of left ventricular dysfunction, either by ECHO or MUGA, screening. Evaluation of LVEF by ECHO or MUGA must be performed at the following timepoints <u>only for patients taking cobimetinib</u>:

- Cycle 2, Day 1 $\pm$ 1 week
- *Day 1 of every three treatment cycles thereafter starting at cycle 5 $\pm$ 2 weeks*
- *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.*
- *All patients restarting treatment with a dose reduction of Cotellic because of a decrease in LVEF should have LVEF measurements taken after approximately 2 weeks, 4 weeks, 10 weeks and 16 weeks, and then resume monitoring LVEF every three treatment cycles.*

k Tumor assessments will continue until disease progression per RECIST v1.1, loss of clinical benefit (patients who continue treatment after disease progression according to RECIST v1.1), consent withdrawal, study termination by the Sponsor, or death, whichever occurs first.

Patients who discontinue treatment for reasons other than disease progression (e.g., toxicity) will continue scheduled tumor assessments until disease progression, withdrawal of consent, study termination by Sponsor, or death, whichever occurs first.

l All patients will be tested for HIV prior to the inclusion into the study and HIV-positive patients will be excluded from the clinical study.
- HBV serology will include HBsAg, antibodies against HBsAg, total HBcAg antibody (anti-HBcAb). HBV DNA should be obtained prior to randomization if patient has a negative serology for HBsAg and a positive serology for anti-HBcAb.
- HCV serology will include HCV antibody (anti-HCV). HCV RNA should be obtained prior to randomization if patient tests positive for anti-HCV

m Thyroid function testing (TSH, free T3, free T4) collected at Day 1 *of every* cycle thereafter for patients on atezolizumab only $\pm$ *3 days*.

Appendix 2
Schedule of Assessments (cont.)

Arm A: Cobimetinib Plus Atezolizumab Schedule of Assessments (cont.)

[n] All patients will undergo ophthalmologic examination (see Protocol Section 4.5.9 for exam requirements) at screening. Ophthalmologic examination must be performed at the following timepoints only for patients taking cobimetinib:

- Cycle 2 Day 1 ± 1 week
- Day 1 of Cycles 5, 8, and 11 (every three treatment cycles) ± 2 weeks
- Day 1 of Cycles 15, 19, and 23 (every four treatment cycles) ± 2 weeks
- On Day 1 of Cycles 29, 35, 41, 47, etc. (every six treatment cycles) ± 2 weeks
- Treatment discontinuation visit. *The treatment discontinuation visit evaluation does not need to be performed if an evaluation has been performed within the last 12 weeks and there are no clinically significant findings and/or changes from baseline.*

[o] *All women of childbearing potential will have a* serum pregnancy test *within 14 days before Cycle 1 Day 1. Urine pregnancy tests will be performed at specific subsequent visits. If a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test. Refer to Protocol Section 5.4.3 for details.*

[p] Only serious adverse events caused by protocol-mandated intervention should be reported.

[q] All serious adverse events and Adverse Events of Special Interest, regardless of relationship to study drug, will be reported until 90 days after the last dose of study drug or initiation of new anti-cancer therapy, whichever occurs first. All other adverse events, regardless of relationship to study drug, will be reported until 30 days after the last dose of study drug or initiation of new anti-cancer therapy, whichever occurs first. After this period the investigator should report any serious adverse events or adverse events of special interest that are believed to be related to prior study drug.

[r] Archival or fresh baseline tumor tissue collected during screening; Optional on treatment biopsy at Cycle 1 Day 15 ± 5 days; Mandatory biopsy at progression if clinically feasible.

[s] PRO instruments EORTC QLQ-C30 and EQ-5D-5L will be completed in this order using an electronic device on Day 1 of each cycle during a visit and prior to any assessments. Data will be collected at end of study and at survival follow-up at 3 and 6 months only. In the event a study visit is conducted by telephone, the PRO data for that visit will be collected via telephone interview and recorded by the investigative staff on the ePRO tablet. To maintain validity and minimize patient burden, the PRO instruments administered via telephone interview will consist of a reduced version of the EORTC QLQ items (Items 1–7, 10, 12, 13, 16, 17, 18, *29, and 30* from the C30 and the two additional items from the item bank) and the telephone interview version of the EQ-5D-5L.

[t] The initial dose will be delivered over 60 (± 10) minutes. If the first infusion is well tolerated all subsequent infusions will be delivered over 30 (± 10) minutes until loss of clinical benefit. *Dose can be given ± 7 days from scheduled Day 1 of each cycle.*

[u] Cobimetinib 60 mg/day PO will be given in a 21/7 dosing schedule. *Dose can be given ± 7 days from scheduled Day 1 of each cycle, but the scheduled 7--day break must be ≥ 5 days.*

Appendix 2
Schedule of Assessments (cont.)

Arm B: Atezolizumab Monotherapy Schedule of Assessments (21-Day Cycle)

	Screening [a]	Cycle 1		Cycle 2	Cycle 3 +	Treatment Disc [b]	ATA Visit	Survival FU [c]
Day	-35 to 1	1	15	1	1	< 30 d after last dose	120 d after last dose	q3m
Informed consent [d]	x							
Demographics	x							
Medical and CRC history	x							
Vital signs [e,f]	x	x		x	x			
ECOG PS	x	x		x	x			
Weight	x	x		x	x			
Height	x							
Complete physical examination	x							
Limited physical examination [g]		x		x	x			
Hematology [h]	x	x		x	x			
Coagulation (INR and aPTT)	x							
Serum sample for autoantibody tests		x				x		
Chemistry [i]	x	x		x	x			
CEA		x		x	x	x		
WGS (optional)		x						
PK and ATA sample	See Appendix 2 of the study protocol						x	
ECHO/MUGA	x							
Tumor assessments [j]	x	Scan assessments every 8 weeks						
Serology [k]	x							
Thyroid function [l]	x	x		x	x			
Ophthalmologic exam	x							
Pregnancy test [m]	x	x		x	x			

Appendix 2
Schedule of Assessments (cont.)

Arm B: Atezolizumab Monotherapy Schedule of Assessments (cont.)

	Screening[a]	Cycle1		Cycle 2	Cycle 3 +	Treatment Disc[b]	ATA Visit	Survival FU[c]
Day	-35 to 1	1	15	1	1	< 30 d after last dose	120 d after last dose	q3m
Adverse events	x^n	x	x	x	x	x		x^o
Tumor *biopsy*[p]	x		x			x		
Concomitant medications	x	x	x	x	x	x		
EORTC QLQ-C30 and EQ-5D-*5L*[q]		x		x	x	x		x^q
Survival and anti-cancer therapy follow-up								x^r
Biomarker blood samples		x		x	x	x		
Atezolizumab *administration*[s]		x		x	x			

ATA=anti-therapeutic antibody; C3=Cycle 3; C4=Cycle 4; CEA=carcinoembryonic antigen; CRC=colorectal cancer; d=day; disc=discontinuation; ECHO=echocardiogram; ECOG PS=Eastern Cooperative Oncology Group Performance Status; EORTC QLQ-C30=European Organization for Research and Treatment of Cancer Quality of Life-C30 questionnaire; EQ-5D-5L=EuroQoL 5 Dimensions; FU=follow-up; MUGA=multigated acquisition scan; PK=pharmacokinetic; q3m=every 3 months; WGS=whole genome sequencing.

[a] Results of standard of care tests or examinations performed prior to obtaining informed consent and within 35 days prior to Day 1 may be used; such tests do not need to be repeated for screening

[b] Patients who discontinue study drug will return to the clinic for a treatment discontinuation visit

[c] Required follow-up information will be collected via telephone calls and/or clinic visits every 3 months until death, withdrawal of consent, the patient is lost to follow-up, or study termination by the Sponsor, whichever occurs first. .

[d] Informed consent must be documented before and study-specific screening procedure is performed and may be obtained up to 35 days before initiation of study treatment

[e] Includes respiratory rate, heart rate, temperature, and systolic and diastolic blood pressure while the patient is in a seated position. Record abnormalities observed at baseline on the General Medical History and Baseline Conditions eCRF. At subsequent visits record new or worsened clinically significant abnormalities on the Adverse Event eCRF

[f] *Vital signs will be measured and recorded at the following timepoints: within 60 minutes prior to infusion and during and after infusion if clinically indicated.*

[g] If physical examinations are assessed within 7 days of the Cycle 1 Day 1 visit, they do not have to be repeated at Day 1.

Appendix 2
Schedule of Assessments (cont.)

Arm B: Atezolizumab Monotherapy Schedule of Assessments (cont.)

[h] Hematology (CBC, hemoglobin, hematocrit, WBC count with differential [neutrophils, eosinophils, lymphocytes], and platelet count) *± 3 days.*

[i] Serum chemistry (glucose, BUN or urea, creatinine, sodium, potassium, magnesium, calcium, phosphorus, total bilirubin, ALT, AST, ALP, LDH, CPK, lipase, amylase, [albumin and LDH at screening only]) *± 3 days.*

[j] Tumor assessments will continue until disease progression per RECIST v1.1, loss of clinical benefit (patients who continue treatment after disease progression according to RECIST v1.1), consent withdrawal, study termination by the Sponsor, or death, whichever occurs first.

Patients who discontinue treatment for reasons other than disease progression (e.g., toxicity) will continue scheduled tumor assessments until disease progression, withdrawal of consent, study termination by Sponsor, or death, whichever occurs first.

[k] All patients will be tested for HIV prior to the inclusion into the study and HIV-positive patients will be excluded from the clinical study.

HBV serology will include HBsAg, antibodies against HBsAg, total HBcAg antibody (anti-HBcAb). HBV DNA should be obtained prior to randomization if patient has a negative serology for HBsAg and a positive serology for anti-HBcAb.

HCV serology will include HCV antibody (anti-HCV). HCV RNA should be obtained prior to randomization if patient tests positive for anti-HCV

[l] Thyroid function testing (TSH, free T3, free T4) collected at Day 1 *of* every cycle thereafter for patients on atezolizumab only *± 3 days.*

[m] *All women of childbearing potential will have a serum pregnancy test within 14 days before Cycle 1 Day 1. Urine pregnancy tests will be performed at specific subsequent visits. If a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test. Refer to Protocol Section 5.4.3 for details.*

[n] Only serious adverse events caused by protocol-mandated intervention should be reported

[o] All serious adverse events and Adverse Events of Special Interest, regardless of relationship to study drug, will be reported until 90 days after the last dose of study drug or initiation of new anti-cancer therapy, whichever occurs first. All other adverse events, regardless of relationship to study drug, will be reported until 30 days after the last dose of study drug or initiation of new anti-cancer therapy, whichever occurs first. After this period the investigator should report any serious adverse events or adverse events of special interest that are believed to be related to prior study drug.

[p] Archival or fresh baseline tumor tissue collected during screening; Optional on treatment biopsy at Cycle 1 Day 15 ± 5 days; Mandatory biopsy at progression if clinically feasible.

[q] PRO instruments EORTC QLQ-C30 and EQ-5D-5L will be completed in this order using an electronic device on Day 1 of each cycle during a visit and prior to any assessments. Data will be collected at end of study treatment and at survival follow-up at 3 and 6 months only. In the event a study visit is conducted by telephone, the PRO data for that visit will be collected via telephone interview and recorded by the investigative staff on the ePRO tablet. To maintain validity and minimize patient burden, the PRO instruments administered via telephone interview will consist of a reduced version of the EORTC QLQ (Items 1–7, 10, 12, 13, 16, 17, 18, *29, and 30* from the C30 and the two additional items from the item bank) and the telephone interview version of the EQ-5D-5L.

[r] Patients who discontinue treatment for reasons other than disease progression (e.g., toxicity) will continue scheduled tumor assessments until disease progression, withdrawal of consent, study termination by Sponsor, or death, whichever occurs first.

Appendix 2
Schedule of Assessments (cont.)

Arm B: Atezolizumab Monotherapy Schedule of Assessments (cont.)

ˢ The initial dose will be delivered over 60 (± 10) minutes. If the first infusion is well tolerated all subsequent infusions will be delivered over 30 (± 10) minutes until loss of clinical benefit. *Dose can be given ±7 days from Day 1.*

Appendix 2
Schedule of Assessments (cont.)

Arm C: Regorafenib Schedule of Assessments

	Screening[a]	Cycle 1				Cycle 2			Cycle 3 +	Treatment Discontinuation[b]	Survival FU[c]
Day	-35 to 1	1	8	15	22	1	8	15	1	< 30 d after last dose	q3m
Informed consent[d]	x										
Demographics	x										
Medical and CRC history	x										
Vital signs[e,f]	x	x	x	x	x	x	x	x	x		
ECOG PS	x	x				x			x		
Weight	x	x				x			x		
Height	x										
Complete physical examination	x										
Limited physical examination		x[g]				x			x		
Hematology[h]	x	x				x			x		
Coagulation (INR and aPTT)	x										
Chemistry[j]	x	x		x		x		x	x		
CEA		x				x			x	x	
WGS (Optional)		x									
ECHO/MUGA	x										
Tumor assessments	x	Scan assessments every 8 weeks [j]									
Serology[k]	x										
Thyroid function	x										
Ophthalmologic exam	x										
Pregnancy test[l]	x	x				x			x		
Adverse events	x[m]	x	x	x	x	x	x	x	x	x[n]	x

Appendix 2
Schedule of Assessments (cont.)

Arm C: Regorafenib Schedule of Assessments (cont.)

	Screening[a]	Cycle 1				Cycle 2			Cycle 3 +	Treatment Discontinuation[b]	Survival FU[c]
Day	-35 to 1	1	8	15	22	1	8	15	1	< 30 d after last dose	q3m
Tumor biopsy[o]	x			x						x	
Concomitant medications	x	x				x			x	x	
EORTC QLQ-C30, EQ-5D-5L[p]		x				x			x	x	x
Survival and anti-cancer therapy follow-up											x[q]
Biomarker blood samples		x				x			x	x	
Regorafenib administration[r]		x				x			x		

ATA = anti-therapeutic antibody; C3 = Cycle 3; C4 = Cycle 4; CEA = carcinoembryonic antigen; CRC = colorectal cancer; d = day; ECHO = echocardiogram; ECOG PS = Eastern Cooperative Oncology Group Performance Status; EORTC QLQ-C30 = European Organization for Research and Treatment of Cancer Quality of Life-C30 questionnaire; EQ-5D-5L = EuroQoL 5 Dimensions; FU = follow-up; MUGA = multigated acquisition scan; PK = pharmacokinetic; q3m = every 3 months; WGS = whole genome sequencing.

[a] Results of standard of care tests or examinations performed prior to obtaining informed consent and within 35 days prior to Day 1 may be used; such tests do not need to be repeated for screening.

[b] Patients who discontinue study drug will return to the clinic for a treatment discontinuation visit

[c] Required follow-up information will be collected via telephone calls and/or clinic visits every 3 months until death, withdrawal of consent, the patient is lost to follow-up, or study termination by the Sponsor, whichever occurs first. .

[d] Informed consent must be documented before and study-specific screening procedure is performed and may be obtained up to 35 days before initiation of study treatment

[e] Includes respiratory rate, heart rate, temperature, and systolic and diastolic blood pressure while the patient is in a seated position. Record abnormalities observed at baseline on the General Medical History and Baseline Conditions eCRF. At subsequent visits record new or worsened clinically significant abnormalities on the Adverse Event eCRF

[f] Monitor vital signs weekly for the first 6 weeks and then with every cycle, especially systolic and diastolic blood pressure.

[g] If physical examinations are assessed within 7 days of the Cycle 1 Day 1 visit, they do not have to be repeated at Day 1.

[h] Hematology (CBC, hemoglobin, hematocrit, WBC count with differential [neutrophils, eosinophils, lymphocytes, monocytes, basophils, and other cells], and platelet count)

Appendix 2
Schedule of Assessments (cont.)

Arm C: Regorafenib Schedule of Assessments (cont.)

[i] Serum chemistry (glucose, BUN or urea, creatinine, sodium, potassium, magnesium, calcium, phosphorus, total bilirubin, ALT, AST, ALP, LDH, CPK, lipase, amylase, [albumin and LDH at screening only]). *LFTs are tested every 2 weeks for the first 2 months of treatment and then at every cycle thereafter. All other labs are tested at the beginning of each cycle.*

[j] Tumor assessments will continue until disease progression per RECIST v1.1, loss of clinical benefit (patients who continue treatment after disease progression according to RECIST v1.1), consent withdrawal, study termination by the Sponsor, or death, whichever occurs first.

Patients who discontinue treatment for reasons other than disease progression (e.g., toxicity) will continue scheduled tumor assessments until disease progression, withdrawal of consent, study termination by Sponsor, or death, whichever occurs first.

[k] All patients will be tested for HIV prior to the inclusion into the study and HIV-positive patients will be excluded from the clinical study.

HBV serology will include HBsAg, antibodies against HBsAg, total HBcAg antibody (anti-HBcAb). HBV DNA should be obtained prior to randomization if patient has a negative serology for HBsAg and a positive serology for anti-HBcAb.

HCV serology will include HCV antibody (anti-HCV). HCV RNA should be obtained prior to randomization if patient tests positive for anti-HCV

[l] *All women of childbearing potential will have a serum pregnancy test within 14 days before Cycle 1 Day 1. Urine pregnancy tests will be performed at specific subsequent visits. If a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test. Refer to Protocol Section 5.4.3 for details.*

[m] Only serious adverse events caused by protocol-mandated intervention should be reported

[n] All serious adverse events and Adverse Events of Special Interest, regardless of relationship to study drug, will be reported until 90 days after the last dose of study drug or initiation of new anti-cancer therapy, whichever occurs first. All other adverse events, regardless of relationship to study drug, will be reported until 30 days after the last dose of study drug or initiation of new anti-cancer therapy, whichever occurs first. After this period the investigator should report any serious adverse events or adverse events of special interest that are believed to be related to prior study drug.

[o] Archival or fresh baseline tumor tissue collected during screening; Optional on treatment biopsy at Cycle 1 Day 15±5 days; Mandatory biopsy at progression.

[p] PRO instruments EORTC QLQ-C30 and EQ-5D-5L will be completed in this order using an electronic device on Day 1 of each cycle during a visit and prior to any assessments. Data will be collected at end of study treatment and at survival follow-up at 3 and 6 months only. In the event a study visit is conducted by telephone, the PRO data for that visit will be collected via telephone interview and recorded by the investigative staff on the ePRO tablet. To maintain validity and minimize patient burden, the PRO instruments administered via telephone interview will consist of a subset of the EORTC QLQ items (Items 1-7, 10, 12, 13, 16, 17, 18, *29 and 30* from the C30 and the two additional items from the item bank) and the telephone interview version of the EQ-5D-5L.

[q] Patients who discontinue treatment for reasons other than disease progression (e.g., toxicity) will continue scheduled tumor assessments until disease progression, withdrawal of consent, study termination by Sponsor, or death, whichever occurs first.

[r] Regorafenib 160 mg/day PO will be given in a 21/7 dosing schedule. *Dose can be given ±7 days from Day 1 but the scheduled 7-day break must be ≥5 days.*

Appendix 3
Schedule of Pharmacokinetic and Immunogenicity Samples

Visit	Timepoint	Sample Type	Drug
Cycle 1 Day 15 [a] Cycle 4 Day 15 [a]	Predose and 3 to 6 hours after dose	Plasma PK	Cobimetinib
Day 1 of Cycles 1–4	Predose (prior to infusion)	Serum PK	Atezolizumab
		Serum ATA	Atezolizumab
Day 1 of Cycles 1 and 4	30 minutes (± 10) after infusion	Serum PK	Atezolizumab
Day 1 of Cycle 8 and every 8 cycles after Cycle 8	Predose (prior to infusion)	Serum PK	Atezolizumab
		Serum ATA	Atezolizumab
Treatment discontinuation [b]	At visit	Serum PK	Atezolizumab
		Serum ATA	Atezolizumab
120 days ± 30 days after treatment discontinuation [b]	At visit	Serum PK	Atezolizumab
		Serum ATA	Atezolizumab

ATA = anti-therapeutic antibody; PK = pharmacokinetic.

[a] Arm A (cobimetinib with atezolizumab) only.

[b] These samples will be collected provided that the blood draws are clinically feasible and do not cause the patient undue hardship (e.g., the patient is in hospice care and not able to come in for a visit).

Appendix 4
Internal Monitoring Committee Charter

The Charter for Internal Monitoring Committee

TITLE:	**A Phase III, open-label, multicenter, three-arm, randomized study to investigate the efficacy and safety of cobimetinib plus atezolizumab and atezolizumab monotherapy vs. regorafenib in patients with previously treated unresectable locally advanced or metastatic colorectal adenocarcinoma**
PROTOCOL:	GO30182
AUTHORS:	███████████ M.D. (Study Medical Monitor) ███████████ Ph.D. (Study Statistician)
SPONSOR:	Genentech, Inc./F. Hoffman-La Roche, Ltd 1 DNA Way South San Francisco, CA, 94080-4990, U.S.A.
DATE FINAL:	05 December 2016

Cobimetinib plus Atezolizumab—F. Hoffmann-La Roche Ltd
46/Statistical Analysis Plan GO30182

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1. INTRODUCTION

Study GO30182 is a Phase III, multicenter, open-label, three-arm, randomized study in patients with unresectable locally advanced or metastatic colorectal cancer (CRC) who have received at least two prior regimens of cytotoxic chemotherapy for metastatic disease. The study compares regorafenib, a standard of care therapy in this setting, to cobimetinib plus atezolizumab and atezolizumab monotherapy.

This study will be conducted globally and approximately 360 patients will be randomized in a 2:1:1 ratio to receive:

- Arm A: cobimetinib 60 mg orally on Days 1–21 plus atezolizumab 840 mg intravenous (IV) on Day 1 and Day 15 in a 28-day cycle (n ≈ 180), or

- Arm B: atezolizumab monotherapy 1200 mg IV on Day 1 in a 21-day cycle (n ≈ 90), or

- Arm C: regorafenib 160 mg orally on Days 1–21 in a 28-day cycle (n ≈ 90).

At least 50% patients with extended RAS-mutant tumors will be enrolled in each arm. Enrollment of patients with MSI-high status will be limited to approximately 5% to reflect the natural prevalence in mCRC (Goldstein 2014). Stratification factors are extended RAS mutation status of the tumor and time since diagnosis of first metastasis (< 18 months vs. ≥ 18 months).

The primary objective of the study is to evaluate efficacy as measured by overall survival of cobimetinib plus atezolizumab compared to regorafenib in patients with unresectable locally advanced or metastatic CRC who have received at least two prior regimens of chemotherapy in the metastatic setting. The efficacy as measured by overall survival of atezolizumab monotherapy compared to regorafenib in the same patient population will also be evaluated as a primary objective. Detailed descriptions of the study design, study objectives and study conduct can be found in the protocol.

This charter defines the roles and responsibility of the Internal Monitroing Committee (IMC) including its membership, scope, timing of meetings and communication plan.

2. ROLE OF THE GO30182 INTERNAL MONITORING COMMITTEE

2.1 Safety
The study medical monitor maintains full sponsor responsibility for regularly monitoring the safety of the patients in the study as stated in the protocol. Through review and summary of study safety data by treatment arm, the IMC will provide a

supplemental assessment of patient safety, identifying potential unexpected risk. The comparative review of safety data by the IMC will be based upon the treatments patients actually received as follows:

- Cobimetinib + Atezolizumab arm: patients who received any amount of cobimetinib
- Atezolizumab arm: patients who received any amount of atezolizumab with no amount of cobimetinib
- Regorafenib arm: patients who received any amount of regorafenib with no amount of either atezolizumab or cobimetinib.

If a patient did not receive any amount of atezolizumab, cobimetnib or regorafenib, the patient will not be included in this safety review.

2.2 Efficacy

Efficacy data will not be reviewed as part of the IMC for the study. As stated in the Study protocol, no interim analyses of any efficacy endpoints, including the primary endpoint of OS, is planned.

3. COMMITTEE MEMBERSHIP

The IMC is planned to consist of employees of Genentech/Roche who are not part of the study team, with the following members:

Members   ▮▮▮▮▮▮▮▮ (Chair)
Clinical Scientist, Genentech/Roche

▮▮▮▮▮▮
Drug Safety, Genentech/Roche

▮▮▮▮▮▮▮
Biostatistician, Genetech/Roche

▮▮▮▮▮
Statistical Programming Analyst, Genentech/Roche

Representatives from other functional areas may serve as ad hoc members of the IMC at the discretion of the IMC Chair (or designee). Membership is to last until the protocol-specified primary efficacy analyses for overall survival (OS) is performed or study closure, whichever occurs first. If a member leaves the committee, a replacement member from the same function must be selected.

4. COMMITTEE MEETINGS

4.1 Frequency of Safety Review by IMC

The data will be reviewed at the following frequencies:

- When the first 60 enrolled patients have received at least two cycles of study drug
- Thereafter, approximately every 6 months until the protocol-specified OS analyses are performed or the study is closed, whichever occurs first.

Additional safety reviews could take place as requested by the study Medical Monitor to review ongoing safety data.

4.2. Organizational Flow

Figure 1 illustrates the relationships between the clinical data manager (CDM), the statistical programming analyst (SPA), the IMC, and the chair of Genentech/Roche's internal governance body of the Development Review Committee (DRC).

Figure 1
Organizational Flow
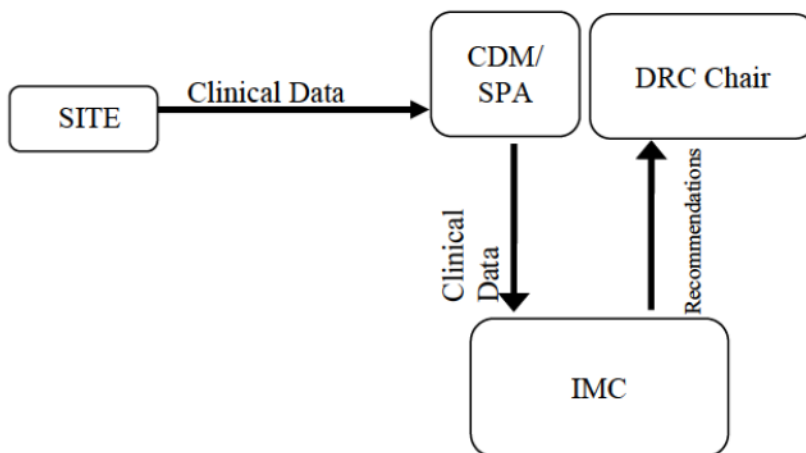
4.3. Reports

The safety reports to be generated for the IMC members and reviewed at the IMC meeting include, but are not limited to:

- Summary of adverse events leading to deaths by system organ class and preferred term
- Summary of grade ≥3 adverse events by system organ class and preferred term
- Summary of serious adverse events by system organ class and preferred term and highest NCI CTCAE Grade
- Listing of adverse events leading to death

5. COMMUNICATION

After each review, the IMC may only make recommendations regarding safety signals, and the recommendations will be documented. The IMC is responsible for documenting any recommendation and action items in the minutes. The IMC biostatistician is responsible for archiving the recommendations, the meeting materials, and minutes in the Trial Master File.

The IMC may share the safety results with other Roche/ Genentech employees as deemed necessary with approval from the DRC chair. If the safety results are shared

internally within Roche/Genentech or externally, the distribution of these results will be documented and any impact on their interpretability will be evaluated.

After each safety review, the IMC may recommend:

- to continue the trial without modification
- to continue the trial with minor recommended modifications
- to stop the trial
- to put enrollment on hold pending further IMC recommendation

The IMC Chair will notify the DRC chair of the IMC recommendation within 24 hours of each review meeting. Upon receipt of the IMC's recommendation, the DRC chair will review the recommendation, seek input from the IMC, and study team as deemed necessary, and ultimately take a decision to accept, reject, or modify the IMC recommendation. The DRC chair will inform the IMC chair and the study medical monitor about the final decision. The study medical monitor communicates the IMC recommendations and decisions to the study team and takes appropriate action with the study team. If IMC recommends to stop the trial and DRC chair agrees with such a recommendation, then the chair of the sponsor's Data Review Board (DRB) will be notified by DRC chair.

Outcomes and conclusions of the IMC that affect study conduct will be communicated by the Regulatory Affairs representative to the U.S. Food Drug Administration and other applicable regulatory agencies in accordance with the appropriate regulatory guidelines.

APPENDIX A. Primary list of outputs for IMC review

- Summary of adverse events leading to death by system organ class and preferred term
- Summary of grade ≥3 adverse events by system organ class and preferred term
- Summary of serious adverse events by system organ class and preferred term and highest NCI CTCAE Grade
- Summary of Adverse Events by System Organ Class, Preferred Term and Highest NCI CTCAE Grade
- Demographics and baseline characteristics
- Listing of Adverse Events

REFERENCES

Goldstein J, Tran B, Ensor J, et al. Multicenter retrospective analysis of metastatic colorectal cancer (CRC) with high-level microsatellite instability (MSI-H) *Annals of Oncology* 2014;25:1032–8.

Internal Monitoring Committee Signatures

TITLE: **A Phase III, open-label, multicenter, three-arm, randomized study to investigate the efficacy and safety of cobimetinib plus atezolizumab and atezolizumab monotherapy vs. regorafenib in patients with previously treated unresectable locally advanced or metastatic colorectal adenocarcinoma**

PROTOCOL: GO30182

I have read this IMC Charter and confirm that the best of my knowledge it accurately describes the conduct of Internal Monitoring Committee.

Approved by:

Functional Area Representatives	Name	Signature	Date
Biostatistics	████████		
Clinical Science	████████		
Drug Safety	██████		
Stat Prog Analyst	██████		

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Functional Area Representatives	Name	Signature	Date
Biostatistics	███████		
Clinical Science	███████	███████	29 · XI · 2016
Drug Safety	████		
Stat Prog Analyst	████		

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Approved by:

Functional Area Representatives	Name	Signature	Date
Biostatistics	███████	███████	12/5/2016
Clinical Science	███████		
Drug Safety	████		
Stat Prog Analyst	█████		

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Approved by:

Functional Area Representatives	Name	Signature	Date
Biostatistics	███████		
Clinical Science	███████	██	
Drug Safety	█████	██████	05 Dec 2016
Stat Prog Analyst	████		

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Functional Area Representatives	Name	Signature	Date
Biostatistics	███████████		
Clinical Science	███████████		
Drug Safety	██████		
Stat Prog Analyst	█████████	████████████	Nov 28, 2016