Official Title: My Pathway: An Open-Label Phase IIA Study Evaluating Trastuzumab/Pertuzumab, Erlotinib, Vemurafenib/Cobimetinib, Vismodegib, Alectinib, and Atezolizumab in Patients Who Have Advanced Solid Tumors With Mutations or Gene Expression Abnormalities Predictive of Response to One of These Agents

NCT Number: NCT02091141

Document Date: SAP Version 3: 17-July-2023

STATISTICAL ANALYSIS PLAN

TITLE:	MY PATHWAY: AN OPEN-LABEL PHASE IIA STUDY EVALUATING TRASTUZUMAB/PERTUZUMAB, ERLOTINIB, VEMURAFENIB/COBIMETINIB, VISMODEGIB, ALECTINIB, AND ATEZOLIZUMAB IN PATIENTS WHO HAVE ADVANCED SOLID TUMORS WITH MUTATIONS OR GENE EXPRESSION ABNORMALITIES PREDICTIVE OF RESPONSE TO ONE OF THESE AGENTS
PROTOCOL NUMBER:	ML28897
STUDY DRUG:	Trastuzumab plus Pertuzumab Erlotinib Vemurafenib (monotherapy) Vismodegib Vemurafenib plus Cobimetinib Alectinib Atezolizumab
IND NUMBER:	118664
SPONSOR:	Genentech, Inc.
PLAN PREPARED BY:	[redacted] Sarah Cannon Development Innovations 1100 Dr. Martin Luther King Jr. Blvd., Suite 800 Nashville, TN 37203
VERSION:	3.0
DATE FINAL:	17 July 2023

TABLE OF CONTENTS

1. Background

Targeted agents have been approved for use in specific cancer types (as defined by primary site). Human epidermal growth factor 2 (HER2)-targeted therapy (trastuzumab plus pertuzumab) has markedly improved the therapy of patients with HER2-positive breast cancer and HER2-overexpressing gastric and gastroesophageal adenocarcinomas. Erlotinib, an epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor, is currently approved for treatment of patients with advanced relapsed non−small cell lung cancer (NSCLC). A BRAF kinase inhibitor, Vemurafenib, has been approved for treatment of unresectable or metastatic melanomas harboring BRAF V600E mutations. Cobimetinib is approved for use in combination with vemurafenib, and the combination regimen will be used in this study to target BRAF-driven tumors. Vismodegib, a small molecule inhibitor of the hedgehog pathway, has been approved for treatment of adult patients with metastatic basal cell carcinoma or with locally advanced basal cell carcinoma that has recurred following surgery. Alectinib is a kinase inhibitor approved for the treatment of patients with anaplastic lymphoma kinase (ALK)-positive, metastatic NSCLC who have progressed on or are intolerant to crizotinib. Atezolizumab is approved in the United States for the treatment of patients with locally advanced or metastatic urothelial carcinoma who have disease progression during or following platinum-containing chemotherapy or have disease progression within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy. Atezolizumab is also approved in the United States for the treatment of patients with metastatic NSCLC who have disease progression during or following platinum-containing chemotherapy.

It is now clear that molecular alterations can be found in cancers from other primary sites. With the recognition of the importance of molecular tumor abnormalities in identifying potentially effective treatment, numerous platforms have been developed to survey the cancer cell genome and detect critical molecular alterations. Molecular profiling demonstrated that gene abnormalities for which a targeted agent exists are being identified more frequently in tumor types for which these agents are currently not approved. These findings present a new opportunity to test the efficacy of currently available targeted agents, based on the presence of the specific target rather than tumor primary site.

This open-label Phase IIa trial (ML28897) will evaluate the efficacy and safety of several targeted agents in tumor types other than their current United States (U.S.) Food and Drug Administration (FDA)-approved indications. The study will focus on the following molecular pathways and abnormalities: HER2, EGFR, BRAF, the hedgehog pathway, ALK, and programmed death-ligand 1 (PD-L1) copy number gain, deficient mismatch repair (dMMR), microsatellite instability-high (MSI-H), elevated tumor mutational burden (TMB) and/or alterations of DNA proofreading/repair genes (e.g., polymerase epsilon [POLE], polymerase delta 1 [POLD1]). The seven drug combinations included in this trial target the molecular abnormalities described above, and are as follows: trastuzumab/pertuzumab, erlotinib, vemurafenib (monotherapy arm discontinued with protocol Version 3), vemurafenib/cobimetinib (protocol Version 3 and above), vismodegib, alectinib and atezolizumab.

The purpose of this Statistical Analysis Plan (SAP) is to provide a detailed description of the statistical and reporting methods to be implemented during the analysis of the data collected in the ML28897 (PRO 02) study, My Pathway: An Open-Label Phase IIa Study Evaluating Trastuzumab/Pertuzumab, Erlotinib, Vemurafenib/Cobimetinib, Vismodegib, Alectinib and Atezolizumab In Patients Who Have Advanced Solid Tumors With Mutations Or Gene Expression Abnormalities Predictive Of Response To One Of These Agents.

This SAP will describe the clinical endpoints that will be employed and the statistical methods that will be used to examine these endpoints

2. Study Design

ML28897 is a multicenter, non-randomized, open-label Phase IIa study conducted in the U.S. Seven different treatment regimens (arms) will be evaluated in groups of patients who have advanced solid tumors that has progressed following administration of standard of care treatment, or for whom no standard therapy exists, or for whom therapies that will convey clinical benefit are not available and/or are not suitable options per the treating

physician's judgment, and in whom a trial of targeted therapy is considered the best available treatment option. The study will include patients with the appropriate molecular alterations, as follows:

- HER2 overexpression or amplification, or HER2 activating mutation – trastuzumab plus pertuzumab
- EGFR-activating mutation – erlotinib
- BRAF-activating mutation – vemurafenib, or vemurafenib plus cobimetinib (see Amendment 2 below)
- Hedgehog pathway potentially clinically relevant mutation (activating mutation of smoothened [SMO] or loss-of-function mutation of protein patched homolog-1 [PTCH 1]) – vismodegib
- ALK genetic alterations (gene rearrangements, putative activating ALK mutations, ALK copy number gain) and selected alterations in ALK expression − alectinib
- PD-L1 copy number gain, dMMR, MSI-H, elevated TMB, and/or alterations of DNA proofreading/repair genes (e.g., POLE, POLD1) − atezolizumab

For each of the study drugs, the dose and dosing schedule used in Study ML28897 is aligned with the currently approved dose and schedule in the product U.S. Package Insert (USPI) and Investigator's Brochures (IBs).

Patients will receive therapy for two cycles (8 weeks for oral drugs, 6 weeks for trastuzumab/pertuzumab and atezolizumab), and will then be evaluated for response. Patients with objective response or stable disease will continue therapy, with repeat evaluations after every two cycles for the first 24 weeks, followed by repeat evaluations every 12 weeks, until tumor progression, occurrence of unacceptable toxicity, or other discontinuation criteria is met. As patients are enrolled and treated, the trial will be closely monitored; if patients with specific cancer subtypes are not benefiting from the targeted therapy, accrual of such patients will not be continued. The main study schema is shown in Appendix A. Treatment-specific study schemas are included in (Appendix B, Appendix C, Appendix D, .Appendix E,. Appendix F, Appendix G and Appendix H).

For patients with mutations in more than one pathway who may be eligible for more than one study drug, the treating physician will determine the first pathway to target. Patients who have disease progression on one study treatment regimen and have another appropriate molecular alteration that is eligible for another targeted-pathway study treatment regimen may re-enroll in the study, provided they meet inclusion criteria for that study treatment regimen. A 21-day washout period is required between the last dose of the first treatment and the first dose of the next treatment.

The original protocol was finalized on 15-Jan-2014, and the following amendments were introduced since the final protocol:

- Amendment 1 (Version 2): 11-Nov-2014
- Amendment 2 (Version 3): 05-May-2016. The major change in Version 3 is to stop the vemurafenib monotherapy treatment arm. The cancer patients with BRAF-activating mutation will be treated with vemurafenib/cobimetinib.
- Amendment 3 (Version 4): 06-Feb-2017. The major change in Version 4 is to add alectinib and atezolizumab treatment arms. In addition, patients with colorectal cancer (CRC) and HER2 amplification or overexpression, an Independent Review Committee (IRC) will review the tumor assessment scans to evaluate the overall response in patients determined by the investigator to have measurable disease and a tumor response of partial response (PR) or complete response (CR).
- Amendment 4 (Version 5): 14-May-2018
- Amendment 5 (Version 6): 29-Aug-2018
- Amendment 6 (Version 7): 26-Jul-2019
- Amendment 7 (Version 8): 07-Nov-2019
- Amendment 8 (Version 9): 27-Apr-2020
- Amendment 9 (Version 10): 22-Feb-2021
- Amendment 10 (Version 11): 19-Jan-2022
- Amendment 11 (Version 12): 17-Dec-2022

2.1 Protocol Synopsis (including Schedule of Assessment)

Refer to the protocol for the protocol synopsis. See Appendix A ~ Appendix H for the schedule of assessments and the work flowcharts.

2.2 Outcome Measures

2.2.1 Primary Efficacy Outcome Measures

The primary endpoint is the Overall Response Rate (ORR) for each disease cohort.

The ORR is defined as the proportion of patients whose best response on or before the first occurrence of disease progression is a complete response (CR) or partial response (PR). In determining the ORR in this trial, only patients with measurable disease will be included. ORR will be determined by RECIST v1.1 for all patients. The specific ORR endpoints are listed below:

- For all tumor-pathway cohorts: ORR, as assessed by the investigator
- For atezolizumab-treated patients with tissue TMB (tTMB) ≥ 16 mutations/Mb (as assessed by FoundationOne or FoundationOne CDx): ORR, as assessed by IRC.

2.2.2 Secondary Efficacy Outcome Measures

The secondary efficacy endpoints for each disease cohort will consist of Disease Control Rate (DCR), Progression-Free Survival (PFS), Duration of Response (DoR), and 1-year Overall Survival (OS).

- DCR is defined as the proportion of patients whose best response is CR, PR or stable disease maintained more than 4 months (SD>4 months). DCR will be summarized in the same fashion as the primary endpoint.
- Progression-Free Survival (PFS, months) is defined as the time from the date of first study treatment (Day 1) to the date of first occurrence of disease progression as assessed by the investigator, or death from any cause (whichever occurs first). Censoring of progression-free survival (PFS) will be performed as detailed in Table 1. The time will be calculated as (date of event or censor - date of first treatment +1)/30.4375.

Table 1: PFS Censoring Methodology

Situation	Date of Event or Censoring	Outcome
No tumor assessments performed	Date of first day of study drug administration	Censored
Documented progression (including clinical progression)	Date of progression	Event
Death within 18 weeks of last non-missing response assessment	Date of death	Event
No documented progression or death, or death more than 18 weeks of last non-missing response assessment	Date of last non-missing response assessment	Censored

- Duration of Response (DoR, months) is defined as the time from the date of first documented response (CR or PR) to date of first occurrence of disease progression as determined by the investigator, or death from any cause, whichever occurs first among patients who have experienced a complete or partial response. Censoring of DoR will be performed as detailed in Table 2. The time will be calculated as (date of event or censor - date of first CR or PR +1)/30.4375.

Table 2: DoR Censoring Methodology

Situation	Date of Event or Censoring	Outcome
Documented progression (including clinical progression)	Date of progression	Event
Death within 18 weeks of last non-missing response assessment	Date of death	Event
No documented progression or death, or death more than 18 weeks of last non-missing response assessment	Date of last non-missing response assessment	Censored
No tumor assessment after PR or CR	Date of PR or CR	Censored

- Overall Survival (OS, months) is defined as the time from the date of the first study treatment (Day 1) to the date of death from any cause. Censoring of OS will be performed as detailed in Table 3. The time will be calculated as (date of event or censor - date of first treatment +1)/30.4375.

Table 3: OS Censoring Methodology

Situation	Date of Event or Censoring	Outcome
Death	Date of death	Event
Treated in multiple study arms	Date of first treatment in the next arm	Censored
No documented death	Date of last known alive (date of last contact by clinic visit or telephone)	Censored

2.2.3 Safety Outcome Measures

The safety outcome measures for this study are as follows:

- Incidence, nature, and severity of adverse events, per the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.03 (NCI CTCAE v4.03) for patients enrolled prior to Version 6 of the protocol. The NCI CTCAE (v5.0) grading scale will be used for assessing adverse event severity for patients enrolled under Version 6 of the protocol and subsequent versions.
- Change from baseline in targeted vital signs
- Change from baseline in targeted clinical laboratory test results

2.3 Determination of Sample Size

The primary goal of this trial is to evaluate the efficacy of these targeted agents across a broad range of tumor types. Except for the atezolizumab arm, treatment of up to approximately 75 patients in a specific tumor type with an individual targeted therapy (tumor-pathway) cohort will allow estimation of the response rate to treatment. For rarer tumor/disease pathway combinations (e.g., HER2+ salivary, biliary, bladder etc.), enrollment may be limited to up to approximately 25 patients. With 25 patients, the margin of error (defined as one-half the width of the confidence interval) does not exceed 19.6% for a 95% confidence interval.
Patients enrolled in the atezolizumab arm under Protocol Version 6 and later are considered IRC-evaluable, as their tumor scans will be submitted to an IRC for central review.

For the atezolizumab arm, up to approximately 70 patients with tTMB ≥ 10 and < 16 mutations/Mb as determined by the FoundationOne or FoundationOne CDx test will be enrolled, with the expectation that up to approximately 50 patients will be IRC-evaluable. Once 50 IRC-evaluable patients with tTMB ≥ 10 and < 16 mutations/Mb have been enrolled, given potential variations in mutations/Mb calling between FoundationOne / FoundationOne CDx and other assays, patients with ≥10 and <16 mutations/Mb from a non-FoundationOne / non□FoundationOne CDx assay will be allowed to continue to enroll, provided there is sufficient tissue available for a retrospective FoundationOne CDx test.

Furthermore, for the atezolizumab arm, up to approximately 200 patients with tTMB ≥ 16 mutations/Mb as determined by the FoundationOne or FoundationOne CDx test (local or by central re-testing) will be enrolled, with the expectation that up to approximately 150 will be IRC-evaluable.

With 180 patients, the margin of error does not exceed 7.5% for a 95% confidence interval.
With 150 patients, the margin of error does not exceed 8.0% for a 95% confidence interval.
With 75 patients, the margin of error does not exceed 11.3% for a 95% confidence interval.
With 50 patients, the margin of error does not exceed 13.9% for a 95% confidence interval.

Additionally, for the atezolizumab arm, enrollment will be restricted for specific subpopulations of patients with tTMB≥ 16 mutations/Mb who would be evaluable by IRC as follows:

- For the subpopulation with NSCLC, metastatic urothelial carcinoma (mUC), or melanoma, enrollment will be capped at up to approximately 30 patients (for all 3 tumor types combined, up to approximately 10 patients each).
- For the subpopulation with co-occuring tTMB ≥ 16 mutations/Mb and MSI-H, enrollment will be capped at up to approximately 20 patients (regardless of tumor type).

The total number of patients enrolled in each (tumor-pathway) cohort will vary depending on the feasibility of enrollment (mutation rates within tumor types) and interim analysis decisions. The specific tumor-pathway cohorts and their sample size are therefore difficult to anticipate in this study setting. It is expected that a total of approximately 765 patients will be enrolled in this study. Based on the results of interim analyses, as well as ongoing enrollment feasibility evaluations, the total target patient accrual to this study may be amended in collaboration with the Steering Committee.

2.4 Analysis timing

Interim Analysis

For all treatment arms except atezolizumab, an interim analysis will be conducted when a cohort of 12 patients with a specific tumor type has been treated with one of the targeted therapies has a baseline and post-baseline scan, or has come off trial for an adverse event.

For the subpopulation with NSCLC, mUC, and melanoma, enrollment will be capped at approximately 10 patients (for all 3 tumor types combined, up to approximately 3 patients each).

These interim analyses will be utilized to identify (tumor-pathway) cohorts in which treatment is ineffective (i.e. futility analysis), either due to lack of efficacy or safety considerations, so that further accrual to such a cohort can be stopped.

Final Analysis

The final analysis will occur after all patients in a specific tumor and study treatment cohort have completed study assessments.

3. Study Conduct

3.1 Randomization Issues

There is no randomization in this study.

3.2 Steering Committee

A Steering Committee will be formed of multidisciplinary members from Genentech, Sarah Cannon Research Institute (SCRI), and external experts to provide clinical and methodological expertise to the oversight of the study. The Steering Committee will operate according to a pre-specified charter.

The Steering Committee will meet approximately two to three times a year to review safety and efficacy data for all patients except those receiving atezolizumab. For the atezolizumab arm, the Steering Committee will review the safety data only. The Steering Committee will also convene to review the interim analysis data. The Steering Committee may convene on an ad hoc basis in the event that a safety signal is identified. Guidelines to assist in decision-making will be developed in collaboration with the study Steering Committee and will be tailored to the specific tumor types and the evolving treatment landscape. These guidelines will be provided in the study Steering Committee charter.

4. Statistical Methods

This is a broad study of patients whose tumors express molecular abnormalities of interest across all potential tumor types and lines of therapy (within the context of the inclusion/exclusion criteria). It is therefore not known which specific patient populations (tumor types and lines of therapy) will be studied with each of the seven therapies and consequently pre-specifying safety and efficacy criteria is not feasible. This study will rely on the Study Steering Committee to develop safety and efficacy criteria for the tumor-pathway cohorts (cohorts will be identified during early accrual and criteria will be developed prior to review of efficacy outcomes). Statistical Analysis Plan will provide the details of criteria and statistical analyses.

No formal hypothesis testing will be performed on the data from this study. All demographic & baseline characteristics, safety, and efficacy data will be summarized and listed. Non-missing values of discrete (binary, ordinal and categorical) variables will be presented as frequencies and percentages. Continuous variables will be presented with the number of non-missing values, arithmetic mean, arithmetic standard deviation, median, minimum values, maximum values, N, and Confidence intervals (CI) will be provided with point estimates where appropriate to provide a benchmark for outcome precision.

Mean change from baseline is the mean of all individual patients' change from baseline values. Each individual change from baseline will be calculated by subtracting the individual patient's baseline value from the value (pre-dosing, if applicable) at the timepoint. The individual patient's change from baseline values will be used to calculate the mean change from baseline using a SAS procedure such as Proc Univariate.

The safety analysis, baseline characteristics and efficacy analysis will be stratified by arm. Section 4.2 through Section 4.5 provide an overview of the data summaries to be performed for this study. Detailed information based on the data collected in the CRF will be provided in TFL shells.

4.1 Analysis Populations

4.1.1 Safety Population

The safety (SAF) population is defined as enrolled patients who receive at least one dose of study medication. Patients will be included in the treatment group to which they were assigned. The safety and baseline characteristics summary will be performed on the safety population.

4.1.2 Efficacy Population

The efficacy (EAF) population includes the treated patients who have baseline tumor measurement and either have a post-baseline tumor measurement or have discontinued treatment for any reason. The efficacy analyses will be performed on the efficacy population. The cohort or arm will not be analyzed if 5 or less patients are enrolled. Ad hoc safety and baseline characteristics summary may be performed on the efficacy population.

4.1.3 Vemurafenib Patients

According to Version 3 of the protocol , the newly enrolled BRAF mutated patients will be treated with vemurafenib/cobimetinib. At the time of this study amendment, 55 BRAF mutated patients had received vemurafenib as a single agent. These patients continued to receive the same vemurafenib monotherapy regimen. The number of these patients by primary site is listed in Table 4. In the tables and figures being presented by arm, all vemurafenib monotherapy patients will be reported in the vemurafenib arm (not vemurafenib/cobimetinib arm).

Table 4. The number of BRAF patients who received Vemurafenib monotherapy

Primary Sites	Number of Patients
APPENDIX	1
BILIARY	3
CERVIX	1
COLON	2
ERDHEIM-CHESTER DISEASE	1
FALLOPIAN TUBE	1
LUNG CANCER, NON-SMALL CELL	24
LUNG CANCER, SMALL CELL	1
OVARY	4
PANCREAS	4
PERITONEAL	1
PROSTATE	3
SALIVARY GLANDS	1
SMALL INTESTINE	1
SOFT TISSUE	1
THYROID	2
UNKNOWN PRIMARY	3
UTERINE BODY	1
Total	**55**

4.2 Analysis of Study Conduct

Disposition of Patients

For each defined analysis population, the number and percentage of enrolled patients, treated patients and patients discontinuing the study will be presented, including the reasons for study discontinuation. The number and percent of patients who died will be presented and will be displayed for all deaths, deaths on treatment and deaths in follow-up.

Protocol Deviations

Major protocol deviations, violations, or study-related extraordinary events will be summarized by site and subject in a detailed listing. The comprehensive list of protocol deviations will be categorized and provided by the Medical Monitor. Categories for deviations and extraordinary events include:

- Violation of inclusion criteria violation
- Violation of exclusion criteria violation
- Use of a prohibited concomitant medication

Subjects or specific subject observations (data points) excluded from analyses due to the above will be summarized in detailed listings as well. All protocol deviations (including major and minor) will be listed.

4.3 Analysis of Baseline Characteristics

Demography and Baseline Characteristics

Demographic characteristics including age, sex, race and ethnicity; as well as baseline characteristics including ECOG performance status will be listed and summarized.

Disease Diagnosis and Staging

Disease history information, such as primary tumor type, histology and stage will be listed and summarized.

Prior Therapies and Surgeries

Prior systemic therapy, prior radiation and prior surgery information will be listed and summarized.

Prior and Concomitant Medications

Prior and concomitant medication information is collected for atezolizumab patients enrolled under Version 6 of the protocol and later. This information will be listed and summarized.

Medical History

Medical history will be listed and summarized.

4.4 Efficacy Analyses

It is expected that approximately 20–75 patients will enroll in a disease and treatment cohort (i.e., specific tumor type treated with one of the study treatments) except for the atezolizumab arm. The final analysis will occur after all patients in a specific tumor and study treatment cohort have completed study assessments. The ORR and DCR will be estimated and the 70% and 95% confidence intervals will be constructed using exact binomial distribution.

Response rates (ORR and DCR) by study treatments will also be estimated across the various tumor types and molecular abnormality (where appropriate) along with 95% confidence intervals.

Median PFS and median DoR and their associated 95% confidence interval, as well as 1-year OS, will be estimated using the Kaplan-Meier method.

4.4.1 Primary Efficacy Endpoint(s)

ORR will be calculated as defined in Section 2.2.1. If a patient has started treatment but does not have any post-baseline tumor assessment (e.g., early withdrawal from the study not due to clinical progression), the patient will be considered as a non-responder (not evaluable, NE) in the ORR analysis. ORR will be presented as a number and percentage with 70% and 95% confidence bounds employing the exact binomial method. The number of percentage of patients with best response (CR, PR, SD >4 months, SD =<4 months, PD [including clinical PD], and NE) in each arm/cohort will be tabulated.

Additionally, a waterfall plot will be drawn to demonstrate the best percentage change in sum of target lesion size from baseline.

4.4.2 Secondary Efficacy Endpoints

Progression-Free Survival (PFS)
PFS will be estimated using the Kaplan-Meier method employing censoring as defined in Section 2.2.2. 2-sided 70% and 95% confidence intervals for the median PFS, time to 25% events, time to 75% events, as well as 6-month and 1-year PFS rates will be produced. The number of patients with events and the number of patients censored will be summarized by number and percent.

Disease Control Rate (DCR)
DCR will be calculated as defined in Section 2.2.2. If a patient has started treatment but does not have any post-baseline tumor assessment (e.g., early withdrawal from the study not due to clinical progression), the patient will be considered as a non-responder (not evaluable, NE) in the DCR analysis. DCR will be presented as a number and percentage with 70% and 95% confidence bounds employing the exact binomial method.

1-year Overall Survival (OS)
1-year Overall Survival will be estimated using the Kaplan-Meier method employing censoring as defined in Section 2.2.2. 2-sided 70% and 95% confidence intervals for the median OS, time to 25% events, time to 75% events, as well as 6-month and 1-year OS rates will be produced. The number of patients with events and the number of patients censored will be summarized by number and percent.

Duration of Response (DoR)
DoR will be estimated using the Kaplan-Meier method employing censoring as defined in Section 2.2.2. 2-sided 70% and 95% confidence intervals for the median DoR, time to 25% events, time to 75% events, as well as 6-month and 1-year DoR rates will be produced. The number of patients with events and the number of patients censored will be summarized by number and percent. DoR analyses will be performed using the subset of patients in the analysis population who exhibited response (CR+PR).

4.4.3 Subgroup Analyses

The primary efficacy endpoint will be analyzed by selected baseline characteristics and primary tumor types using a forest plot of ORR including 95% confidence intervals (CIs) for the treatment arms with sufficient sample sizes in order to warrant meaningful subgroup analysis.

4.5 Safety Analyses

4.5.1 Exposure of Study Medication

Exposure to Study Drug

Number of cycles started will be summarized by thresholds of >=1, >=2, etc. using number and percentage. Cumulative dose (mg), relative dose intensity and treatment duration will be summarized. Parameters will be calculated as follows:

- Cumulative dose (mg) is defined as the sum of actual dose received (mg) from cycle 1 up to and including cycle N
- Relative dose intensity (%) is defined as the cumulative dose divided by the intended dose multiplied by 100
- Treatment duration is defined as the time, in weeks, from first study drug exposure to last study drug exposure: (final exposure date – first exposure date + 1) / 7

Trastuzumab dosing is based on body weight, which is not collected in the study. As a result, relative dose intensity for trastuzumab will not be calculated.

Dose Modifications

The number and percent of patients with at least one dose modification (e.g., dose reduction, dose delay, treatment discontinuation) will be summarized. Each modification will be summarized in a separate adverse event table.

4.5.2 Adverse Events

Adverse events will be coded using MedDRA version 25.1 or higher to group AEs by System Organ Class (SOC) and Preferred Term (PT).

Adverse events will be graded by the Investigator using the NCI CTCAE version 4.03 (patients enrolled prior to Version 6 of the protocol) or NCI CTCAE v5.0 (patients enrolled under Version 6 and later versions). In the event that multiple AEs with different relationship assignments exist for a study subject at the same CTCAE grade, the relationship with the stronger association to study drug will be used for reporting purposes.

AEs occurring from the first treatment until 30 days (45 days for vismodegib), or 90 days for atezolizumab patients enrolled under Version 6 and later versions, after the last dose of study treatment will be tabulated. A treatment-emergent adverse event is defined as any adverse event (AE) that starts or worsens after the start of the first dose of study treatment. The onset date of an adverse event will be compared to the date of first dose of any study medication to determine if the adverse event is treatment-emergent or not. Adverse events with an onset date on or after the date of first dose of any study medication will be classified as treatment emergent. If a partial date is adequate to determine when the onset date of an event occurred relative to first dose of any study medication, then the partial date will be used. If a partial date does not provide enough information to determine the onset date relative to first dosing date, then the adverse event will be assumed as treatment-emergent. Adverse events will be assumed to be treatment-emergent, unless there is clear evidence (through comparison of partial dates) to suggest that the adverse event started prior to first dose of any study medication.

Summaries (number and percent of patients) will be provided as follows:

- All AEs by MedDRA SOC, PT
- All SAEs by MedDRA SOC, PT
- All AESIs by MedDRA SOC, PT
- All AEs by MedDRA SOC ,PT and maximum CTCAE Grade

- All Treatment-Related AEs by MedDRA SOC, PT and maximum CTCAE Grade
- All SAEs by MedDRA SOC, PT and maximum CTCAE Grade
- All Treatment-Related SAEs by MedDRA SOC, PT and maximum CTCAE Grade
- Related AEs with at least 5% incidence rate by MedDRA SOC, PT and maximum CTCAE Grade
- Related AEs with Maximum CTCAE Grade 3 or Higher by System Organ Class, Preferred Term and Maximum CTCAE Grade
- All AEs Leading to Dose Reduction by MedDRA SOC, PT and maximum CTCAE Grade
- All AEs Leading to Dose Interruption by MedDRA SOC, PT and maximum CTCAE Grade
- All AEs Leading to Treatment Discontinuation by MedDRA SOC, PT and maximum CTCAE Grade
- All AEs Leading to Death by MedDRA SOC, PT and maximum CTCAE Grade

Tables structured as listings will be provided for the following:

- Listing of all Adverse Events
- Listing of all Serious Adverse Events
- Listing of all Fatal Adverse Events
- Listing of all Adverse Events Leading to Dose Modification
- Listing of all Adverse Events Leading to Treatment Discontinuation
- Listing of Adverse Events of Special Interest
- Listing of Deaths on Study (all-causes)

4.5.3 Vital Signs Data

Vital signs assessments for this study include: weight, pulse rate, respiratory rate, systolic blood pressure, diastolic blood pressure, and temperature. Values will be analyzed after conversion into standard international (SI) units, where applicable.

Continuous vital sign results will be summarized by parameter and by visit including unscheduled visit. Summary statistics for the change from baseline at end-of-treatment (EOT), where end-of-treatment will be summarized using the last non-missing post-baseline result no more than 90 days after treatment discontinuation or initiation of subsequent therapy (whichever is first, if applicable), will be tabulated. The largest change from baseline (increase and decrease) will be summarized as a continuous variable. Results pertaining to unscheduled assessments will be included in summaries of results by toxicity grade as well as summaries pertaining to actual vital sign values.

4.5.4 Laboratory Data

Clinical laboratory assessments for this study include: hematology, blood chemistry and liver function tests (LFT). Most hematology, blood chemistry and LFT parameters will be graded according to NCI CTCAE version 4.03, as applicable. Laboratory findings with a grade 3 or higher will be evaluated in further detail for potential clinical significance. Values will be analyzed after conversion into standard international (SI) units, where applicable. A complete listing of all laboratory parameters with normal ranges is included in Appendix I. Treatment-emergent laboratory abnormalities—irrespective of baseline results—will be reported using CTCAE v4.03, as applicable.

Continuous clinical laboratory results will be summarized by test and by visit including unscheduled visit. Summary statistics for the change from baseline at end-of-treatment (EOT), where end-of-treatment will be summarized using the last non-missing post-baseline result no more than 30 days after treatment discontinuation (45 days for vismodegib, 90 days for atezolizumab) or initiation of subsequent therapy (whichever is first, if applicable), will be tabulated. The largest change from baseline (increase and decrease) will be summarized as a continuous variable. Results pertaining to unscheduled assessments will be included in summaries of results by toxicity grade as well as summaries pertaining to actual laboratory values.

Laboratory-based summaries will be provided as follows:

- Change from baseline at each visit and EOT in parameters for Hematology Laboratory results
- Change from baseline at each visit and EOT in parameters for Chemistry Laboratory results
- Shift from Baseline to Maximum Post-Baseline CTCAE Grade for Hematology Laboratory results
- Shift from Baseline to Maximum Post-Baseline CTCAE Grade for Chemistry Laboratory results
- Elevations in AST, ALT, Total Bilirubin, and Alkaline Phosphatase as outlined in the FDA Guidance for Industry pertaining to premarketing clinical evaluations for drug-induced liver injury (DILI):
    - Shifts based on 3x-, 5x-, 10x-, and 20xULN elevations of AST, ALT, and either ALT or AST.
    - Elevations of bilirubin defined as total bilirubin >2xULN
    - Elevations of alkaline phosphatase >1.5xULN
    - Elevations of ALT or AST (>3xULN) accompanied by elevated total bilirubin (>1.5xULN, >2xULN)

Tables structured as listings will be provided for the following:

- Listing of Potential Hy's Law Cases: Patients with elevations of AST or ALT >3xULN in combination with total bilirubin >2xULN will be presented. Results from unscheduled or repeated assessments will be included in the DILI evaluations.
- Listing of Hematology Laboratory Results with CTCAE Grade 3 or Higher
- Listing of Chemistry Laboratory Results with CTCAE Grade 3 or Higher

4.5.5 ECG measurements

The assessment will be performed in erlotinib, vemurafenib, vemurafenib/cobimetinib, alectinib and atezolizumab arms. QTcF values will be calculated with the following formula:

QTcF= QT/([RR interval]^0.33)
where RR interval = 60 / Heart Rate (in seconds)

QTcF values during study and the changes from pre-dose on study will be derived per FDA Guidance for Industry and the categories will be mutually exclusive:

Change from pre-dose decrease:

- QTcF > 30 msec
- QTcF > 60 msec

Change from pre-dose increase:

- QTcF > 30 msec
- QTcF > 60 msec

And any time on treatment value:

- QTcF > 450 msec
- QTcF > 480 msec
- QTcF > 500 msec

4.5.6 Ejection Fraction Assessments

The assessment will be performed in trastuzumab/pertuzumab and vemurafenib/cobimetinib arms. The qualitative results of LVEF Assessments will correspond to the numeric equivalents as follows: Hyperdynamic = LVEF greater than 70%; Normal = LVEF 50% to 70% (midpoint 60%); Mild dysfunction = LVEF 40% to 49% (midpoint 45%); Moderate dysfunction = LVEF 30% to 39% (midpoint 35%); and Severe dysfunction = LVEF less than 30%.

- Shift from baseline to post-baseline categories by visit.

4.5.7 Safety Endpoints of Special Interest

The number and percentage of patient experiencing adverse events of special interest will be tabulated upon the ad hoc request and presented as specified in Section 4.5.2. Special Interest adverse events include:

Adverse Events of Special Interest – All Study Drugs

- Cases of potential drug-induced liver injury (DILI) that include an elevated ALT or AST in combination with either an elevated bilirubin or clinical jaundice, as defined by Hy's law (see protocol Section 5.3.5.6) and based on the following observations:
  - Treatment-emergent ALT or AST >3 × baseline value in combination with total bilirubin >2 × ULN (of which ≥35% is direct bilirubin)
  - Treatment-emergent ALT or AST >3 × baseline value in combination with clinical jaundice

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

Adverse Events of Special Interest – Specific to Each Study Drug

- Trastuzumab/Pertuzumab
  - Asymptomatic decline in left ventricular ejection fraction (LVEF) requiring treatment or leading to discontinuation of trastuzumab and pertuzumab
  - Congestive heart failure (symptomatic LVSD dysfunction)

- Erlotinib
  - Interstitial lung disease

- Vemurafinib (monotherapy)
  - Non-cutaneous squamous cell carcinoma
  - Skin cancers
  - Any second primary cancers
  - Gastrointestinal polyps
  - Grade ≥ 3 elevations of AST, ALT, serum bilirubin, gamma-glutamyl transferase (GGT), or cases of elevated ALT or AST in combination with either an elevated bilirubin or clinical jaundice

- Vismodegib
  - Grade ≥3 elevations of AST, ALT, serum bilirubin, GGT, or cases of elevated ALT or AST in combination with either an elevated bilirubin or clinical jaundice
  - Pregnancy

- Vemurafenib/Cobimetinib
  - Serious retinopathy including events of retinal detachment, retinal pigment epithelium detachment, neurosensory retinal detachment or central serous chorioretinopathy
  - Any grade retinal vein occlusion (RVO)

- Symptomatic Heart Failure and/or Grade ≥2 left ventricular ejection fraction reduction
- Rhabdomyolysis
  - Includes Grade ≥3 elevations of creatine phosphokinase (CPK) in conjunction with other laboratory evidence (aldolase and urine myoglobin) and clinical presentation consistent with rhabdomyolysis (such as muscle pain, signs of renal failure, dark red or brown urine)
- Grade ≥3 hemorrhage event or any grade cerebral hemorrhage
- Grade ≥3 rash
- Events suggestive of DILI or other Grade ≥ 3 hepatotoxicity
  - Grade ≥3 elevations of AST, ALT, serum bilirubin, gamma-glutamyl transferase (GGT), or cases of elevated ALT or AST in combination with either an elevated bilirubin or clinical jaundice
- AEs potentially associated with prolongation of cardiac repolarization (Grade ≥3 QT interval prolongation)
- Non-cutaneous squamous cell carcinoma
- Skin cancers
- Any new or worsening malignancies, including progression of RAS mutant malignancy, cutaneous squamous cell carcinoma (cuSCC), new primary melanoma, or basal cell carcinoma
- Grade ≥ 3 photosensitivity (when administered with vemurafenib)
- Gastrointestinal polyps
- Pneumonitis
- Grade ≥3 diarrhea

- Atezolizumab
  - Pneumonitis
  - Colitis
  - Endocrinopathies: diabetes mellitus, pancreatitis, adrenal insufficiency, hyperthyroidism, and hypophysitis
  - Hepatitis, including AST or ALT > 10 × ULN
  - Systemic lupus erythematosus
  - Neurological disorders, such as Guillain-Barré syndrome, myasthenic syndrome or myasthenia gravis, and meningoencephalitis
  - Events suggestive of hypersensitivity, infusion-related reactions, influenza like illness, cytokine-release syndrome, HLH, and MAS
  - Nephritis
  - Ocular toxicities (e.g., uveitis, retinitis, optic neuritis)
  - Myositis
  - Myopathies, including rhabdomyolysis
  - Grade ≥ 2 cardiac disorders (e.g., atrial fibrillation, myocarditis, pericarditis)
  - Vasculitis
  - Autoimmune hemolytic anemia
  - Severe cutaneous reactions (e.g., Stevens-Johnson syndrome, dermatitis bullous, toxic epidermal necrolysis)

4.6 Handling of Dropouts, Missing/Incomplete DATA, or Outliers

4.6.1 Handling of study dates

All start and end dates, where applicable, for study drug exposure, safety, efficacy evaluation and study milestones must be complete dates (i.e., day, month and year must be present).

Dates associated with prior medications, prior therapies, and other historical data, whether complete or not, that typically are not involved in direct calculations affecting safety or efficacy will be listed in the manner of their recording on the eCRF. If any calculations are required for partial dates, then the following imputations will be used:

- If day is missing, date will be imputed as 01-MMM-YYYY
- If day/month are missing, date will be imputed as 01-JUL-YYYY

4.6.2 Handling Lost to Follow-Up and Consent Withdrawal

All data collected up through the date(s) of lost to follow-up and/or withdrawal of consent, whichever occurred first where applicable, will be available for presentation and analysis.

1-year OS: If the 1-year survival status of the patient, defined as 365 days after the date of first treatment, cannot be ascertained, the date will be censored at the date of last contact (clinic visit or telephone) with the patient.

Valid tTMB results from FoundationOne or FoundationOne CDx: If a patient with IRC evaluable-disease does not have a valid tTMB result determined by FoundationOne or FoundationOne CDx, the patient will be excluded from efficacy analyses being performed in the FoundationOne or FoundationOne CDx tTMB selected patient population.

4.6.3 Handling of Missing Tumor Assessment

ORR and DCR: If a patient has started treatment but does not have any post-baseline tumor assessment (e.g., early withdrawal from the study is not due to clinical progression), the patient will be considered as a non-responder in the ORR and DCR analyses (not available, NA). The visit missing one or more target lesion/non-target lesion measurement, the visit RECIST response of target lesion/non-target lesion will be considered as not evaluable (NE).

PFS: see Table 1 for the details.

4.7 Interim Analyses

Interim Analyses

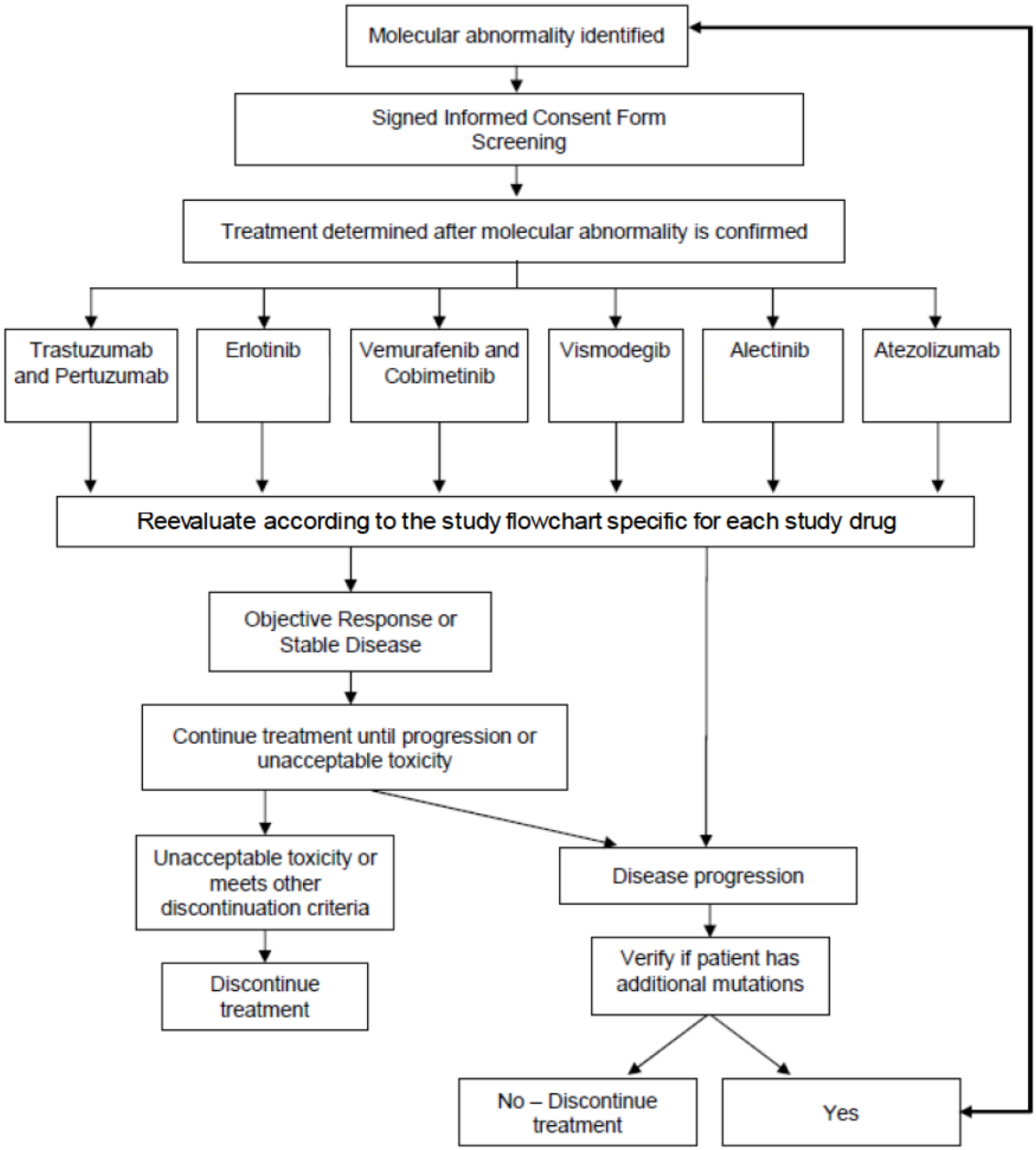
An initial efficacy analysis will be conducted when a cohort of 12 patients with a specific tumor type has been treated with one of the targeted therapies has a baseline and post-baseline scan, or has come off trial for an adverse event. This interim analysis will be utilized to identify (tumor-pathway) cohorts in which treatment is ineffective (i.e., futility analysis), either due to lack of efficacy or safety considerations, so that further accrual to such a cohort can be stopped.

For this interim analysis, ORR and DCR will be the efficacy endpoints considered. Any PFS data available will also be considered, although short follow-up may limit interpretation. Guidelines to assist in decision-making will be developed in collaboration with the study Steering Committee and will be tailored to the specific tumor types and the evolving treatment landscape.

TFLs for interim analysis may be prepared upon the request from SCRI-Genentech core team meeting.

5. Appendices

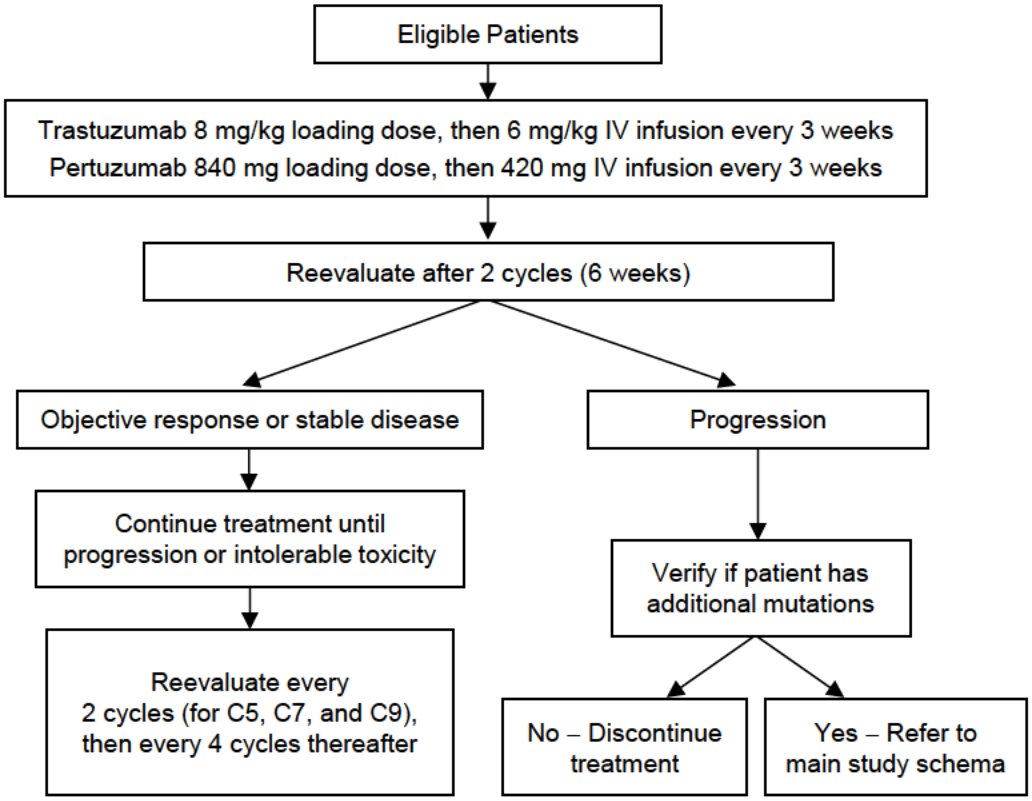
5.1 Appendix A - Main Study Schema (see related appendix in protocol)



The schedule of assessments for each treatment are provided in Appendix B – Appendix H.

5.2 Appendix B - Assessment and Flowchart: Trastuzumab plus Pertuzumab for Patients with Cancers Characterized by HER2 Overexpression, Amplification, or HER2-Activating Mutation

Study Schema: Trastuzumab plus Pertuzumab



C = cycle.

Screening and Pretreatment Assessments

- Written informed consent form prior to any other trial-related procedures
- Review of molecular profiling report and confirmation of HER2 overexpression, or amplfication (should occur prior to obtaining other study-specific assessments). For patients screened using a blood assay: obtain tissue-based testing result confirming study eligibility (within first 4 weeks after enrollment).
- Medical history
- ECOG PS
- Measurement of LVEF (MUGA or ECHO)
- CBC, including 3-part differential and platelets
- CMP
- Serum pregnancy test (must be performed within 7 days of Cycle 1, Day 1)
- Confirm availability of an archival or new pretreatment tissue sample (refer to protocol Section A6-4.5.1.2 for tissue requirements)
- Tumor markers (only if clinically indicated)
- CT scans of the chest, abdomen, and pelvis

- Positron emission tomography (PET) scans or bone scan (only if clinically indicated)
- CT or MRI of brain (all patients with history of treated brain metastases; otherwise, only if clinically indicated)

Patients who have disease progression on one study treatment regimen and are eligible for another study treatment regimen must be re-consented and re-screened for the new study treatment and must be registered as a new patient via the interactive web response system (IWRS) prior to initiation of the new study treatment. In these cases, results of assessments done at treatment completion may be used as screening assessments for the subsequent study treatment. These tests do not have to be repeated if the timeframe is as required for screening.

Assessments during Treatment
Patients will visit the study center once every 3 weeks on the day of each scheduled treatment (± 72 hours). Protocol treatments will continue until tumor progression or intolerable toxicity occurs. The following assessments will be performed:

a. Day 1 of Every Cycle

- Adverse event (AE) evaluation
  - Only significant AEs, defined as serious AEs (SAEs), AEs leading to treatment modification (e.g., dose reduction, dose delay, treatment discontinuation), or protocol-defined AEs of special interest (see protocol Section 5.2.3) will be captured in the electronic Case Report Form (eCRF).

b. Day 1 of Cycles 1 and 3

- Plasma biomarker collection

c. Day 1 of Cycles 1, 2, 3, and 7; and Every Three Cycles Thereafter

- CBC, including 3-part differential and platelets
- CMP

d. Day 1 of Cycles 3 and 5

- Tumor markers (only if clinically indicated)
- Response assessment – CT scans of chest, abdomen, and/or pelvis (repeat only scans that were abnormal at baseline)

e. Day 1 of Cycle 4 and Every Three Cycles Thereafter

- Urine or serum pregnancy test – any positive urine pregnancy test must be confirmed by a serum pregnancy test. During the treatment period, pregnancy test results must be available prior to administration of study drug. Patients who have a positive pregnancy test may not receive study drug.

f. Day 1 of Cycle 5

- Measurement of LVEF (use the same test that was used for baseline measurement). MUGA or ECHO will be repeated every 12 weeks, or as clinically indicated, during treatment.

g. Day 1 of Cycle 7

- Tumor markers (only if clinically indicated)
- Response assessment – CT scans of chest, abdomen, and/or pelvis (repeat only scans that were abnormal at baseline)
- PET scan or bone scan (only if abnormal at baseline and necessary to document response to treatment)
- CT scan or MRI of brain (only if abnormal at baseline)

h. Day 1 of Cycle 9 and Every Four Cycles Thereafter

- Measurement of LVEF (use the same test that was used for baseline measurement). MUGA or ECHO will be repeated every 12 weeks, or as clinically indicated, during treatment.

i. As Clinically Indicated

- Tumor markers (only if clinically indicated)
- Response assessment – CT scans of chest, abdomen, and/or pelvis (repeat only scans that were abnormal at baseline)
- PET scan or bone scan (only if abnormal at baseline and necessary to document response to treatment)
- CT scan or MRI of brain (only if abnormal at baseline)

End of Treatment

At the end of treatment, a safety follow-up visit will occur within 30 days from discontinuation of trastuzumab and pertuzumab. The following assessments will be conducted at the follow-up visit:

- AE evaluation
  - Only significant AEs, defined as SAEs, AEs leading to treatment discontinuation, or protocol-defined AEs of special interest (see protocol Section 5.2.3) will be captured in the eCRF.
- CBC, including 3-part differential and platelets
- CMP
  - Urine or serum pregnancy test - Any positive urine pregnancy test must be confirmed by a serum pregnancy test. A urine or serum pregnancy test must be performed at the treatment discontinuation visit and then every 3 months thereafter until 7 months post-discontinuation of study treatment.
- CT scans of the chest, abdomen, and/or pelvis (only scans that were abnormal at baseline and necessary to document response to treatment)
  - For patients who come off study treatment without progressive disease (PD), tumor assessments are required at the end-of-treatment visit, only if not obtained within the past 6 cycles.
- At disease progression, an optional FFPE tissue sample may be submitted for exploratory research, if available.

If the patient's worsening disease combined with travel distance makes the safety follow-up visit too difficult, follow-up with the patient may take place by telephone to include an assessment of AEs. Alternatively, the patient's local physician may be contacted to collect AE data and any standard of care laboratory and CT data, if performed.

PATIENT DISCONTINUATION

Please refer to Section 4.6 in the main body of the protocol for patient discontinuation descriptions.

Trastuzumab and Pertuzumab Study Flowchart

Assessments	Pre-Treatment	Trial Treatment							
		All Cycles	Reassessments						
	Screening [a]	Day 1 (± 3 Days)	Cycles 3 and 5, Day 1 (± 3 Days)	Cycle 4, Day 1 (and Every 3 Cycles After) (± 3 Days)	Cycle 7, Day 1 (± 3 Days)	Cycle 9, Day 1 (and Every 4 Cycles After) (± 3 Days)	Cycle 13, Day 1 (and Every 6 Cycles After) (± 3 Days)	As Clinically Indicated [b]	End of Treatment Safety Follow-Up [c]
Tests and Observations									
Informed consent [d]	x								
Obtain/review molecular profiling report/ pathology report [e]	x								
Medical history	x								
ECOG PS	x								
LVEF (ECHO or MUGA)	x		x [f] [Cycle 5, Day 1 only]			x [f]			
Adverse event evaluation [g]		x							x
Laboratory Evaluations									
CBC, 3-part differential, and platelets	x	x [Day 1 of Cycles 1, 2, 3 & 7; and every 3 cycles afterw ard]							x

Genentech
A Member of the Roche Group

Data Analysis Plan Module 1 Template

	Pre-Treatment	Trial Treatment							
		All Cycles	Reassessments						
Assessments	Screening [a]	Day 1 (± 3 Days)	Cycles 3 and 5, Day 1 (± 3 Days)	Cycle 4, Day 1 (and Every 3 Cycles After) (± 3 Days)	Cycle 7, Day 1 (± 3 Days)	Cycle 9, Day 1 (and Every 4 Cycles After) (± 3 Days)	Cycle 13, Day 1 (and Every 6 Cycles After) (± 3 Days)	As Clinically Indicated [b]	End of Treatment Safety Follow-Up [c]
Plasma biomarkers		x [Day 1, Cycle 1 and 3 only]							x
CMP [h]	x	x [Day 1 of Cycles 1, 2, 3 & 7; and every 3 cycles afterward]							x
Pregnancy test [i]	x			x					x [j]

Genentech
A Member of the Roche Group

Data Analysis Plan Module 1 Template

Assessments	Pre-Treatment	Trial Treatment							
		All Cycles	Reassessments						
	Screening [a]	Day 1 (± 3 Days)	Cycles 3 and 5, Day 1 (± 3 Days)	Cycle 4, Day 1 (and Every 3 Cycles After) (± 3 Days)	Cycle 7, Day 1 (± 3 Days)	Cycle 9, Day 1 (and Every 4 Cycles After) (± 3 Days)	Cycle 13, Day 1 (and Every 6 Cycles After) (± 3 Days)	As Clinically Indicated [b]	End of Treatment Safety Follow-Up [c]
Optional molecular profiling results [k]	x								
Archival tumor sample [l]	x [l]								x [l]
Staging									
Tumor markers [m]	x		x		x			x	
CT scan of chest, abdomen, pelvis [n]	x		x [o]		x [o]			x [o]	x [o]
PET scan or bone scan [n]	x [m]				x [p]			x [p]	
Head CT or MRI scan [n]	x [q]				x [r]			x [r]	
Treatment									
Trastuzumab + Pertuzumab		x	x	x	x	x	x		

CBC = complete blood count; CMP = comprehensive metabolic profile; CT = computerized tomography; ECHO = echocardiogram; ECOG PS = Eastern Cooperative Oncology Group Performance Status; MRI = magnetic resonance imaging; MUGA = multiple-gated acquisition; PET = positron emission tomography.

[a] The medical history, ECOG PS, CBC, and CMP should be done ≤21 days prior to initiation of treatment. However, if the CBC and CMP are obtained within 72 hours of Cycle 1, Day 1 they do not have to be repeated on Day 1. Scans to document measurable or evaluable disease (i.e., tumor measurement) should be performed ≤4 weeks prior to initiation of treatment. ECHO/MUGA for LVEF assessment should be performed ≤4 weeks prior to initiation of treatment.

[b] Assessments should be performed when clinically indicated.

[c] After treatment is discontinued, patients will visit the study center within 30 days after the last dose of study treatment for end-of-treatment safety follow-up assessments. All patients will be followed until treatment-related toxicities resolve or for at least 30 days post-study drug discontinuation. If the patient's worsening diseases combined with travel distance makes this visit too difficult, follow-up with the patient may take place by telephone to include an assessment of AEs. Alternatively, the patient's local physician may be contacted to collect AE data and any standard of care laboratory and CT data, if performed. For patients who come off study treatment without PD, tumor assessments are required at the end-of-treatment visit, only if not obtained within the past 6 cycles.

[d] Informed consent must be obtained prior to performing any trial-related screening assessments.

[e] Confirmation of HER2 overexpression or amplification (see protocol Appendix 5) should occur prior to performing other trial-related assessments. For patients screened using a blood assay: obtain tissue-based testing result confirming study eligibility (within first 4 weeks after enrollment).

[f] Measurement of LVEF (use the same test that was used for baseline measurement). MUGA or ECHO will be repeated every 12 weeks, or as clinically indicated, during treatment.

[g] Only significant AEs, defined as SAEs, AEs leading to treatment modification (e.g., dose reduction, dose delay, treatment discontinuation), or protocol-defined AEs of special interest (see protocol Section 5.2.3) occurring from the first treatment until 30 days after the last dose of study treatment will be captured in the eCRF.

[h] CMP will include measurements of glucose, BUN, creatinine, sodium, potassium, chloride, calcium, CO_2, alkaline phosphatase, AST (SGOT), ALT (SGPT), total bilirubin, total protein, and albumin.

[i] All women of childbearing potential (including those who have had a tubal ligation) will have a serum pregnancy test at screening, within 7 days before the first dose of study drug. Urine or serum pregnancy tests may be performed at subsequent visits, as indicated in the schedule of assessments. Any positive urine pregnancy test must be confirmed by a serum pregnancy test. During the treatment period, pregnancy test results must be available prior to administration of study drug. Patients who have a positive pregnancy test may not receive study drug.

[j] At the treatment discontinuation visit and then every 3 months thereafter until 7 months post-discontinuation of study treatment.

[k] If additional molecular profiling is done at the site while the patient is on study, the results may be reported in the eCRF.

[l] Submission of an archival or new pretreatment tissue sample is required for all patients where molecular testing was not performed by Foundation Medicine. For other patients, submission of an archival or new pretreatment tissue sample is requested. The tissue sample must be submitted within 4 weeks after enrollment (refer to protocol Section A6-4.5.1.2 for tissue requirements). At disease progression, an optional FFPE tissue sample may be submitted for exploratory research, if available.

[m] Only if clinically indicated.

[n] Performed within 7 days prior to the next cycle, with results available for review before Day 1 of the next cycle. For patients with CRC and HER2 amplification or overexpression, with a PR or CR as assessed by the investigator, scans should be submitted for central review.

[o] Only scans (chest, abdomen, and/or pelvis) that were abnormal at baseline need to be repeated. For patients who come off study treatment without PD, tumor assessments are required at the end-of-treatment visit, only if not obtained within the past 6 cycles.

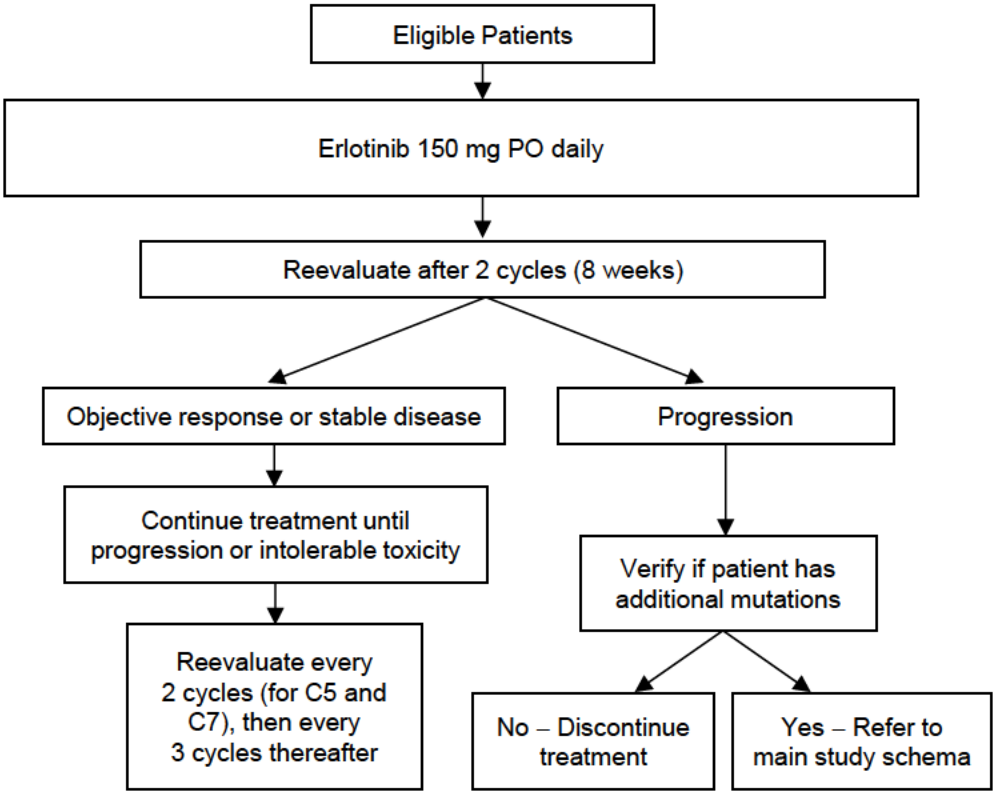
[p] Only if abnormal at baseline and if necessary to determine response to treatment.

[q] Required for patients with a history of treated brain metastases. Otherwise, repeat only if clinically indicated.

[r] Only if abnormal at baseline.

5.3 Appendix C - Assessment and Flowchart: Erlotinib in Patients with EGFR-Activating Mutations

Study Schema: Erlotinib



C=cycle; PO=orally.

Screening and Pretreatment Assessments

- Written informed consent form prior to any other trial-related procedures
- Review of molecular profiling report and confirmation of EGFR-activating mutation (should occur prior to obtaining other study-specific assessments)
- Medical history
- ECOG PS
- ECG, QTc interval measurement
- CBC, including 3-part differential and platelets
- CMP
- Serum pregnancy test (must be performed within 7 days of Cycle 1, Day 1)
- Optional archival tumor sample
- Tumor markers (only if clinically indicated)
- CT scans of the chest, abdomen, and pelvis
- PET scans or bone scan (only if clinically indicated)
- CT or MRI of brain (all patients with history of treated brain metastases; otherwise, only if clinically indicated)

Patients who have disease progression on one study treatment regimen and are eligible for another study treatment regimen must be re-consented and re-screened for the new study treatment and must be registered as a new patient via the interactive web response system (IWRS) prior to initiation of the new study treatment. In these cases, results of assessments done at treatment completion may be used as screening assessments for the subsequent study treatment. These tests do not have to be repeated if the timeframe is as required for screening.

Assessments during Treatment
Patients will visit the study center once every 4 weeks (± 72 hours) during the first three cycles of treatment (i.e., on Day 1 of Cycles 1, 2, and 3). The initial reevaluation will occur after 8 weeks of treatment (Cycle 3, Day 1). For patients who remain on treatment (i.e., responding or stable) and who are doing well on Cycle 7, Day 1, subsequent visits will be every 12 weeks, with reevaluations at these intervals. Assessments to be performed at each visit are as follows:

a. Day 1 of Cycle 1

- Plasma biomarker collection

b. Day 1 of Cycles 1, 2, and 3

- Adverse event (AE) evaluation
  - Only significant AEs, defined as serious AEs (SAEs), AEs leading to treatment modification (e.g., dose reduction, dose delay, treatment discontinuation), or protocol-defined AEs of special interest (see protocol Section 5.2.3) will be captured in the electronic Case Report Form (eCRF).
- Review study drug compliance with patient
- CBC, including 3-part differential and platelets
- CMP

c. Day 1 of Cycle 3

- Plasma biomarker collection

d. Day 1 of Cycles 3 and 5

- Tumor markers (only if clinically indicated)
- Response assessment – CT scans of chest, abdomen, and pelvis (repeat only scans that were abnormal at baseline)
- Review study drug compliance with patient

e. Day 1 of Cycle 7 and Every Three Cycles Thereafter

- AE evaluation
  - Only significant AEs, defined as SAEs, AEs leading to treatment modification (e.g., dose reduction, dose delay, treatment discontinuation), or other protocol-defined AEs of special interest (see protocol Section 5.2.3) will be captured in the eCRF.
- Review study drug compliance with patient
- CBC, including 3-part differential and platelets
- CMP
- Tumor markers (only if clinically indicated)
- CT scans of the chest, abdomen, and/or pelvis (repeat only scans that were abnormal at baseline)
- PET scans or bone scan (only if abnormal at baseline and necessary to determine response to treatment)
- CT or MRI of brain (only if abnormal at baseline)

End of Treatment
At the end of treatment, a safety follow-up visit will occur within 30 days from discontinuation of erlotinib. The following assessments will be conducted at the visit:

- Plasma biomarker collection
- AE evaluation
  - Only significant AEs, defined as SAEs, AEs leading to treatment discontinuation, or protocol-defined AEs of special interest (see protocol Section 5.2.3) will be captured in the eCRF.
- Review study drug compliance with patient
- CBC, including 3-part differential and platelets
- CMP
- Tumor markers (only if clinically indicated)
- CT scans of the chest, abdomen, and/or pelvis (repeat only scans that were abnormal at baseline)
  - For patients who come off study treatment without progressive disease (PD), tumor assessments are required at the end-of-treatment visit, only if not obtained within the past 3 cycles.

If the patient's worsening disease combined with travel distance makes the safety follow-up visit too difficult, follow-up with the patient may take place by telephone to include an assessment of AEs. Alternatively, the patient's local physician may be contacted to collect AE data and any standard of care laboratory and CT data, if performed.

Follow-Up Assessments
Please refer to the main body of the protocol for the follow-up assessments.

PATIENT DISCONTINUATION
Please refer to Section 4.6 in the main body of the protocol for patient discontinuation descriptions.

Genentech
A Member of the Roche Group

Data Analysis Plan Module 1 Template

Erlotinib Study Flowchart

Assessments	Pre-Treatment	Trial Treatment			End of Treatment Safety Follow-Up [b]	Follow-Up	
			Reassessments				
	Screening [a]	Cycles 1, 2, and 3, Day 1 (±3 Days)	Cycles 3 and 5, Day 1 (±3 Days)	Cycle 7, Day 1 (and Every 3 Cycles After) (±3 Days)		Every 3 Months After End of Treatment (Prior to Progression) [c] (±14 Days)	Survival [d] (±14 Days)
Tests and Observations							
Informed consent [e]	x						
Obtain/review molecular profiling report/ pathology report [f]	x						
Medical history	x						
ECOG PS	x						
ECG, QTc interval measurement	x [g]						
Adverse event evaluation (all cycles) [h]		x	x	x	x		
Study drug compliance review [i]		x	x	x	x		
Survival status							x
Laboratory Evaluations							
CBC, 3-part differential, and platelets	x	x		x	x		
CMP [j]	x	x		x	x		
Plasma biomarkers		x [Day 1 of Cycle 1 only]	x [Day 1 of Cycle 3 only]		x		
Pregnancy test [k]	x						

Genentech
A Member of the Roche Group

Data Analysis Plan Module 1 Template

Assessments	Pre-Treatment	Trial Treatment			End of Treatment Safety Follow-Up [b]	Follow-Up	
			Reassessments				
	Screening [a]	Cycles 1, 2, and 3, Day 1 (±3 Days)	Cycles 3 and 5, Day 1 (±3 Days)	Cycle 7, Day 1 (and Every 3 Cycles After) (±3 Days)		Every 3 Months After End of Treatment (Prior to Progression) [c] (±14 Days)	Survival [d] (±14 Days)
Laboratory Evaluations (cont)							
Optional molecular profiling results [l]		x					
Optional archival tumor sample	x [m]						
Staging							
Tumor markers [n]	x		x	x	x	x	
CT scan of chest, abdomen, and pelvis [o]	x		x [p]	x [p]	x [p]	x	
PET scan or bone scan [o]	x [n]			x [q]			
Head CT or MRI scan [o]	x [r]			x [s]			
Treatment							
Erlotinib (all cycles)		x	x	x			

CBC = complete blood count; CMP = comprehensive metabolic profile; CT = computerized tomography; ECG = electrocardiogram; ECOG PS = Eastern Cooperative Oncology Group Performance Status; MRI = magnetic resonance imaging; PET = positron emission tomography.

[a] The medical history, ECOG PS, CBC, CMP, and ECG should be done ≤21 days prior to initiation of treatment. However, if the CBC and CMP are obtained within 72 hours of Cycle 1, Day 1 they do not have to be repeated on Day 1. Scans to document measurable or evaluable disease (i.e., tumor measurement) should be performed ≤4 weeks prior to initiation of treatment.

[b] After treatment is discontinued, patients will visit the study center within 30 days after the last dose of study treatment for end-of-treatment safety follow-up assessments. All patients will be followed until treatment-related toxicities resolve or for at least 30 days post-study drug discontinuation. If the patient's worsening diseases combined with travel distance makes this visit too difficult, follow-up with the patient may take place by telephone to include an assessment of AEs. Alternatively, the patient's local physician may be contacted to collect AE data and

any standard of care laboratory and CT data, if performed. For patients who come off study treatment without PD, tumor assessments are required at the end-of-treatment visit, only if not obtained within the past 3 cycles.

[c] Patients completing treatment with no evidence of disease progression will be followed every 3 months until disease progression. The patient's physician will be contacted to collect follow-up information. This information will only include the assessments listed above if they are being performed as part of the patient's standard of care.

[d] Patients who discontinue study treatment regardless of reason for discontinuation will be followed for survival every 3 months until death, lost to follow-up, withdrawal of consent, or study termination by the Sponsor, whichever comes first. Patients may be contacted during outpatient visits or by telephone if unable to come to the study center.

[e] Informed consent must be obtained prior to performing any trial-related screening assessments.

[f] Confirmation of EGFR activating mutation (see protocol Appendix 5) should occur prior to performing other trial-related assessments.

[g] ECG to determine QTc interval measurement.

[h] Only significant AEs, defined as SAEs, AEs leading to treatment modification (e.g., dose reduction, dose delay, treatment discontinuation), or protocol-defined AEs of special interest (see protocol Section 5.2.3) occurring from the first treatment until 30 days after the last dose of study treatment will be captured in the eCRF.

[i] Study drug compliance will be reviewed with the patient.

[j] CMP will include measurements of glucose, BUN, creatinine, sodium, potassium, chloride, calcium, CO_2, alkaline phosphatase, AST (SGOT), ALT (SGPT), total bilirubin, total protein, and albumin.

[k] For women of childbearing potential, including women who have had a tubal ligation, a serum pregnancy test will be performed ≤ 7 days prior to first dose of trial treatment.

[l] If additional molecular profiling is done at the site while the patient is on study, the results may be reported in the eCRF.

[m] Archival tissue, if available and with specific consent, will be requested and collected for future correlative research studies. The sample can be provided during or after screening while the patient is on study.

[n] Only if clinically indicated.

[o] Performed within 7 days prior to the next cycle, with results available for review before Day 1 of the next cycle.

[p] Only scans (chest, abdomen, and/or pelvis) that were abnormal at baseline need to be repeated. For patients who come off study treatment without PD, tumor assessments are required at the end-of-treatment visit, only if not obtained within the past 3 cycles.

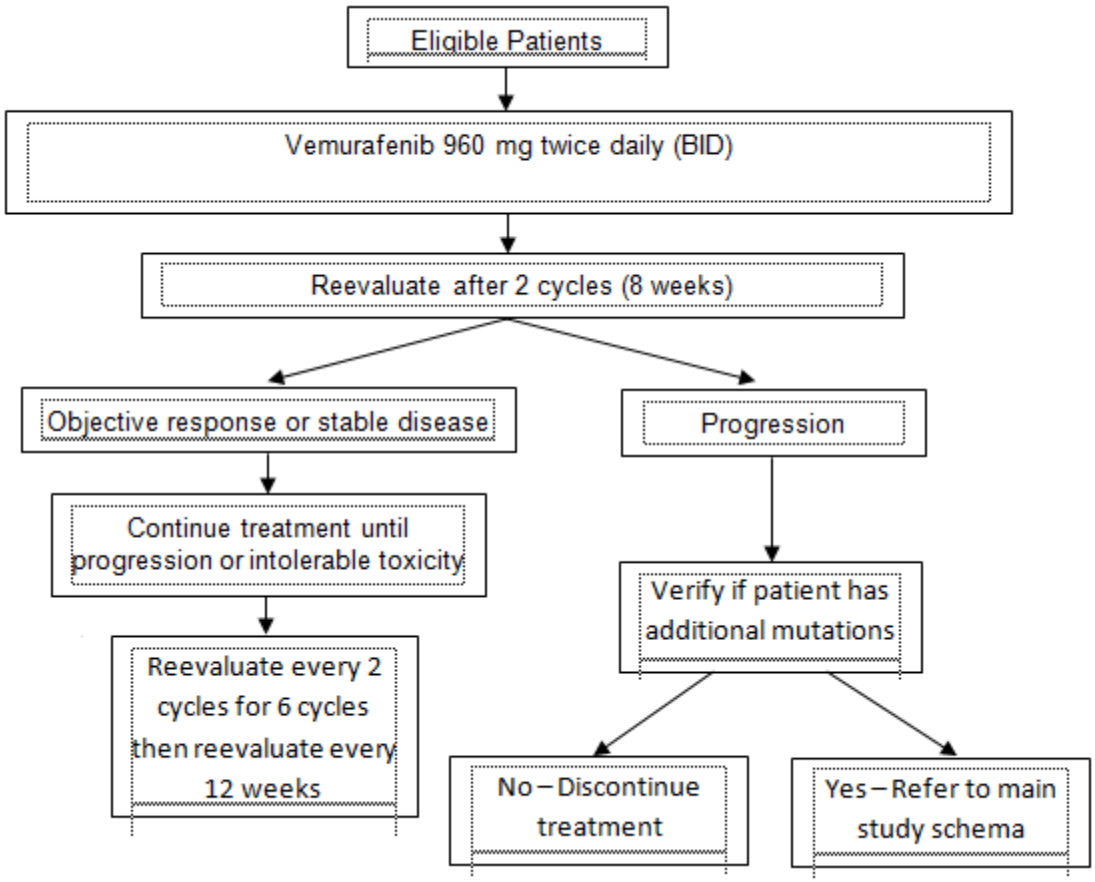
[q] Only if abnormal at baseline and if necessary to determine response to treatment.

[r] Required for patients with a history of treated brain metastases. Otherwise, repeat only if clinically indicated.

[s] Only if abnormal at baseline.

5.4 Appendix D - Assessment and Flowchart: Vemurafenib in Patients with BRAF-Mutated Cancers

Study Schema: Vemurafenib



Note: Vemuratenib monotherapy was applicable through Protocol V2 (see Section 2: Study Design) and was superceded by Vemuratenib plus Cobemetinib in Protocol V3.

Screening and Pretreatment Assessments

- Informed consent form prior to any other trial-related procedures
- Review of molecular profiling report and confirmation of BRAF mutation (should occur prior to obtaining other study-specific assessments)
- Medical history)
- Dermatologic examination for squamous carcinoma/other suspicious skin lesions (anal/pelvic areas to be included if per standard practice)
- Head and neck examination for squamous carcinomas
- ECOG PS
- ECG, QTc interval measurement
- CBC, including 3-part differential and platelets

- CMP
- Serum pregnancy test (must be performed within 7 days of Cycle 1, Day 1)
- Optional archival tumor sample
- Tumor markers (only if clinically indicated)
- CT scans of the chest, abdomen, and/or pelvis
- Positron emission tomography (PET) scans or bone scan (only if clinically indicated)
- CT or MRI of brain (all patients with a history of treated brain metastases; otherwise, only if clinically indicated)

Patients who have disease progression on one study treatment regimen and are eligible for another study treatment regimen must be re-consented and re-screened for the new study treatment and must be registered as a new patient via the interactive web response system (IWRS) prior to initiation of the new study treatment. In these cases, results of assessments done at treatment completion may be used as screening assessments for the subsequent study treatment. These tests do not have to be repeated if the timeframe is as required for screening.

Assessments during Treatment
Patients will visit the study center once every 4 weeks (± 72 hours) during the first three cycles of treatment (i.e., on Day 1 of Cycles 1, 2, and 3). The initial reevaluation will occur after 8 weeks of treatment (Cycle 3, Day 1). For patients who remain on treatment (i.e., responding or stable) and who are doing well on Cycle 3, Day 1, subsequent visits will be every 12 weeks with reevaluations at these intervals. Assessments to be performed at each visit are as follows:

a. Day 1 of Cycles 1, 2, and 3
- Dermatologic exam for squamous carcinoma/other suspicious skin lesions (anal/pelvic areas to be included if per standard practice)
- ECG, QTc interval measurement
- AE evaluation
  - Only significant AEs, defined as SAEs, AEs leading to treatment modification (e.g., dose reduction, dose delay, treatment discontinuation), or protocol-defined AEs of special interest (see protocol Section 5.2.3) will be captured in the electronic Case Report Form (eCRF).
- Review study drug compliance with patient
- CBC, including 3-part differential and platelets
- CMP

b. Day 1 of Cycles 3 and 5
- Head and neck examination for developing squamous carcinomas
- Tumor markers (only if clinically indicated)
- Response assessment - CT scans of chest, abdomen, and/or pelvis (repeat only scans that were abnormal at baseline)

c. Day 1 of Cycle 7 and Every Three Cycles Thereafter
- Dermatologic examination for squamous carcinoma/other suspicious skin lesions (anal/pelvic areas to be included if per standard practice)
- Head and neck examination for developing squamous carcinomas
- ECG, QTc interval measurement
- AE evaluation
  - Only significant AEs, defined as SAEs, AEs leading to treatment modification (e.g., dose reduction, dose delay, treatment discontinuation), or protocol-defined AEs of special interest (see protocol Section 5.2.3) will be captured in the eCRF.
- Review study drug compliance with patient

- CBC, including 3-part differential and platelets
- CMP
- Tumor markers (only if clinically indicated)
- CT scans of the chest, abdomen, and/or pelvis (only scans that were abnormal at baseline need to be repeated)
- PET scans or bone scan (only if abnormal at baseline and necessary to determine response to treatment)
- CT or MRI of brain (only if abnormal at baseline)

End of Treatment
At the end of treatment, a safety follow-up visit will occur within 30 days from discontinuation of vemurafenib. The following assessments will be conducted at the follow up visit:

- Dermatologic exam for squamous carcinoma/other suspicious skin lesions (anal/pelvic areas to be included if per standard practice)
- AE evaluation
  - Only significant AEs, defined as SAEs, AEs leading to treatment discontinuation, or protocol-defined AEs of special interest (see protocol Section 5.2.3) will be captured in the eCRF.
- Review study drug compliance with patient
- CBC, including 3-part differential and platelets
- CMP
- Tumor markers (only if clinically indicated)
- CT scans of the chest, abdomen, and/or pelvis (only scans that were abnormal at baseline need to be repeated)
  - For patients who come off study treatment without progressive disease (PD), tumor assessments are required at the end-of-treatment visit, only if not obtained within the past 3 cycles.

If the patient's worsening disease combined with travel distance makes the safety follow-up visit too difficult, follow-up with the patient may take place by telephone to include an assessment of AEs. Alternatively, the patient's local physician may be contacted to collect AE data and any standard of care laboratory and CT data, if performed.

Follow-Up Assessments
Please refer to the main body of the protocol for the follow-up assessments.

PATIENT DISCONTINUATION
Please refer to Section 4.6 in the main body of the protocol for patient discontinuation descriptions.

Vemurafenib Study Flowchart

Assessments	Pre-Treatment	Trial Treatment			End-of-Treatment Safety Follow-Up[b]	Follow-Up	
			Reassessments			Every 3 Months After End of Treatment (Prior to Progression)[c]	
	Screening[a]	Cycles 1, 2, and 3, Day 1 (± 3 Days)	Cycles 3 and 5, Day 1 (± 3 Days)	Cycle 7, Day 1 (and Every 3 Cycles After) (± 3 Days)			Survival[d] (± 14 Days)
Tests and Observations							
Informed consent[e]	x						
Obtain/review molecular profiling report/pathology report[f]	x						
Medical history	x						
Dermatologic exam[g]	x	x		x	x		
Head/neck exam[h]	x		x	x			
ECOG PS	x						
ECG, QTc interval measurement[i]	x	x		x			
Adverse event evaluation[j]		x	x	x	x		
Study drug compliance review[k]		x	x	x	x		
Survival status							x
Laboratory Evaluations							
CBC, 3-part differential, and platelets	x	x		x	x		
CMP[l]	x	x		x	x		
Pregnancy test[m]	x						
Optional molecular profiling results[n]		x					
Optional archival tumor sample	x[o]						
Staging							
Tumor markers[p]	x		x	x	x	x	

Genentech
A Member of the Roche Group

Data Analysis Plan Module 1 Template

Assessments	Pre-Treatment	Trial Treatment			End-of-Treatment Safety Follow-Up [b]	Follow-Up	
			Reassessments			Every 3 Months After End of Treatment (Prior to Progression) [c]	
	Screening [a]	Cycles 1, 2, and 3, Day 1 (± 3 Days)	Cycles 3 and 5, Day 1 (± 3 Days)	Cycle 7, Day 1 (and Every 3 Cycles After) (± 3 Days)		(± 14 Days)	Survival [d] (± 14 Days)
Staging (cont)							
CT scan of chest, abdomen, pelvis [q]	x		x [r]	x [r]	x [r]	x	
PET scan or bone scan [q]	x [p]			x [s]			
Head CT or MRI scan [q]	x [t]			x [u]			
Treatment							
Vemurafenib		x	x	x			

CBC = complete blood count; CMP = comprehensive metabolic profile; CT = computerized tomography; ECG = electrocardiogram; ECOG PS = Eastern Cooperative Oncology Group Performance Status; MRI = magnetic resonance imaging; PET = positron emission tomography.

[a] The medical history, ECOG PS, CBC, CMP, and ECG should be done ≤ 7 days prior to initiation of treatment. However, if the CBC and CMP are obtained within 72 hours of Cycle 1, Day 1 they do not have to be repeated on Day 1. Scans to document measurable or evaluable disease (i.e., tumor measurement) should be performed ≤ 4 weeks prior to initiation of treatment.

[b] After treatment is discontinued, patients will visit the study center within 30 days after the last dose of study treatment for end-of-treatment safety follow-up assessments. All patients will be followed until treatment-related toxicities resolve or for at least 30 days post-study drug discontinuation. If the patient's worsening diseases combined with travel distance makes this visit too difficult, follow-up with the patient may take place by telephone to include an assessment of AEs. Alternatively, the patient's local physician may be contacted to collect AE data and any standard of care laboratory and CT data, if performed. For patients who come off study treatment without PD, tumor assessments are required at the end-of-treatment visit, only if not obtained within the past 3 cycles.

[c] Patients completing treatment with no evidence of disease progression will be followed every 3 months until disease progression. The patient's physician will be contacted to collect follow-up information. This information will only include the assessments listed above if they are being performed as part of the patient's standard of care.

[d] Patients with documented disease progression will be followed every 3 months for a minimum of 1 year from the date of first dose of study drug or until death, whichever comes first. Patients may be contacted during outpatient visits or by telephone if unable to come to the study center.

[e] Informed consent must be obtained prior to performing any trial-related screening assessments.

[f] Confirmation of BRAF mutation should occur prior to performing other trial-related assessments.

[g] Full dermatologic examination for squamous carcinoma/other suspicious lesions, including, if per standard practice, an examination of the anal and pelvic areas. Lesions suspicious for squamous cell carcinoma should be treated appropriately.

[h] To be performed by the treating physician to monitor for developing squamous cancers.

[i] ECG and electrolytes, including potassium, magnesium, and calcium, should be monitored before treatment with vemurafenib and after dose modification. Monitoring of ECGs should occur on Day 1 of Cycles 1, 2, 3, 7, and every 3 cycles thereafter, or more often as clinically indicated. Patients with baseline QTc $>$ 450 ms are not eligible for this study. If during treatment the QTc exceeds 500 ms (CTCAE Grade 3), vemurafenib treatment should be temporarily interrupted, electrolyte abnormalities should be corrected, and cardiac risk factors for QT prolongation (e.g., congestive heart failure, bradyarrhythmias) should be controlled. Re-initiation of treatment should occur at a lower dose once the QTc decreases below 500 ms.

[j] Only significant AEs, defined as SAEs, AEs leading to treatment modification (e.g., dose reduction, dose delay, treatment discontinuation), or protocol-defined AEs of special interest (see protocol Section 5.2.3) occurring from the first treatment until 30 days after the last dose of study treatment will be captured in the eCRF.

[k] Study drug compliance will be reviewed with the patient.

[l] CMP will include measurements of glucose, BUN, creatinine, sodium, potassium, chloride, calcium, CO2, alkaline phosphatase, AST (SGOT), ALT (SGPT), total bilirubin, total protein, and albumin.

[m] For women of childbearing potential, including women who have had a tubal ligation, a serum pregnancy test will be performed $\leq$ 7 days prior to first dose of trial treatment.

[n] If additional molecular profiling is done at the site while the patient is on study, the results may be reported in the eCRF.

[o] Archival tissue, if available and with specific consent, will be requested and collected for future correlative research studies. The sample can be provided during or after screening while the patient is on study.

[p] Only if clinically indicated.

[q] Performed within 7 days prior to the next cycle, with results available for review before Day 1 of the next cycle.

[r] Only scans (chest, abdomen, and/or pelvis) that were abnormal at baseline need to be repeated. For patients who come off study treatment without PD, tumor assessments are required at the end-of-treatment visit, only if not obtained within the past 3 cycles.

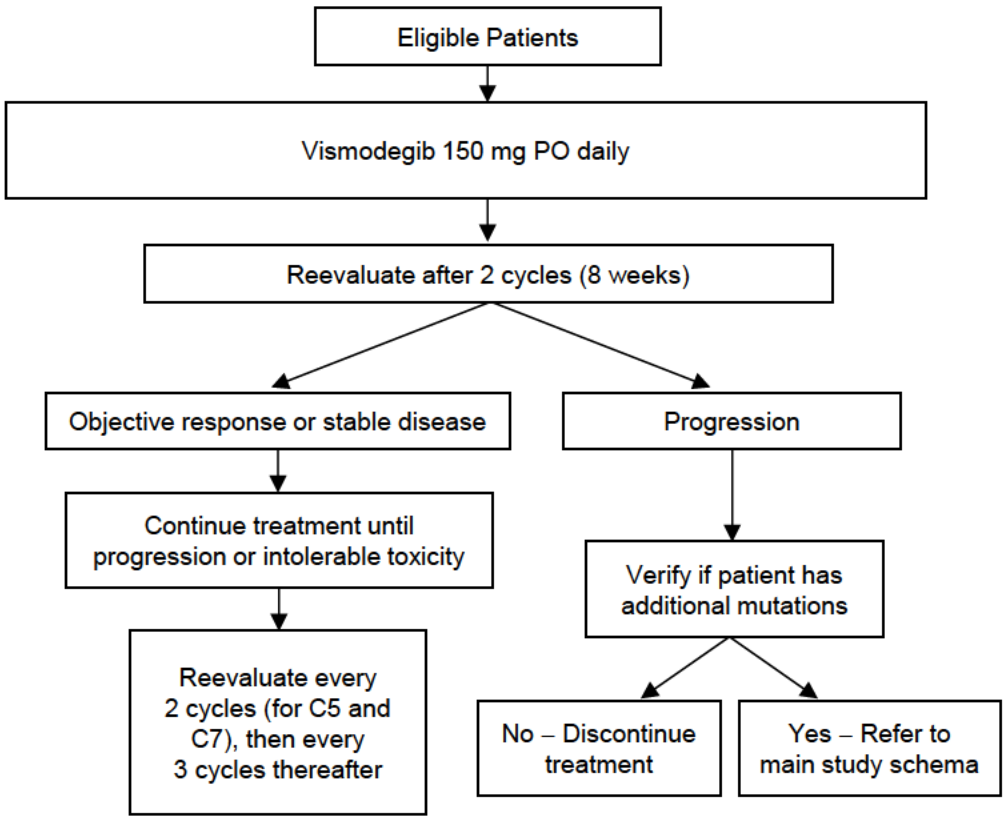
[s] Only if abnormal at baseline and if necessary to determine response to treatment.

[t] Required for patient with a history of treated brain metastases. Otherwise, repeat only if clinically indicated.

[u] Only if abnormal at baseline

5.5 Appendix E - Assessment and Flowchart: Vismodegib in Patients with Hedgehog Pathway-Mutated Cancers (Activating Mutation of Smoothened or Loss-of-Function Mutation of Protein Patched Homolog-1)

Study Schema: Vismodegib



C = cycle.

Screening and Pretreatment Assessments

- Written informed consent form prior to any other trial-related procedures
- Review of molecular profiling report and confirmation of clinically relevant hedgehog pathway mutations (activating mutations of SMO or loss-of-function mutations of PTCH-1) should occur prior to obtaining other study-specific assessments. For patients screened using a blood assay: obtain tissue-based testing result confirming study eligibility (within first 4 weeks after enrollment).
- Medical history
- ECOG performance status
- CBC, including 3-part differential and platelets
- CMP
- Serum pregnancy test (must be performed within 7 days of Cycle 1, Day 1)
- Optional archival tumor sample
- Tumor markers (only if clinically indicated)
- CT scans of the chest, abdomen, and/or pelvis
- Positron emission tomography (PET) scans or bone scan (only if clinically indicated)
- CT or MRI of brain (only if clinically indicated or patient has a history of treated brain metastases)

Patients who have disease progression on one study treatment regimen and are eligible for another study treatment regimen must be re-consented and re-screened for the new study treatment and must be registered as a new patient via the interactive web response system (IWRS) prior to initiation of the new study treatment. In these cases, results of assessments done at treatment completion may be used as screening assessments for the subsequent study treatment. These tests do not have to be repeated if the timeframe is as required for screening.

Assessments during Treatment
Patients will visit the study center once every 4 weeks (± 72 hours) during the first three cycles of treatment (i.e., on Day 1 of Cycles 1, 2, and 3). The initial reevaluation will occur after 8 weeks of treatment (Cycle 3, Day 1). For patients who remain on treatment (i.e., responding or stable) and who are doing well on Cycle 3, Day 1, subsequent visits will be every 12 weeks with reevaluations at these intervals. Assessments to be performed at each visit are as follows:

a. Day 1 of Cycles 1
- Plasma biomarker collection

b. Day 1 of Cycles 1, 2, and 3
- Adverse event (AE) evaluations
  - Only significant AEs, defined as serious AEs (SAEs), AEs leading to treatment modification (e.g., dose reduction, dose delay, treatment discontinuation), or protocol-defined AEs of special interest (see protocol Section 5.2.3) will be captured in the electronic Case Report Form (eCRF).
- Review study drug compliance with patient
- CBC, including 3-part differential and platelets
- CMP
- Urine or serum pregnancy test – any positive urine pregnancy test must be confirmed by a serum pregnancy test. During the treatment period, pregnancy test results must be available prior to administration of study drug. Patients who have a positive pregnancy test must not receive study drug. Pregnancy tests must be done on Day 1 prior to starting every cycle.

c. Day 1 of Cycle 3
- Plasma biomarker collection

d. Day 1 of Cycles 3 and 5
- Urine or serum pregnancy test – any positive urine pregnancy test must be confirmed by a serum pregnancy test. During the treatment period, pregnancy test results must be available prior to administration of study drug. Patients who have a positive pregnancy test must not receive study drug. Pregnancy tests must be done on Day 1 prior to starting every cycle.
- Tumor markers (only if clinically indicated)
- Response assessment – CT scans of chest, abdomen, and pelvis (repeat only scans that were abnormal at baseline

e. Cycle 4
- Urine or serum pregnancy test: any positive urine pregnancy test must be confirmed by a serum pregnancy test. During the treatment period, pregnancy test results must be available prior to administration of study drug. Patients who have a positive pregnancy test must not receive study drug. Pregnancy tests must be done on Day 1 prior to starting every cycle.

f. Day 1 of Cycle 7 and Every Three Cycles Thereafter
- AE evaluations

  - Only significant AEs, defined as SAEs, AEs leading to treatment modification (e.g., dose reduction, dose delay, treatment discontinuation), or protocol-defined AEs of special interest (see protocol Section 5.2.3) will be captured in the eCRF.
- Review study drug compliance with patient
- CBC, including 3-part differential and platelets
- CMP
- Urine or serum pregnancy test – any positive urine pregnancy test must be confirmed by a serum pregnancy test. During the treatment period, pregnancy test results must be available prior to administration of study drug. Patients who have a positive pregnancy test must not receive study drug. Pregnancy tests must be done on Day 1 prior to starting every cycle.
- Tumor markers (only if clinically indicated)
- CT scans of the chest, abdomen, and/or pelvis (only scans that were abnormal at baseline need to be repeated)
- PET scans or bone scan (only if abnormal at baseline and necessary to determine response to treatment)
- CT or MRI of brain (only if abnormal at baseline)

End of Treatment
At the end of treatment, a safety follow-up visit will occur within 45 days from discontinuation of vismodegib. The following assessments will be conducted at the follow-up visit:
- Plasma biomarker collection
- AE evaluation
  - Only significant AEs, defined as SAEs, AEs leading to treatment discontinuation, or protocol-defined AEs of special interest (see protocol Section 5.2.3) will be captured in the eCRF.
- Review study drug compliance with patient
- CBC, including 3-part differential and platelets
- CMP
- Tumor markers (only if clinically indicated)
- CT scans of the chest, abdomen, and/or pelvis (only scans that were abnormal at baseline need to be repeated)
  - For patients who come off study treatment without progressive disease (PD), tumor assessments are required at the end-of-treatment visit, only if not obtained within the past 3 cycles.

If the patient's worsening disease combined with travel distance makes the safety follow-up visit too difficult, follow-up with the patient may take place by telephone to include an assessment of AEs. Alternatively, the patient's local physician may be contacted to collect AE data and any standard of care laboratory and CT data, if performed.

Follow-Up Assessments
Please refer to the main body of the protocol for the follow-up assessments.

PATIENT DISCONTINUATION
Please refer to Section 4.6 in the main body of the protocol for patient discontinuation descriptions.

Genentech
A Member of the Roche Group

Data Analysis Plan Module 1 Template

Vismodegib Study Flowchart

Assessments	Pre-Treatment	Trial Treatment			End of Treatment Safety Follow-Up [b]	Follow-Up	
			Reassessments			Every 3 Months After End of Treatment (Prior to Progression) [c]	
	Screening [a]	Cycles 1, 2, and 3, Day 1 (±3 Days)	Cycles 3 and 5, Day 1 (±3 Days)	Cycle 7, Day 1 (and Every 3 Cycles After) (±3 Days)		(±14 Days)	Survival [d] (±14 Days)
Tests and Observations							
Informed consent [e]	x						
Obtain/review molecular profiling report/pathology report [f]	x						
Medical history	x						
ECOG PS	x						
Adverse event evaluation (all cycles) [g]		x	x	x	x		
Study drug compliance review [h]		x		x	x		
Survival status							x
Laboratory Evaluations							
CBC, 3-part differential, and platelets	x	x		x	x		
CMP [i]	x	x		x	x		
Plasma biomarkers		x [Day 1 of Cycle 1 only]	x [Day 1 of Cycle 3 only]		x		
Pregnancy test [j]	x	x	x [and Cycle 4]	x			
Optional molecular profiling results [k]		x					
Optional archival tumor sample	x [l]						

Genentech
A Member of the Roche Group

Data Analysis Plan Module 1 Template

Assessments	Pre-Treatment	Trial Treatment			End of Treatment Safety Follow-Up [b]	Follow-Up	
			Reassessments			Every 3 Months After End of Treatment (Prior to Progression) [c] (±14 Days)	Survival [d] (±14 Days)
	Screening [a]	Cycles 1, 2, and 3, Day 1 (±3 Days)	Cycles 3 and 5, Day 1 (±3 Days)	Cycle 7, Day 1 (and Every 3 Cycles After) (±3 Days)			
Staging							
Tumor markers [m]	x		x	x	x	x	
CT scan of chest, abdomen, pelvis [n]	x		x [o]	x [o]	x [o]	x	
PET scan or bone scan [n]	x [m]			x [p]			
Head CT or MRI scan [n]	x [q]			x [r]			
Treatment							
Vismodegib (all cycles)		x	x	x			

CBC = complete blood count; CMP = comprehensive metabolic profile; CT = computerized tomography; ECOG PS = Eastern Cooperative Oncology Group Performance Status; MRI = magnetic resonance imaging; PET = positron emission tomography.

[a] The medical history, ECOG PS, CBC, and CMP should be done ≤21 days prior to initiation of treatment. However, if the CBC and CMP are obtained within 72 hours of Cycle 1, Day 1 they do not have to be repeated on Day 1. Scans to document measurable or evaluable disease (i.e., tumor measurement) should be performed ≤4 weeks prior to initiation of treatment.

[b] After treatment is discontinued, patients will visit the study center within 45 days after the last dose of study treatment for end-of-treatment safety follow-up assessments. All patients will be followed until treatment-related toxicities resolve or for at least 45 days post-study drug discontinuation. If the patient's worsening diseases combined with travel distance makes this visit too difficult, follow-up with the patient may take place by telephone to include an assessment of AEs. Alternatively, the patient's local physician may be contacted to collect AE data and any standard of care laboratory and CT data, if performed. For patients who come off study treatment without PD, tumor assessments are required at the end-of-treatment visit, only if not obtained within the past 3 cycles.

[c] Patients completing treatment with no evidence of disease progression will be followed every 3 months until disease progression. The patient's physician will be contacted to collect follow-up information. This information will only include the assessments listed above if they are being performed as part of the patient's standard of care.

[d] Patients who discontinue study treatment regardless of reason for discontinuation will be followed for survival every 3 months until death, lost to follow-up, withdrawal of consent, or study termination by the Sponsor, whichever comes first. Patients may be contacted during outpatient visits or by telephone if unable to come to the study center.

[e] Informed consent must be obtained prior to performing any trial-related screening assessments.

[f] Confirmation of hedgehog pathway mutation (activating mutation of SMO or loss-of-function mutation of PTCH-1; see protocol Appendix 5) should occur prior to performing other trial-related assessments. For patients screened using a blood assay: obtain tissue-based testing result confirming study eligibility (within first 4 weeks after enrollment).

[g] Only significant AEs, defined as SAEs, AEs leading to treatment modification (e.g., dose reduction, dose delay, treatment discontinuation), or protocol-defined AEs of special interest (see protocol Section 5.2.3) occurring from the first treatment until 45 days after the last dose of study treatment will be captured in the eCRF.

[h] Study drug compliance will be reviewed with the patient.

[i] CMP will include measurements of glucose, BUN, creatinine, sodium, potassium, chloride, calcium, CO_2, alkaline phosphatase, AST (SGOT), ALT (SGPT), total bilirubin, total protein, and albumin.

[j] All women of childbearing potential (including those who have had a tubal ligation) will have a serum pregnancy test at screening, within 7 days before the first dose of study drug. Urine or serum pregnancy tests may be performed at subsequent visits, as indicated in the schedule of assessments. Note: Pregnancy tests must be done Day 1 prior to starting every cycle. Any positive urine pregnancy test must be confirmed by a serum pregnancy test. During the treatment period, pregnancy test results must be available prior to administration of study drug. Patients who have a positive pregnancy test must not receive study drug.

[k] If additional molecular profiling is done at the site while the patient is on study, the results may be reported in the eCRF.

[l] Archival tissue, if available and with specific consent, will be requested and collected for future correlative research studies. The sample can be provided during or after screening while the patient is on study.

[m] Only if clinically indicated.

[n] Performed within 7 days prior to the next cycle, with results available for review before Day 1 of the next cycle.

[o] Only scans (chest, abdomen, and/or pelvis) that were abnormal at baseline need to be repeated. For patients who come off study treatment without PD, tumor assessments are required at the end-of-treatment visit, only if not obtained within the past 3 cycles.

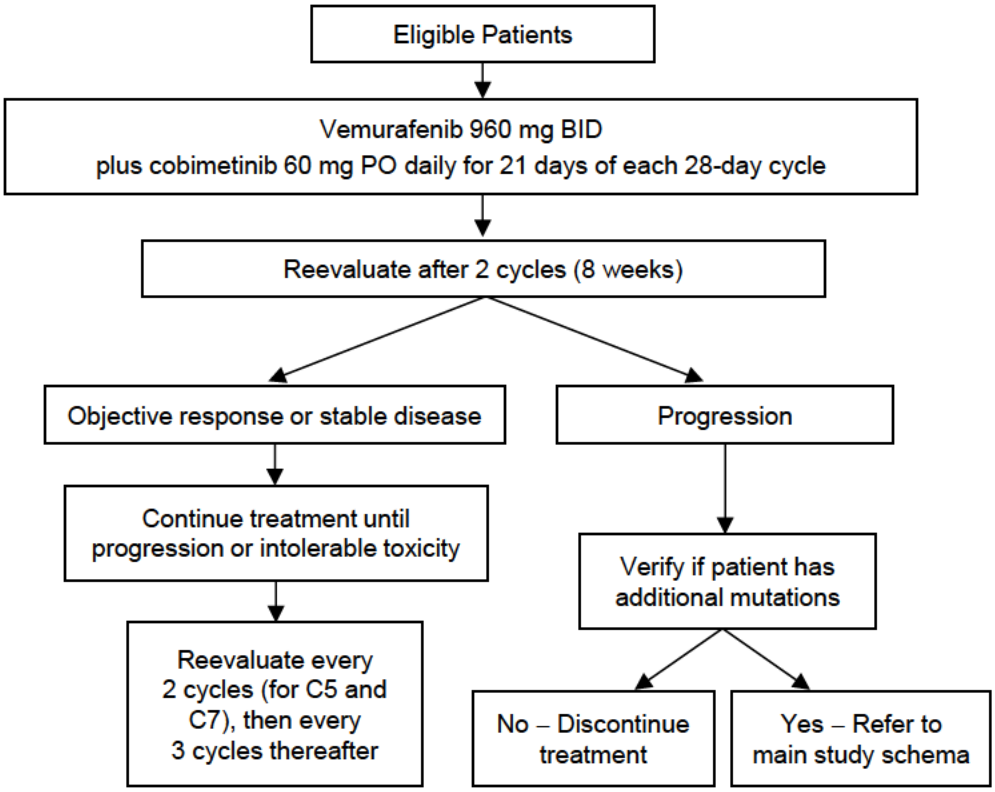
[p] Only if abnormal at baseline and if necessary to determine response to treatment.

[q] Required for patients with a history of treated brain metastases. Otherwise, repeat only if clinically indicated.

[r] Only if abnormal at baseline.

5.6 Appendix F - Assessment and Flowchart: Vemurafenib plus Cobimetinib in Patients with BRAF Mutated Cancers

Study Schema: Vemurafenib plus Cobimetinib



C=cycle.

Screening and Pretreatment Assessments

- Written informed consent form prior to any trial-related procedures
- Review of molecular profiling report and confirmation of BRAF mutation (should occur prior to obtaining other study-specific assessments). For patients screened using a blood assay: obtain tissue-based testing result confirming study eligibility (within first 4 weeks after enrollment).
- Medical history
- Dermatologic examination for squamous carcinoma/other suspicious skin lesions (anal/pelvic areas to be included if per standard practice)
- Ophthalmologic examination including visual acuity testing, intraocular pressure measurements by tonometry, slit lamp ophthalmoscopy, indirect ophthalmoscopy and spectral domain optical coherence tomography (spectral domain optical coherence tomography [OCT], if not available, may be substituted with time domain OCT) to evaluate evidence of retinal pathology that is considered a risk factor for neurosensory retinal detachment, RVO, or neovascular macular degeneration
  - Risk factors for RVO include elevated serum cholesterol, hypertriglyceridemia, hyperglycemia, hypertension, and glaucoma. Ophthalmologic examination should be performed by a qualified ophthalmologist.

- Head and neck examination for squamous carcinomas
- ECOG Performance Status
- ECG, QTc interval measurement
- LVEF assessment with ECHO or MUGA
- CBC, including 3-part differential and platelets
- CMP
- CPK
- Serum pregnancy test (must be performed within 7 days of Cycle 1, Day 1)
- Optional archival tumor sample
- Tumor markers (only if clinically indicated)
- CT scans of the chest, abdomen, and/or pelvis
- Positron emission tomography (PET) scans or bone scan (only if clinically indicated)
- CT or MRI of brain (all patients with a history of treated brain metastases; otherwise, only if clinically indicated)

Patients who have disease progression on one study treatment regimen and are eligible for another study treatment regimen must be re-consented and re-screened for the new study treatment and must be registered as a new patient via the interactive web response system (IWRS) prior to initiation of the new study treatment. In these cases, results of assessments done at treatment completion may be used as screening assessments for the subsequent study treatment. These tests do not have to be repeated if the timeframe is as required for screening.

Assessments during Treatment
Patients will visit the study center once every 4 weeks (± 72 hours) during the first three cycles of treatment (i.e., on Day 1 of Cycles 1, 2, and 3). The initial reevaluation will occur after 8 weeks of treatment (Cycle 3, Day 1). For patients who remain on treatment (i.e., responding or stable) and who are doing well on Cycle 3, Day 1, subsequent visits will be every 12 weeks with reevaluations at these intervals. Assessments to be performed at each visit are as follows:

a. Day 1 of Cycle 1
- Plasma biomarker collection

b. Day 1 of Cycles 1, 2, and 3
- Dermatologic exam for squamous carcinoma/other suspicious skin lesions (anal/pelvic areas to be included if per standard practice)
- ECG, QTc interval measurement
- AE evaluation
  - Only significant AEs, defined as SAEs, AEs leading to treatment modification (e.g., dose reduction, dose delay, treatment discontinuation), or protocol-defined AEs of special interest (see protocol Section 5.2.3) will be captured in the electronic Case Report Form (eCRF).
- Review study drug compliance with patient
- CBC, including 3-part differential and platelets
- CMP
- CPK

c. Day 1 of Cycle 2 and Every Three Cycles Thereafter
- LVEF assessment with ECHO or MUGA
- Ophthalmologic examination

d. Day 1 of Cycle 3
- Plasma biomarker collection

e. Day 1 of Cycles 3 and 5

- Head and neck examination for developing squamous carcinomas
- Tumor markers (only if clinically indicated)
- Response assessment – CT scans of chest, abdomen, and/or pelvis (repeat only scans that were abnormal at baseline)

f. Day 1 of Cycle 7 and Every Three Cycles Thereafter

- Dermatologic examination for squamous carcinoma/other suspicious skin lesions (anal/pelvic areas to be included if per standard practice)
- Head and neck examination for developing squamous carcinomas
- ECG, QTc interval measurement
- AE evaluation
  - Only significant AEs, defined as SAEs, AEs leading to treatment modification (e.g., dose reduction, dose delay, treatment discontinuation), or protocol-defined AEs of special interest (see protocol Section 5.2.3) will be captured in the eCRF.
- Review study drug compliance with patient
- CBC, including 3-part differential and platelets
- CMP
- Tumor markers (only if clinically indicated)
- CT scans of the chest, abdomen, and/or pelvis (only scans that were abnormal at baseline need to be repeated)
- PET scans or bone scan (only if abnormal at baseline and necessary to determine response to treatment)
- CT or MRI of brain (only if abnormal at baseline)

End of Treatment

At the end of treatment, a safety follow-up visit will occur within 30 days from discontinuation of combination vemurafenib plus cobimetinib. The following assessments will be conducted at the follow-up visit:

- Plasma biomarker collection
- Dermatologic exam for squamous carcinoma/other suspicious skin lesions (anal/pelvic areas to be included if per standard practice)
- AE evaluation
  - Only significant AEs, defined as SAEs, AEs leading to treatment discontinuation, or protocol-defined AEs of special interest (see protocol Section 5.2.3) will be captured in the eCRF.
- Review study drug compliance with patient
- CBC, including 3-part differential and platelets
- CMP
- CPK
- LVEF assessment with ECHO or MUGA
- Ophthalmologic evaluation
- Tumor markers (only if clinically indicated)
- CT scans of the chest, abdomen, and/or pelvis (only scans that were abnormal at baseline need to be repeated)
  - For patients who come off study treatment without progressive disease (PD), tumor assessments are required at the end-of-treatment visit, only if not obtained within the past 3 cycles.

If the patient's worsening disease combined with travel distance makes the safety follow up visit too difficult, follow-up with the patient may take place by telephone to include an assessment of AEs. Alternatively, the patient's local physician may be contacted to collect AE data and any standard of care laboratory and CT data, if performed.

Discontinuation of Cobimetinib
Safety follow-up within 30 days of cobimetinib discontinuation should include the following:

- LVEF assessment with ECHO or MUGA
- Ophthalmologic evaluation

CPK, LVEF, and the ophthalmologic evaluation do not need to be repeated when vemurafenib is subsequently discontinued.

PATIENT DISCONTINUATION
Please refer to Section 4.6 in the main body of the protocol for patient discontinuation descriptions.

Vemurafenib plus Cobimetinib Study Flowchart

Assessments	Pre-Treatment	Trial Treatment			
			Reassessments		
	Screening [a]	Cycles 1, 2, and 3, Day 1 (±3 Days)	Cycles 3 and 5, Day 1 (±3 Days)	Cycle 7, Day 1 (and Every 3 Cycles After) (±3 Days)	End-of-Treatment Safety Follow-Up [b]
Tests and Observations					
Informed consent [c]	x				
Obtain/review molecular profiling report/pathology report [d]	x				
Medical history	x				
Dermatologic exam [e]	x	x		x	x
Head/neck exam [f]	x		x	x	
ECOG PS	x				
ECG, QTc interval measurement [g]	x	x		x	
LVEF with ECHO or MUGA	x	x [Day 1 of Cycle 2 & every 3 cycles thereafter]			x [and at discontinuation of cobimetinib [h]]
Ophthalmologic exam	x	x [Day 1 of Cycle 2 & every 3 cycles thereafter]			x [and at discontinuation of cobimetinib [h]]
Adverse event evaluation (all cycles) [i]		x	x	x	x
Study drug compliance review [j]		x	x	x	x
Laboratory Evaluations					
CBC, 3-part differential, and platelets	x	x		x	x

Genentech
A Member of the Roche Group

Data Analysis Plan Module 1 Template

Assessments	Pre-Treatment	Trial Treatment			
			Reassessments		
	Screening [a]	Cycles 1, 2, and 3, Day 1 (±3 Days)	Cycles 3 and 5, Day 1 (±3 Days)	Cycle 7, Day 1 (and Every 3 Cycles After) (±3 Days)	End-of-Treatment Safety Follow-Up [b]
CMP [k]	x	x		x	x
CPK	x	x		x	x [and at discontinuation of cobimetinib [h]]
Plasma biomarkers		x [Day 1 of Cycle 1 only]	x [Day 1 of Cycle 3 only]		x
Pregnancy test [l]	x				
Optional molecular profiling results [m]		x			
Optional archival tumor sample	x [n]				
Staging					
Tumor markers [o]	x		x	x	x
CT scan of chest, abdomen, pelvis [p]	x		x [q]	x [q]	x [q]
PET scan or bone scan [p]	x [o]			x [r]	
Head CT or MRI scan [p]	x [s]			x [t]	
Treatment					
Vemurafenib plus cobimetinib (all cycles) [u]		x	x	x	

CBC = complete blood count; CMP = comprehensive metabolic profile; CT = computerized tomography; ECG = electrocardiogram; ECOG PS = Eastern Cooperative Oncology Group Performance Status; LVEF = left ventricular ejection fraction; MRI = magnetic resonance imaging; PET = positron emission tomography.

[a] The medical history, ECOG PS, CBC, CMP, CPK, and ECG should be done ≤21 days prior to initiation of treatment. However, if the CBC and CMP are obtained within 72 hours of Cycle 1, Day 1 they do not have to be repeated on Day 1. Scans to document measurable or evaluable disease (i.e., tumor measurement) should be performed ≤4 weeks prior to initiation of treatment. ECHO/MUGA for LVEF assessment should be performed ≤4 weeks prior to initiation of treatment.

[b] After treatment is discontinued, patients will visit the study center within 30 days after the last dose of study treatment for end-of-treatment safety follow-up assessments. All patients will be followed until treatment-related toxicities resolve or for at least 30 days post-study drug discontinuation. If the patient's worsening diseases combined with travel distance makes this visit too difficult, follow-up with the patient may take place by telephone to include an assessment of AEs. Alternatively, the patient's local physician may be contacted to collect AE data and any standard of care laboratory and CT data, if performed. For patients who come off study treatment without PD, tumor assessments are required at the end-of-treatment visit, only if not obtained within the past 3 cycles.

[c] Informed consent must be obtained prior to performing any trial-related screening assessments.

[d] Confirmation of BRAF gene alteration (see protocol Appendix 5) should occur prior to performing other trial-related assessments. For patients screened using a blood assay: obtain tissue-based testing result confirming study eligibility (within first 4 weeks after enrollment).

[e] Full dermatologic examination for squamous carcinoma/other suspicious lesions, including, if per standard practice, an examination of the anal and pelvic areas. Lesions suspicious for squamous cell carcinoma should be treated appropriately.

[f] To be performed by the treating physician to monitor for developing squamous cancers.

[g] ECG and electrolytes, including potassium, magnesium, and calcium, should be monitored before treatment with vemurafenib and after dose modification. Monitoring of ECGs should occur on Day 1 of Cycles 1, 2, 3, 7, and every 3 cycles thereafter, or more often as clinically indicated. **Patients with baseline QTc > 450 ms are not eligible for this study.** If during treatment the QTc exceeds 500 ms (CTCAE Grade 3), vemurafenib treatment should be temporarily interrupted, electrolyte abnormalities should be corrected, and cardiac risk factors for QT prolongation (e.g., congestive heart failure, bradyarrhythmias) should be controlled. Re-initiation of treatment should occur at a lower dose once the QTc decreases below 500 ms.

[h] To be conducted/collected within 30 days of cobimetinib discontinuation. CPK, LVEF, and the ophthalmologic examination do not need to be repeated when vemurafenib is subsequently discontinued.

[i] Only significant AEs, defined as SAEs, AEs leading to treatment modification (e.g., dose reduction, dose delay, treatment discontinuation), or protocol-defined AEs of special interest (see protocol Section 5.2.3) occurring from the first treatment until 30 days after the last dose of study treatment will be captured in the eCRF.

[j] Study drug compliance will be reviewed with the patient.

[k] CMP will include measurements of glucose, BUN, creatinine, sodium, potassium, magnesium, chloride, calcium, CO_2, alkaline phosphatase, AST (SGOT), ALT (SGPT), total bilirubin, total protein, and albumin.

[l] For women of childbearing potential, including women who have had a tubal ligation, a serum pregnancy test will be performed ≤ 7 days prior to first dose of trial treatment.

[m] If additional molecular profiling is done at the site while the patient is on study, the results may be reported in the eCRF.

[n] Archival tissue, if available and with specific consent, will be requested and collected for future correlative research studies. The sample can be provided during or after screening while the patient is on study.

[o] Only if clinically indicated.

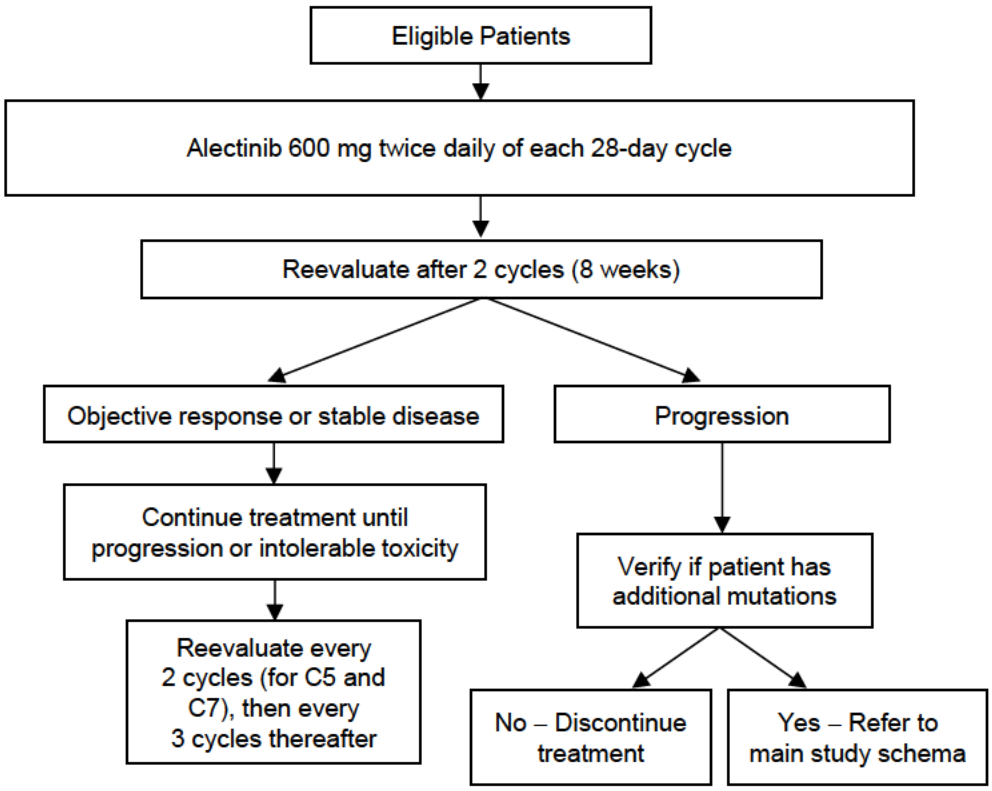
[p] Performed within 7 days prior to the next cycle, with results available for review before Day 1 of the next cycle.

[q] Only scans (chest, abdomen, and/or pelvis) that were abnormal at baseline need to be repeated. For patients who come off study treatment without PD, tumor assessments are required at the end-of-treatment visit, only if not obtained within the past 3 cycles.

[r] Only if abnormal at baseline and if necessary to determine response to treatment.
[s] Required for patient with a history of treated brain metastases. Otherwise, repeat only if clinically indicated.
[t] Only if abnormal at baseline.
[u] If cobimetinib is discontinued, treatment with vemurafenib can continue.

5.7 Appendix G - Assessment and Flowchart: Alectinib in Patients with ALK Alterations

Study Schema: Alectinib



C=cycle.

Screening and Pretreatment Assessments

- Written informed consent form prior to any other trial-related procedures
- Review of molecular profiling report and confirmation of ALK alterations as outlined in Appendix 5 of the protocol (should occur prior to obtaining other study-specific assessments). For patients screened using a blood assay: obtain tissue-based testing result confirming study eligibility (within first 4 weeks after enrollment).
- Medical history
- ECOG PS
- Blood Pressure and Heart Rate
- ECG
- CBC, including 3-part differential and platelets
- CMP
- CPK
- Serum pregnancy test (must be performed within 7 days of Cycle 1, Day 1)
- Collection of archival tumor tissue, optional
- Tumor markers (only if clinically indicated)
- CT scans of the chest, abdomen, and pelvis

- PET scans or bone scan (only if clinically indicated)
- CT or MRI of brain (all patients with history of treated brain metastases; otherwise, only if clinically indicated)

Patients who have disease progression on one study treatment regimen and are eligible for another study treatment regimen must be re-consented and re-screened for the new study treatment and must be registered as a new patient via the interactive web response system (IWRS) prior to initiation of the new study treatment. In these cases, results of assessments done at treatment completion may be used as screening assessments for the subsequent study treatment. These tests do not have to be repeated if the timeframe is as required for screening.

Assessments during Treatment
Patients will visit the study center once every 4 weeks (± 72 hours) during the first three cycles of treatment (i.e., on Day 1 of Cycles 1, 2, and 3). The initial reevaluation will occur after 8 weeks of treatment (Cycle 3, Day 1). For patients who remain on treatment (i.e., responding or stable) and who are doing well on Cycle 7, Day 1, subsequent visits will be every 12 weeks, with reevaluations at these intervals. Assessments to be performed at each visit are as follows:

a. Day 1 of Cycle 1
- Plasma biomarker collection

b. Day 1 of Cycles 1, 2, and 3
- Adverse event (AE) evaluation
  - Only significant AEs, defined as serious AEs (SAEs), AEs leading to treatment modification (e.g., dose reduction, dose delay, treatment discontinuation), or protocol-defined AEs of special interest (see protocol Section 5.2.3) will be captured in the electronic Case Report Form (eCRF).
- Review study drug compliance with patient
- CBC, including 3-part differential and platelets
- CMP every 2 weeks for 3 months (Cycles 1–3) and as clinically indicated
- CPK every 2 weeks for first month (Cycle 1), then Day 1 of Cycles 2 and 3
- ECG (Cycle 1 and Cycle 3)
- Blood pressure and heart rate

c. Day 1 of Cycle 3
- Plasma biomarker collection
- Tumor markers (only if clinically indicated)
- Response assessment – CT scans of chest, abdomen, and pelvis (repeat only scans that were abnormal at baseline)

d. Day 1 of Cycle 5
- AE evaluation
  - Only significant AEs, defined as serious AEs (SAEs), AEs leading to treatment modification (e.g., dose reduction, dose delay, treatment discontinuation), or other protocol-defined AEs of special interest (see protocol Section 5.2.3) will be captured in the eCRF.
- Tumor markers (only if clinically indicated)
- Response assessment − CT scans of chest, abdomen, and pelvis (repeat only scans that were abnormal at baseline)
- Review study drug compliance with patient
- CMP
- CPK
- ECG
- Blood pressure and heart rate

e. Day 1 of Cycle 7 and Every Three Cycles Thereafter

- AE evaluation
  - Only significant AEs, defined as SAEs, AEs leading to treatment modification (e.g., dose reduction, dose delay, treatment discontinuation), or other protocol-defined AEs of special interest (see protocol Section 5.2.3) will be captured in the eCRF.
- Review study drug compliance with patient
- CBC, including 3-part differential and platelets
- CMP
- CPK
- Tumor markers (only if clinically indicated)
- ECG (Day 1 of Cycle 7 only)
- Blood pressure and heart rate
- CT scans of the chest, abdomen, and/or pelvis (repeat only scans that were abnormal at baseline)
- PET scans or bone scan (only if abnormal at baseline and necessary to determine response to treatment)
- CT or MRI of brain (only if abnormal at baseline)

End of Treatment

At the end of treatment, a safety follow-up visit will occur within 30 days from discontinuation of alectinib. The following assessments will be conducted at the visit:

- Plasma biomarker collection
- AE evaluation
  - Only significant AEs, defined as SAEs, AEs leading to treatment discontinuation, or protocol-defined AEs of special interest (see protocol Section 5.2.3) will be captured in the eCRF.
- Review study drug compliance with patient
- CBC, including 3-part differential and platelets
- CMP
- CPK
- Tumor markers (only if clinically indicated)
- CT scans of the chest, abdomen, and/or pelvis (repeat only scans that were abnormal at baseline)
  - For patients who come off study treatment without progressive disease (PD), tumor assessments are required at the end-of-treatment visit, only if not obtained within the past 3 cycles.
- At disease progression, an optional FFPE tissue sample may be submitted for exploratory research, if available.

If the patient's worsening disease combined with travel distance makes the safety follow up visit too difficult, follow-up with the patient may take place by telephone to include an assessment of AEs. Alternatively, the patient's local physician may be contacted to collect AE data and any standard of care laboratory and CT data, if performed.

Follow-Up Assessments

Please refer to the main body of the protocol for the follow-up assessments.

PATIENT DISCONTINUATION

Please refer to Section 4.6 in the main body of the protocol for patient discontinuation descriptions.

Alectinib Study Flowchart

Assessments	Pre-Treatment	Trial Treatment			End of Treatment Safety Follow-Up [b]	Follow-Up	
			Reassessments				
	Screening [a]	Cycles 1, 2, and 3, Day 1 (±3 Days)	Cycles 3 and 5, Day 1 (±3 Days)	Cycle 7, Day 1 (and Every 3 Cycles After) (±3 Days)		Every 3 Months After End of Treatment (Prior to Progression) [c] (±14 Days)	Survival [d] (±14 Days)
Tests and Observations							
Informed consent [e]	x						
Obtain/review molecular profiling report/ pathology report [f]	x						
Medical history	x						
ECOG PS	x						
Blood pressure and heart rate	x	x	x	x			
ECG	x	x [g] [Day 1 of Cycles 1 and 3 only]	x [g]	x [g] (Day 1 of Cycle 7 only)			
Adverse event evaluation (all cycles) [h]		x	x	x	x		
Study drug compliance review [i]		x	x	x	x		
Survival status							x

Genentech
A Member of the Roche Group

Data Analysis Plan Module 1 Template

Assessments	Pre-Treatment	Trial Treatment			End of Treatment Safety Follow-Up [b]	Follow-Up	
			Reassessments			Every 3 Months After End of Treatment (Prior to Progression) [c] (±14 Days)	Survival [d] (±14 Days)
	Screening [a]	Cycles 1, 2, and 3, Day 1 (±3 Days)	Cycles 3 and 5, Day 1 (±3 Days)	Cycle 7, Day 1 (and Every 3 Cycles After) (±3 Days)			
Laboratory evaluations							
CBC, 3-part differential, and platelets	x	x		x	x		
CMP [j]	x	x (every 2 weeks for the first 3 months [Cycle 1–Cycle 3])	x	x	x		
CPK	x	x (every 2 weeks for first month [Cycle 1], then Day 1 of Cycles 2 and 3)	x	x	x		
Plasma biomarkers		x [Day 1 of Cycle 1 only]	x [Day 1 of Cycle 3 only]		x		
Pregnancy test [k]	x						
Molecular profiling results [l]		x					

Genentech
A Member of the Roche Group

Data Analysis Plan Module 1 Template

Assessments	Pre-Treatment	Trial Treatment			End of Treatment Safety Follow-Up [b]	Follow-Up	
			Reassessments			Every 3 Months After End of Treatment (Prior to Progression) [c]	
	Screening [a]	Cycles 1, 2, and 3, Day 1 (±3 Days)	Cycles 3 and 5, Day 1 (±3 Days)	Cycle 7, Day 1 (and Every 3 Cycles After) (±3 Days)		(±14 Days)	Survival [d] (±14 Days)
Archival tumor sample, optional	x [m]				x [m]		
Staging							
Tumor markers [n]	x		x	x	X	x	
CT scan of chest, abdomen, and pelvis [o]	x		x [p]	x [p]	x [p]	x	
PET scan or bone scan [o]	x [n]			x [q]			
Head CT or MRI scan [o]	x [r]			x [s]			
Treatment							
Alectinib (all cycles)		x	x	x			

CBC = complete blood count; CMP = comprehensive metabolic profile; CT = computerized tomography; ECG = electrocardiogram; ECOG PS = Eastern Cooperative Oncology Group Performance Status; MRI = magnetic resonance imaging; PET = positron emission tomography.

[a] The medical history, ECOG PS, CBC, CMP, and ECG should be done ≤21 days prior to initiation of treatment. However, if the CBC and CMP are obtained within 72 hours of Cycle 1, Day 1 they do not have to be repeated on Day 1. Scans to document measurable or evaluable disease (i.e., tumor measurement) should be performed ≤4 weeks prior to initiation of treatment.

[b] After treatment is discontinued, patients will visit the study center within 30 days after the last dose of study treatment for end-of-treatment safety follow-up assessments. All patients will be followed until treatment-related toxicities resolve or for at least 30 days post-study drug discontinuation. If the patient's worsening diseases combined with travel distance makes this visit too difficult, follow-up with the patient may take place by telephone to include an assessment of AEs. Alternatively, the patient's local physician may be contacted to collect AE data and any standard of care laboratory and CT data, if performed. For patients who come off study treatment without PD, tumor assessments are required at the end-of-treatment visit, only if not obtained within the past 3 cycles.

[c] Patients completing treatment with no evidence of disease progression will be followed every 3 months until disease progression. The patient's physician will be contacted to collect follow-up information. This information will only include the assessments listed above if they are being performed as part of the patient's standard of care.

[d] Patients who discontinue study treatment regardless of reason for discontinuation will be followed for survival every 3 months until death, lost to follow-up, withdrawal of consent, or study termination by the Sponsor, whichever comes first. Patients may be contacted during outpatient visits or by telephone if unable to come to the study center.

[e] Informed consent must be obtained prior to performing any trial-related screening assessments.

[f] Confirmation of ALK alterations (see protocol Appendix 5) should occur prior to performing other trial-related assessments. For patients screened using a blood assay: obtain tissue-based testing result confirming study eligibility (within first 4 weeks after enrollment).

[g] Cycle 1 Day 1, Cycle 3 Day 1, Cycle 5 Day 1 and Cycle 7 Day 1.

[h] Only significant AEs, defined as SAEs, AEs leading to treatment modification (e.g., dose reduction, dose delay, treatment discontinuation), or protocol-defined AEs of special interest (see protocol Section 5.2.3) occurring from the first treatment until 30 days after the last dose of study treatment will be captured in the eCRF.

[i] Study drug compliance will be reviewed with the patient.

[j] CMP will include measurements of glucose, BUN, creatinine, sodium, potassium, chloride, calcium, CO_2, alkaline phosphatase, AST (SGOT), ALT (SGPT), total bilirubin, total protein, and albumin.

[k] For women of childbearing potential, including women who have had a tubal ligation, a serum pregnancy test will be performed $\leq$ 7 days prior to first dose of trial treatment.

[l] If additional molecular profiling is done at the site while the patient is on study, the results may be reported in the eCRF.

[m] Archival tissue will be requested and collected for future correlative research studies, if available and with specific consent. The sample can be provided during or after screening while the patient is on study. An optional tissue sample collected at end of treatment / disease progression can be submitted, if available.

[n] Only if clinically indicated.

[o] Performed within 7 days prior to the next cycle, with results available for review before Day 1 of the next cycle.

[p] Only scans (chest, abdomen, and/or pelvis) that were abnormal at baseline need to be repeated. For patients who come off study treatment without PD, tumor assessments are required at the end-of-treatment visit, only if not obtained within the past 3 cycles.

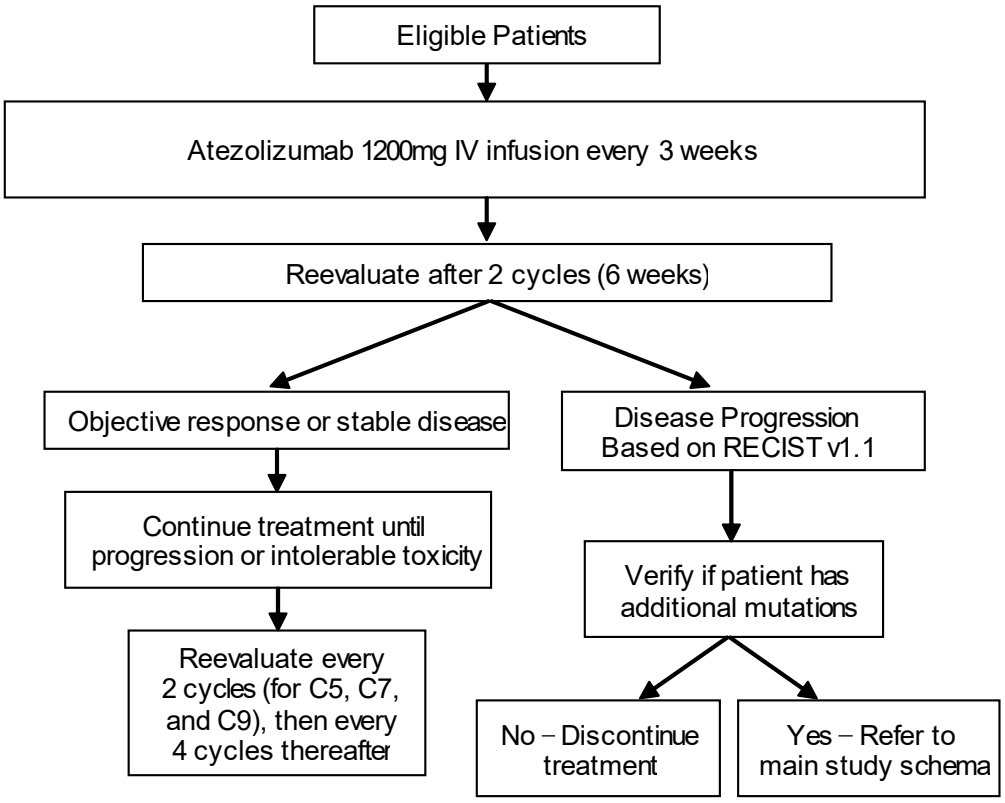
[q] Only if abnormal at baseline and if necessary to determine response to treatment.

[r] Required for patients with a history of treated brain metastases. Otherwise, repeat only if clinically indicated.

[s] Only if abnormal at baseline.

5.8 Appendix H - Atezolizumab for Patients with Cancers Characterized by PD L1 Copy Number Gain, Deficiency in Mismatch Repair Enzymes, High Levels of Microsatellite Instability, and High Tumor Mutational Burden and/or Alterations of DNA Proofreading/Repair Genes

Study Schema: Atezolizumab



C = cycle. RECIST v1.1 = Response Evaluation Criteria in Solid Tumors v1.1.

Note: At the discretion of the treating physician and after approval from the Medical Monitor, treatment with atezolizumab may be continued beyond progression if the anticipated clinical benefit outweighs the risk.

Screening and Pretreatment Assessments

- Written informed consent form prior to any other trial-related procedures
- Review of molecular profiling report and confirmation of elevated tTMB (should occur prior to obtaining other study-specific assessments)
- Medical history
- Vital signs
- ECOG PS (must be performed within 21 days of Cycle 1, Day 1). Confirmation of ECOG PS must be entered into the IWRS at the time of enrollment.
- ECG

- Hematology: WBC count, RBC count, hemoglobin, hematocrit, platelet count, differential count (neutrophils, eosinophils, basophils, monocytes, lymphocytes, other cells)
- Chemistry panel (serum or plasma): sodium, potassium, magnesium, chloride, bicarbonate, glucose, BUN or urea, creatinine, total protein, albumin, phosphorus, calcium, total bilirubin, alkaline phosphatase, ALT, AST, LDH.
- Coagulation: INR, aPTT
- Thyroid function testing: thyroid-stimulating hormone, free triiodothyronine (T3) (or total T3 for sites where free T3 is not performed), free thyroxine (also known as T4)
- HIV serology
- HBV serology: HBsAg, hepatitis B surface antibody (HBsAb), and total HBcAb
  - If a patient has a negative HBsAg result and a positive total HBcAb result, an HBV DNA test must also be performed to determine if the patient has an HBV infection.
- HCV serology: HCV antibody and (if HCV antibody test is positive) HCV RNA
  - If a patient has a positive HCV antibody test at screening, an HCV RNA test must also be performed to determine if the patient has an active HCV infection
- Serum pregnancy test (must be performed within 7 days of Cycle 1, Day 1)
- Urinalysis
- Confirm availability of an archival or new pretreatment tissue sample (refer to protocol Section A11-4.5.1.2.1)
- Tumor markers (only if clinically indicated)
- CT scans of the chest, abdomen, and pelvis
- Positron emission tomography (PET) scans or bone scan (only if clinically indicated)
- CT or MRI of brain (all patients with history of treated brain metastases; otherwise, only if clinically indicated)

Patients who have disease progression on one study treatment regimen and are eligible for another study treatment regimen must be re-consented and re-screened for the new study treatment and must be registered as a new patient via the interactive web response system (IWRS) prior to initiation of the new study treatment. In these cases, results of assessments done at treatment completion may be used as screening assessments for the subsequent study treatment. These tests do not have to be repeated if the timeframe is as required for screening.

Assessments during Treatment
Patients will visit the study center once every 3 weeks on the day of each scheduled treatment (± 72 hours). Protocol treatments will continue until tumor progression or intolerable toxicity occurs. The following assessments will be performed:

a. Day 1 of Every Cycle
- Vital signs
- ECOG status
- ECG, if clinically indicated
- Hematology
- Chemistry
- Urinalysis (only if clinically indicated)
- Adverse event (AE) evaluation (see Atezolizumab Study Flowchart for details)
- Concomitant medication evaluation (only collected for patients enrolled under Version 6 of the protocol and later)

b. Day 1 of Cycle 1
- Plasma/serum biomarker collection (pre-dose)
- Thyroid function testing
- Whole blood sample collection (normal germline DNA control; only collected for patients enrolled under Version 6 of the protocol and later) (pre-dose)

- Serum sample collection for PK and ADA analyses (pre-dose; only collected for patients enrolled under Version 6 of the protocol and later)
- Serum sample for CRP assessment (pre-dose; only collected for patients enrolled under Version 6 of the protocol and later)

c. Day 1 of Cycle 2
- Optional tissue sample collection (FFPE) for future exploratory analysis (see protocol Section A11-4.5.1.2.1 for tissue requirements)
- Serum sample collection for PK and ADA analyses (pre-dose; only collected for patients enrolled under Version 6 of the protocol and later)

d. Day 1 of Cycle 3
- Plasma/serum biomarker collection (pre-dose)
- Serum sample collection for PK and ADA analyses (pre-dose; only collected for patients enrolled under Version 6 of the protocol and later)
- Serum sample for CRP assessment (pre-dose; only collected for patients enrolled under Version 6 of the protocol and later)

e. Day 1 of Cycles 3 and 5
- Tumor markers (only if clinically indicated)
- Response assessment - CT scans of chest, abdomen, and/or pelvis (repeat only scans that were abnormal at baseline). For patients enrolled under Version 6 of the protocol or later, scans for response assessment must be submitted for IRC review.

f. Day 1 of Cycle 4
- Serum sample collection for PK and ADA analyses (pre-dose; only collected for patients enrolled under Version 6 of the protocol and later)

g. Day 1 of Cycle 4 and Every Three Cycles Thereafter
- Thyroid function testing
- Urine or serum pregnancy test - any positive urine pregnancy test must be confirmed by a serum pregnancy test. During the treatment period, pregnancy test results must be available prior to administration of study drug. Patients who have a positive pregnancy test may not receive study drug.

h. Day 1 of Cycle 7
- Tumor markers (only if clinically indicated)
- Response assessment - CT scans of chest, abdomen, and/or pelvis (repeat only scans that were abnormal at baseline), or MRI as clinically indicated.
- PET scan or bone scan (only if abnormal at baseline and necessary to document response to treatment)
- CT scan or MRI of brain (only if abnormal at baseline)

i. Day 1 of Cycle 8
- Serum sample collection for PK and ADA analyses (pre-dose; only collected for patients enrolled under Version 6 of the protocol and later)

j. Day 1 of Cycle 12
- Serum sample collection for PK and ADA analyses (pre-dose; only collected for patients enrolled under Version 6 of the protocol and later)

k. Day 1 of Cycle 13 and Every Six Cycles Thereafter (or sooner if clinically indicated)
- Tumor markers (only if clinically indicated)

- Response assessment - CT scans of chest, abdomen, and/or pelvis (repeat only scans that were abnormal at baseline)
- PET scan or bone scan (only if abnormal at baseline and necessary to document response to treatment)
- CT scan or MRI of brain (only if abnormal at baseline)

I. Day 1 of Cycle 16

- Serum sample collection for PK and ADA analyses (pre-dose; only collected for patients enrolled under Version 6 of the protocol and later)

End of Treatment

At the end of treatment, a safety follow-up visit will occur within 30 days from discontinuation of atezolizumab. The following assessments will be conducted at the follow-up visit:

- Vital signs
- ECOG status
- Hematology
- Chemistry
- Coagulation
- Thyroid function testing
- Plasma biomarker collection
- Serum sample collection for PK and ADA analyses (only collected for patients enrolled under Version 6 of the protocol and later)
- Serum sample for CRP assessment (only collected for patients enrolled under Version 6 of the protocol and later)
- AE evaluation (see Atezolizumab Study Flowchart for details)
- Concomitant medication evaluation (only collected for patients enrolled under Version 6 of the protocol and later)
- Urine or serum pregnancy test - Any positive urine pregnancy test must be confirmed by a serum pregnancy test.
- Optional tissue sample collection (FFPE) for future exploratory analysis (see protocol Section A11-4.5.1.2.1 for tissue requirements)
- Response assessment - CT scans of chest, abdomen, and/or pelvis (only scans that were abnormal at baseline).
  - For patients who come off study treatment without progressive disease (PD), tumor assessments are required at the end-of-treatment visit, only if not obtained within the past 6 cycles.

If the patient's worsening disease combined with travel distance makes the safety follow up visit too difficult, follow-up with the patient may take place by telephone to include an assessment of AEs and concomitant medications. Alternatively, the patient's local physician may be contacted to collect AE data, concomitant medications and any standard of care laboratory and CT data, if performed.

PATIENT DISCONTINUATION

Please refer to Section 4.6 in the main body of the protocol for patient discontinuation descriptions.

Atezolizumab Study Flowchart

Assessments	Pre-Treatment	Trial Treatment					End of Treatment Safety Follow-Up [c]
		All Cycles	Reassessments				
	Screening [a]	Day 1 (±3 Days)	Cycles 3 and 5, Day 1 (±3 Days)	C4, D1 (and Every 3 Cycles After) (±3 Days)	Cycle 7, Day 1 (±3 Days)	C13, D1 (and Every 6 Cycles After, or as clinically indicated)[b] (±3 Days)	
Tests and Observations							
Informed consent	x						
Obtain/review molecular profiling report/ pathology report [d]	x						
Medical history	x						
Vital signs [e]	x	x					x
ECOG PS	x (within 21 days of C1D1)	x					x
ECG [f]	x	x					
Adverse event and concomitant medication evaluation [g]	x	x					x

Genentech
A Member of the Roche Group

Data Analysis Plan Module 1 Template

Assessments	Pre-Treatment	Trial Treatment					End of Treatment Safety Follow-Up [c]
		All Cycles	Reassessments				
	Screening [a]	Day 1 (±3 Days)	Cycles 3 and 5, Day 1 (±3 Days)	C4, D1 (and Every 3 Cycles After) (±3 Days)	Cycle 7, Day 1 (±3 Days)	C13, D1 (and Every 6 Cycles After, or as clinically indicated)[b] (±3 Days)	
Laboratory Evaluations							
Hematology [h]	x [i]	x [j]					x
Chemistry panel [k]	x [i]	x [j]					x
Coagulation (INR, aPTT)	x [i]						x
Thyroid function [l]	x [i]	x [C1 only]		x			x
Viral serology [m]	x [i]						
Urinalysis [n]	x [i]	x [o]					
Plasma/serum biomarkers		x [C1 only]	x [C3 only]				x
Serum CRP sample [p]		x [C1 and C3 only]					x
Whole blood sample (normal control DNA) [q]		x [C1 only]					
Pregnancy test [r]	x			x			x
Molecular profiling results [s]		x					

Genentech
A Member of the Roche Group

Data Analysis Plan Module 1 Template

Assessments	Pre-Treatment	Trial Treatment					End of Treatment Safety Follow-Up [c]
		All Cycles	Reassessments				
	Screening [a]	Day 1 (±3 Days)	Cycles 3 and 5, Day 1 (±3 Days)	C4, D1 (and Every 3 Cycles After) (±3 Days)	Cycle 7, Day 1 (±3 Days)	C13, D1 (and Every 6 Cycles After, or as clinically indicated)[b] (±3 Days)	
Laboratory Evaluations (cont).							
Archival tumor sample or new pre-treatment biopsy [t]	x [t]						
Optional new tissue biopsy [u]	x [v]	C2 only					x
Serum PK sample [p]		x [Cycles 1,2,3,4,8, 12,16 only]					x
Serum ADA sample [p]		x [Cycles 1,2,3,4,8, 12,16 only]					x
Staging							
Tumor markers [u]	x		x		x	x	
CT scan of chest, abdomen, pelvis	x [w]		x [x]		x [x]	x [x]	x [x]
PET scan or bone scan	x [u]				x [y]	x [y]	
Head CT or MRI scan	x [z]				x [aa]	x [aa]	
Treatment							
Atezolizumab [bb]		x					

ADA = anti-drug antibody; C = cycle; CRP = C-reactive protein; CT = computerized tomography; D = day; ECOG PS = Eastern Cooperative Oncology Group Performance Status; IRC = independent review committee; MRI = magnetic resonance imaging; HBcAb = hepatitis B core antibody; HBsAb = hepatitis B surface antibody; HBsAg = hepatitis B surface antigen; HBV = hepatitis B virus ; HCV = hepatitis C virus; PET = positron emission tomography; PK = pharmacokinetics.

[a] The medical history, physical examination, vital signs, weight, ECOG PS, Hematology and Chemistry panels should be done $\leq$ 21 days prior to initiation of treatment. However, if the Hematology and Chemistry panels are performed within 72 hours of Cycle 1, Day 1 they do not have to be repeated on Day 1. Scans to document measurable or evaluable disease (i.e., tumor measurement) should be performed $\leq$ 4 weeks prior to initiation of treatment.

[b] Assessments should be done every 6 cycles, or sooner if clinically indicated.

[c] After treatment is discontinued, patients will visit the study center within 30 days after the last dose of study treatment for end-of-treatment safety follow-up assessments. All patients will be followed until treatment-related toxicities resolve or for at least 30 days post-study drug discontinuation. If the patient's worsening diseases combined with travel distance makes this visit too difficult, follow-up with the patient may take place by telephone to include an assessment of AEs. Alternatively, the patient's local physician may be contacted to collect AE data and any standard of care laboratory and CT data, if performed. For patients who come off study treatment without PD, tumor assessments are required at the end-of-treatment visit, only if not obtained within the past 6 cycles.

[d] Confirmation of eligible genetic alterations (see protocol Appendix 5) should occur prior to performing other trial-related assessments.

[e] Includes respiratory rate, pulse rate, and systolic and diastolic blood pressure while the patient is in a seated position, and temperature. 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. For the first infusion, vital signs should be measured within 60 minutes prior to the infusion and, if clinically indicated, every 15 ($\pm$5) minutes during and 30 ($\pm$10) minutes after the infusion. For subsequent infusions, vital signs should be measured within 60 minutes prior to the infusion and, if clinically indicated or if symptoms occurred during the previous infusion, during and 30 ($\pm$10) minutes after the infusion.

[f] ECG recordings will be obtained during screening and as clinically indicated at other timepoints. Patients should be resting in a supine position for at least 10 minutes prior to ECG recording.

[g] For patients enrolled under Version 6 of the protocol or later, after informed consent has been obtained but prior to initiation of study treatment, only serious adverse events caused by a protocol-mandated intervention should be reported in the eCRF. After initiation of study treatment, all adverse events will be reported until 30 days after the last dose of study treatment or until initiation of new systemic anti-cancer therapy, whichever occurs first, and serious adverse events and adverse events of special interest will continue to be reported until 90 days after the last dose of study treatment or until initiation of new systemic anti-cancer therapy, whichever occurs first. For patients enrolled prior to Version 6 of the protocol, adverse events (see protocol Section 5.2.1), protocol-defined events of special interest (see protocol Section 5.2.3), and serious adverse events (except those unequivocally related to disease progression), will be collected until 30 days following the last administration of study treatment or study discontinuation/termination, whichever is later. After this period, all deaths, regardless of cause, should be reported. In addition, the Sponsor should be notified if the investigator becomes aware of any serious adverse event that is believed to be related to prior exposure to study treatment (see protocol Section 5.6). The investigator should follow each adverse event until the event has resolved to baseline grade or better, the event is assessed as stable by the

investigator, the patient is lost to follow-up, or the patient withdraws consent. Every effort should be made to follow all serious adverse events considered to be related to study treatment or trial-related procedures until a final outcome can be reported. Concomitant medications should only be collected for patients enrolled under Version 6 of the protocol and later, and should be reported from ≤ 7 days prior to the first dose of study drug to the end-of-treatment visit and reported in the eCRF.

[h] Hematology includes WBC count, RBC count, hemoglobin, hematocrit, platelet count, differential count (neutrophils, eosinophils, basophils, monocytes, lymphocytes, other cells).

[i] Screening laboratory test results must be obtained within 21 days prior to initiation of study treatment.

[j] If Hematology and Chemistry panels are performed within 72 hours prior to Day 1 of Cycle 1, they do not have to be repeated.

[k] Chemistry panel (serum or plasma) includes sodium, potassium, magnesium, chloride, bicarbonate, glucose, BUN or urea, creatinine, total protein, albumin, phosphorus, calcium, total bilirubin, alkaline phosphatase, ALT, AST, LDH.

[l] TSH, free T3 (or total T3 for sites where free T3 is not performed), and free T4 will be assessed on Day 1 of Cycle 1 and every third cycle thereafter.

[m] At screening, patients will be tested for HIV, HBsAg, HBsAb, total HBcAb, and HCV antibody. If a patient has a negative HBsAg test and a positive total HBcAb test at screening, an HBV DNA test must also be performed to determine if the patient has an HBV infection. If a patient has a positive HCV antibody test at screening, an HCV RNA test must also be performed to determine if the patient has an active HCV infection.

[n] Includes pH, specific gravity, glucose, protein, ketones, and blood; dipstick permitted.

[o] Urinalysis should be performed as clinically indicated during study treatment.

[p] Serum samples should only be collected from patients enrolled under Version 6 of the protocol or later. On days the patient receives study treatment, samples should be collected pre-dose.

[q] Sample collection is only required for patients enrolled under Version 6 of the protocol or later,

[r] All women of childbearing potential (including those who have had a tubal ligation) will have a serum pregnancy test at screening, within 7 days before the first dose of study drug. Urine or serum pregnancy tests may be performed at subsequent visits, as indicated in the schedule of assessments. Any positive urine pregnancy test must be confirmed by a serum pregnancy test. During the treatment period, pregnancy test results must be available prior to administration of study drug. Patients who have a positive pregnancy test may not receive study drug.

[s] If additional molecular profiling is done at the site while the patient is on study, the results may be reported in the eCRF.

[t] For patients receiving atezolizumab where molecular testing was not performed using FoundationOne or FoundationOne CDx, submission of an archival or new pretreatment tissue sample is mandatory. For patients receiving atezolizumab where molecular testing was performed using FoundationOne or FoundationOne CDx, submission of an archival or new pretreatment tissue sample is required, if available. The tissue sample must be submitted within 4 weeks after enrollment (refer to protocol Section A11-4.5.1.2.1 for tissue requirements).

[u] Only if clinically indicated.

[v] A new pre-treatment tissue biopsy is highly encouraged, but not required, for all patients with molecular profile data obtained from biopsies that were collected more than 6 months prior to enrollment.

[w] All measurable and evaluable lesions should be assessed and documented at screening. Tumor assessments performed as standard of care prior to obtaining informed consent and within 28 days prior to initiation of study treatment do not have to be repeated at screening. Screening assessments must include CT scans (with oral or IV contrast) or MRI scans of the chest, abdomen, pelvis, and head. A spiral CT scan of the chest may be obtained but is not a requirement. If a CT scan with contrast is contraindicated (i.e., in patients with contrast allergy or impaired renal clearance), a non-contrast CT scan of the chest may be performed and MRI scans of the abdomen, pelvis, and head should be performed. An MRI scan of the head is required to confirm or refute the diagnosis of CNS metastases at baseline in the event of an equivocal CT scan. Bone scans and CT scans of the neck should also be performed if clinically indicated. At the investigator's discretion, other methods of assessment of measurable disease as per RECIST v1.1 may be used.

[x] Only scans (chest, abdomen, and/or pelvis) that were abnormal at baseline need to be repeated. For patients who come off study treatment without PD, tumor assessments are required at the end-of-treatment visit, only if not obtained within the past 6 cycles. .

[y] Only if abnormal at baseline and if necessary to determine response to treatment.

[z] Required for patients with a history of treated brain metastases. Otherwise, repeat only if clinically indicated.

[aa] Only if abnormal at baseline.

[bb] The initial dose of atezolizumab will be delivered over 60 (±15) minutes. Subsequent infusions will be delivered over 30 (±10) minutes if the previous infusion was tolerated without infusion-associated adverse events, or 60 (±15) minutes if the patient experienced an infusion-associated adverse event with the previous infusion.

5.9 Appendix I - Summary of Laboratory Parameters and Standardized Normal from JAMA

Lab Type	Parameter	Standard Units	Standard Reference Range
Hematology	Hemoglobin	g/L	140-175
	Hematocrit	fraction	0.41-0.50
	Platelet	10^9/L	150-350
	WBC	10^9/L	4.5-11.0
	Lymphocytes	10^9/L	1-4.8
	Monocytes	10^9/L	0-0.8
	Granulocytes*	10^9/L	
	ANC	10^9/L	1.8-7.8
Blood Chemistry	Albumin	g/L	35-50
	Amylase	U/L	27-131
	BUN	mmol/L	2.9-8.2
	Calcium	mmol/L	2.05-2.55
	Chloride	mmol/L	96-106
	CO_2	mmol/L	22-28
	Glucose	mmol/L	3.9-6.1
	LDH	U/L	100-200
	Magnesium	mmol/L	0.65-1.05
	Phosphorus	mmol/L	0.74-1.52
	Potassium	mmol/L	3.5-5.0
	Serum Creatinine	umol/L	53-106
	Sodium	mmol/L	136-142
	Total Protein	g/L	60-80
	Triacylglycerol Lipase*	U/L	
Liver Function Tests	ALT(SGPT)	U/L	10-40
	AST(SGOT)	U/L	10-30
	Alkaline phosphatase	U/L	30-120
	Total Bilirubin	umol/L	5-21

* not available in JAMA

From Iverson C, Christiansen S, Flanagin A, et al. AMA Manual of Style: A Guide for Authors and Editors. 10th ed. New York, NY: Oxford University Press; 2007

5.10 Appendix J - Statistical Methods Requiring Input

A total of approximately 500 patients are planned to be enrolled. It is anticipated that the efficacy of these targeted agents will vary depending on tumor-pathway cohorts. Interim analyses (Simon's two-stage design) will be utilized to identify tumor-pathway cohorts in which treatment is ineffective (i.e., futility analysis), either due to lack of efficacy or safety considerations. Enrollment to the various tumor-pathway cohorts can be expanded or stopped based on interim analyses in collaboration with the Study Steering Committee (SSC).

The Simon two-stage design criteria (type-1 error rate =10%, power=80%) will be developed for individual tumor types based on historical information and will be developed as tumor-pathway cohorts being to enroll.

The following design criteria have been set for Colorectal cancer (CRC) and Non-small cell lung cancer (NSCLC) tumor types:

For CRC tumor cohorts (across four pathways) the criteria for guiding expansion decisions are:

If 2 or more responses are observed among an initial N=13 patients (stage 1) with evaluable response data then N=34 patients can be enrolled (additional 21 patients in Stage 2). If 6 or more responses are observed (among N=34) then this can be considered evidence of activity. These criteria are based on considering an ORR of 10% to be "low activity" and an ORR of 25% to be "high activity".

For NSCLC tumor cohorts (across four pathways) the criteria for guiding expansion decisions are:

If 1 or more responses are observed among an initial N=12 patients (stage 1) with evaluable response data then N=21 patients can be enrolled (additional 9 patients in Stage 2). If 3 or more responses are observed (among N=21) then this can be considered evidence of activity. These criteria are based on considering an ORR of 5% to be "low activity" and an ORR of 20% to be "high activity".

These criteria will guide decision criteria in collaboration with the SSC where the totality of available data will also be considered (e.g., Safety, PFS, and OS).

5.11 Appendix K - Programming Codes for Statistical Analysis

- Programming of the tables, listings and figures will be performed using SAS Version 9.4 or later, running under Windows 10 environment. The following table presents the SAS code for the efficacy analysis.

Endpoint	Test	SAS Code
Response rates (ORR and DCR)	70% and 95% Clopper-Pearson confidence interval for the proportion calculated using the exact binomial method	Proc freq data=orr order=data; Table rs/nocom binomial (exact) alpha = 0.05; Run; Proc freq data=orr order=data; Table rs/nocom binomial (exact) alpha = 0.30; Run;
PFS, OS, DoR	Kaplan-Meier method and 95% confidence interval for median calculated using the complementary log-log transformation	Proc lifetest data=xx; TIME time*censor(0); Survival conftype=LOGLOG; Run; Note: 0=censored; 1=event.