Official Title: **A PHASE II SINGLE-ARM STUDY OF ATEZOLIZUMAB MONOTHERAPY IN LOCALLY ADVANCED OR METASTATIC NON-SMALL CELL LUNG CANCER: CLINICAL EVALUATION OF NOVEL BLOOD-BASED DIAGNOSTICS**

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Statistical Analysis Plan

PROTOCOL TITLE: **A PHASE II SINGLE-ARM STUDY OF ATEZOLIZUMAB MONOTHERAPY IN LOCALLY ADVANCED OR METASTATIC NON–SMALL CELL LUNG CANCER: CLINICAL EVALUATION OF NOVEL BLOOD-BASED DIAGNOSTICS**

PROTOCOL NUMBER: ML39237

TEST PRODUCT: Atezolizumab (MPDL3280A)

SPONSOR: Genentech, Inc.

PLAN PREPARED BY: [redacted]

ERSION: version 1.0 (January 17, 2018)

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1. LIST OF ABBREVIATIONS

Abbreviation	Definition
ALK	anaplastic lymphoma kinase
ATA	anti-therapeutic antibody
Baseline	last available data obtained prior to patients receiving the first dose of study drug.In case of multiple assesments, average will be taken
CR	complete response
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
DOR	duration of response
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic Case Report Form
HR	hazard ratio
ICH	International Conference on Harmonisation
IgG1	immunoglobulin G subclass 1
IMP	investigational medicinal product
ITT	intent-to-treat
IRB	Institutional Review Board
IV	Intravenous
IxRS	interactive voice/Web response system
KM	Kaplan-Meier
ML	mutational load
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
NaF-PET	sodium fluoride positron emission tomography
NCI	National Cancer Institute
NGS	next-generation sequencing
NSCL	C non−small cell lung cancer
ORR	objective response rate
OS	overall survival
PBMC	peripheral blood mononuclear cell
PD	progressive disease
PD-1	programmed death-1
PD-L	1 programmed death-ligand 1
PFS	progression-free survival
PK	pharmacokinetic
PR	partial response
q21d	every 21 days
RCC	renal cell carcinoma

2. BACKGROUND

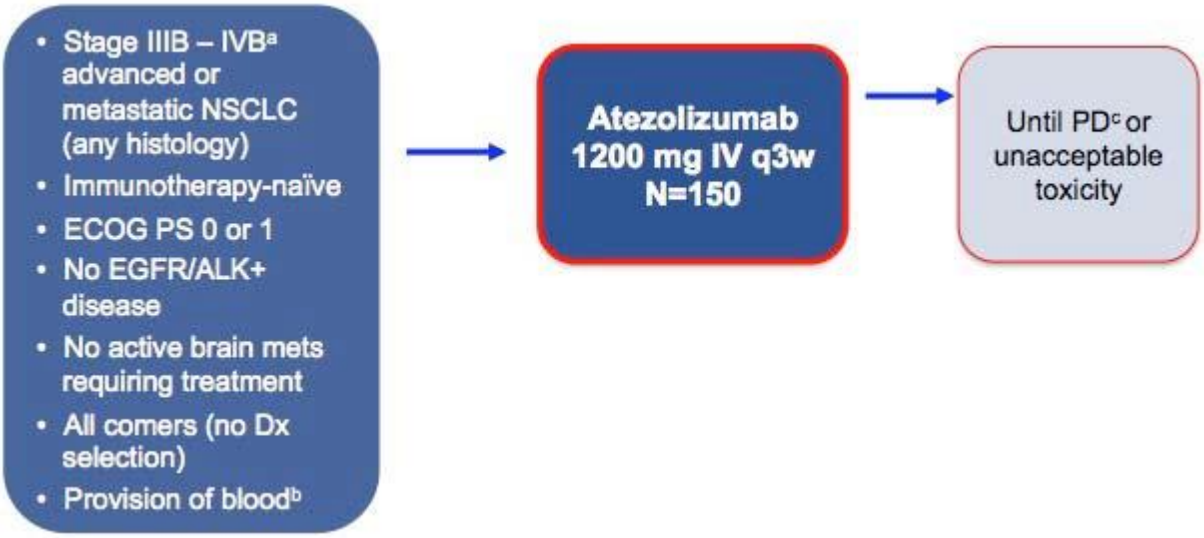
(See protocol background section for study scientific background)

This document specifies the statistical analyses for Study ML39237.

3. STUDY DESIGN

This is a Phase II, open-label, prospective, multicenter study designed to evaluate the efficacy and safety of single-agent atezolizumab as a first-line therapy in patients with locally advanced or metastatic NSCLC In addition, the primary biomarker objective is to measure bTMB and evaluate whether it can predict for improved clinical outcome with atezolizumab.

There will be approximately 150 patients with Stage IIIB−IVB, locally advanced or metastatic, EGFR/ALK−negative NSCLC (any histology) who are immunotherapy-naive enrolled at approximately 25−30 study sites in the United States. In case there are patients who are determined to be EGFR/ALK−positive by retrospective blood analysis, recruitment will continue until 150 patients who are negative for EGFR and ALK are enrolled.



AJCC = American Joint Committee on Cancer; Dx = diagnosis; ECOG = Eastern Cooperative Oncology Group; EGFR/ALK = epidermal growth factor receptor/anaplastic lymphoma kinase; IASLC = International Association for the Study of Lung Cancer; IV = intravenous; mets = metastases; NSCLC = non−small cell lung cancer; PD = progressive disease; PS =performance status; q3w = once every three weeks; RECIST = Response Evaluation Criteria in Solid Tumors.

a Staging criteria based on the IASLC Lung Cancer Staging Project proposed for the eighth edition of the AJCC NSCLC staging system (see Appendix 3). Patients with histologically or cytologically confirmed Stage IIIB-IV NSCLC based on the seventh edition of the AJCC NSCLC staging system are also eligible for study entry.
b Blood samples will be taken at baseline and at progression (all samples will be tested retrospectively).
c Treatment beyond RECIST v1.1 progression may be permitted if the patient continues to derive clinical benefit as determined by the investigator.

Atezolizumab (fixed dose of 1200 mg) will be administered intravenously on Day 1 of each 21-day cycle.

Patients who meet the Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 criteria for progressive disease (PD) at any timepoint during treatment will be permitted to continue atezolizumab treatment if there is evidence of clinical benefit, defined as meeting all of the following criteria:

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

Patients for whom approved therapies exist must provide written consent to acknowledge deferring these treatment options in favor of continuing study drug at the time of initial progression.

When a patient discontinues study drug, regardless of the reason for discontinuation, the patient will be asked to return to the clinic within 30 days after the last dose of study drug for a treatment discontinuation visit. Patients who discontinue will not be replaced.

Screening tests and evaluations will be performed within 28 days prior to treatment initiation.

Blood samples will be collected at screening, baseline, during therapy, and at first evidence of radiographic disease progression or loss of clinical benefit. Data from the latter blood draws will be used to explore whether the radiographic findings are consistent with changes in *bTMB* as measured by the blood-based diagnostic assays and to explore possible mutational mechanisms of resistance. Additional blood samples may be taken at each scan as defined in protocol Appendix 1.

Tissue biopsies (tissue blocks preferred) may be submitted at any time during the study, with biopsies from diagnosis (archival or fresh) and at progression preferred. For patients who provide tissue samples, next generation sequencing (NGS) may be performed by Foundation Medicine. Results may not be available for samples that do not meet testing criteria. Patients who are unable to undergo biopsy sample collection but otherwise meet the eligibility criteria may still be enrolled to receive atezolizumab.

All patients will undergo tumor assessment at baseline and every 6 weeks (± 7 days) thereafter regardless of dose delays for the first 12 months following Cycle 1, Day 1. After 12 months, tumor assessment will be required every 9 weeks (± 7 days); tumor assessments will continue until disease progression per RECIST v1.1 or loss of clinical benefit, consent withdrawal, study discontinuation, study completion or death, whichever occurs first. All patients will be followed for survival and anti-cancer therapy while in the study and will be given the option of participating in a long-term follow-up during which survival data will be collected from public resources (e.g., death dates from online obituaries or the National Death Index).

Safety will be assessed on the basis of vital sign measurements, ECOG performance status scores, physical examination findings, clinical laboratory test results, and the frequency, severity, and relationship to atezolizumab of adverse events.

3.1 Protocol Synopsis

The protocol synopsis (see protocol).

3.2 Objectives and Endpoints:

The objectives and corresponding endpoints for the study are outlined in table below.

Objectives	Corresponding Endpoints
Primary Efficacy Objective:	
To evaluate the clinical efficacy of Atezolizumab	ORR according to RECIST v1.1 as assessed by the investigator
Secondary Efficacy Objective:	
To evaluate the efficacy of Atezolizumab	Investigator-assessed PFS according to RECIST v1.1
	Investigator-assessed disease control rate and duration of response according to RECIST v1.1
	Overall survival
Safety Objective:	
To evaluate the safety and tolerability of atezolizumab	Incidence of adverse events, with severity determined through use of NCI CTCAE v4.0
Primary Biomarker Objectives:	
To evaluate whether “positive” bTMB (defined as bTMB >=16, and bTMB >=10) is associated with improved PFS with the treatment of atezolizumab	Relationship between PFS and bTMB (≥16 vs <16) and between PFS and bTMB (≥10 vs <10)
Secondary Biomarker Objective:	
To evaluate whether “positive bTMB” defined at various bTMB cutoff points or quantiles can predict for improved PFS with atezolizumab.	Relationship between PFS and various bTMB cutoff points, defined as range 4 to 24 by twos, and quartiles, except the primary cutoff points16 and 10
To evaluate the correlation between clinical outcomes including but not limited to PFS rate at 6, 9, and 12 months, ORR, disease control rate and various definitions of positive bTMB.	Relationship between efficacy endpoints including PFS rate at 6, 9, and 12 months, disease control rate, ORR and various bTMB cutoff pints and quantiles

Exploratory Biomarker Objectives in Blood:	
To evaluate whether higher expression of an immune-related gene signature in blood PBMCs predicts for improved PFS with atezolizumab	Relationship between PFS and expression of an immune gene signature in PBMCs
To assess whether bTMB is altered as a result of treatment with immunotherapy	Relationship between bTMB and treatment with immunotherapy
To assess the status of additional circulating biomarkers related to immunotherapy and NSCLC and outcomes with atezolizumab	Relationship between circulating biomarkers related to immunotherapy and NSCLC and efficacy
Exploratory Biomarker Objectives in Tissue:	
To perform retrospective tTMB analysis and NGS-based mutation testing on tissue biopsies for patients providing specific consent and viable samples	Relationship between somatic mutations and tTMB on efficacy. All mutations will be identified through NGS performed on DNA extracted from tumor tissue.

3.3 Timing of Analyses

The primary efficacy analysis measured by ORR may be performed after all patients complete 6 months of follow-up (i.e. 6 months after last patient enrolled into the study). If the primary efficacy analysis is not performed at 6 months of follow-up, it will be performed during the final analysis. The final analysis will be performed at the end of the study, 18 months after all patients have been enrolled.

One interim analysis is planned 6 months after one-half of the patients have been enrolled. The purpose of the interim analysis is to provide preliminary results in evaluating the biomarker cutoff and to perform a futility analysis. The futility criteria to stop the study will be met if the true ORR is more likely ≤5% rather than ≥ 15%, or if 4 or fewer patients have an objective response from the first 75 enrolled and treated patients. The chance of stopping the study is > 67% if the true ORR is 5% or less. The chance of stopping the study is < 1% if the true ORR is 15% or larger. No type-1 error adjustments will be made for the interim analysis.

4. STATISTICAL METHODOLOGIES

4.1 Sample size:

The sample size for this study is based on the primary efficacy objective and primary biomarker objectives. Based on 150 patients, the maximum half width of the 2-sided 95% CI of the estimated ORR will be within 8%. Additionally, based on 150 patients, there will be at least 80% power to detect a statistical improvement in PFS for bTMB high group vs bTMB low subgroup. The power listed in the table below is based on the following assumptions: the test is 2-sided, significance level is 0.10, both biomarker subgroups have at least 25% of the patients (i.e., 37 or more patients in both groups), median PFS is 4 months for the subgroup with a shorter median PFS, the HR of PFS between the subgroup with a shorter PFS versus the other subgroup is 0.6 or lower, the recruitment duration is one year, the follow-up time from last patient in is 18 months, and the dropout rate is 5%.

n =150	**Power**		
Hazard Ratio	**Biomarker ≥ 25th percentile vs.< 25th percentile**	**Biomarker ≥ 50th percentile vs. < 50th percentile**	**Biomarker ≥ 75th percentile vs. < 75th percentile**
0.4	100%	100%	100%
0.5	97%	99%	97%
0.6	83%	92%	84%
0.7	58%	69%	58%

4.2 Analysis Populations

Efficacy Analysis Population:

The primary Efficacy analyses will include all patients who receive at least one dose of study drug.

Safety Analysis Population:

The safety analyses will be based on all patients who received any dose of atezolizumab during the study treatment period.

Biomarker Analysis Population:

Biomarker analyses will include all patients who receive at least one dose of study drug and have evaluable baseline biomarker assessment.

4.3 Demographic and Baseline Characteristics

Demographic characteristics, such as age, sex, race/ethnicity, and baseline characteristics, such as weight, BMI, tobacco use history, histology subtype, ECOG performance status, metastatic lung cancer history, prior cancer radiotherapy, and PD-L1 status, will be summarized. Descriptive statistics (mean, median, standard deviation, and range) will be presented for continuous data, and frequencies and percentages will be presented for categorical data.

Demographic and baseline characteristics will be summarized for safety analysis population and possibly additional analysis populations including selected biomarker sub-populations if necessary.

4.4 Analysis of Study Conduct

The number of patients who enroll in, discontinue, or complete the treatment and study will be summarized. Major protocol deviation including enrollment criteria exceptions will be listed and evaluated for their potential effects on the interpretation of study results.

4.5 Efficacy Analyses

The efficacy analysis will be based on Efficacy Analysis Population (see section 4.2)

4.5.1 Primary Efficacy Endpoint

The primary efficacy endpoint of this study is investigator-assessed ORR, defined as the proportion of patients whose confirmed best overall response is either a PR or CR per RECIST v1.1. For this analysis, patients not meeting these criteria, including patients without at least one post-baseline response assessment, will be considered non-responders. An estimate of the ORR from all patients who received study drug and the 95% CI will be calculated by using the Blaker method.

4.5.2 Secondary Efficacy Endpoints

Secondary efficacy endpoints include disease control rate (DCR), duration of response (DOR), and PFS, per RECIST v1.1, and OS. Disease control rate (DCR) is defined as the rate of patients with complete or partial response as best response or stable disease maintained for 24 weeks per RECIST v1.1. DOR will be analyzed for the subset of patients who achieved an objective response. DOR is defined as the time from the initial occurrence of documented CR or PR until documented disease progression as determined by the investigator or death, whichever occurs first. Median and range will be presented for a descriptive summary. Responders with no PD or death, DOR will be censored at last post-baseline tumor assessment. Responders with no post-baseline tumor assessment will be censored at the date of first dose plus 1.

PFS is defined as the time from the first dose of study drug to the time of disease progression or death from any cause during the study, whichever occurs first. Patients who have not experienced disease progression or death at the time of analysis will be censored at the time of the last tumor assessment. Patients with no post-baseline tumor assessment will be censored at the date of first dose plus 1.

OS is defined as the time from the first dose of study drug to the time of death from any cause during the study. Patients who are still alive at the time of analysis will be censored at the date of their last study assessment (for active patients) or at the last date known alive (for patients in follow-up). Patients with no post-baseline assessment will be censored at the date time of first dose plus 1.

PFS and OS of patients in this study will be summarized graphically and with descriptive statistics such as median and landmark PFS by using the Kaplan-Meier (K-M) methodology. The Brookmeyer-Crowley methodology will be used to construct the 95% CI for the median PFS and OS (Brookmeyer and Crowley 1982). K-M methods will also be used to estimate landmark PFS and OS at various time points (i.e., 6, 12, 18, and 24 months), along with the corresponding 95% CI, by using Greenwood's formula.

4.5.3 Exploratory Analysis

Unconfirmed ORR will be summarized. Duration of stable disease or response will also be summarized for the subset of patients who were responders or achieved stable disease. Duration of stable disease or response is defined as the time from the start of study medication to documented disease progression as determined by the investigator or death, whichever occurs first.

The relationship between efficacy and baseline characteristics may also be explored. Descriptive statistics for efficacy endpoints in important subgroups defined by baseline characteristics may be summarized. The impact of baseline characteristics on efficacy may be also evaluated using Cox model for time to event endpoints and logistic regression model for dichotomous endpoints respectively.

4.6 Safety Analyses

Safety analysis will be performed on safety analysis population (see section 4.2). Safety will be assessed through summaries of adverse events, including protocol defined events of special interest, changes in laboratory test results, changes in vital signs, and exposure to study drug. Additional safety summaries may also be provided for applicable biomarker selected sub-groups.

4.6.1 Exposure of Study Drug

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

4.6.2 Adverse Events

Verbatim description of adverse events (AEs) will be mapped to Medical Dictionary for Regulatory Activities (MedDRA) thesaurus terms and graded according to the NCI CTCAE v4.0. AEs will be summarized by NCI CTCAE grade. Multiple occurrences of the same event will be counted once at the maximum severity.

All AE data will be listed by study site, patient number, AE starting and ending study days, and study day of initiation of another non-protocol anti-cancer therapy after the last administration of study drug. SAEs and deaths data will also be listed.

All AEs occurring on the day of or after administration of the first dose of treatment will be summarized by thesaurus term, appropriate thesaurus levels, and NCI CTCAE v4.0 grade. Severe AEs (Grade >=3), infusion related reactions, AEs relation to study drug, and AEs leading to study drug discontinuation or interruption will be summarized.

Serious adverse events (SAEs), AESIs, and adverse events leading to study drug discontinuation or interruption will be summarized separately.

Deaths and causes of death will be summarized.

Protocol Defined AE Reporting Period

After initiation of study drug, all AEs will be reported until 30 days after the last dose of study drug or until initiation of new anti-cancer therapy, whichever occurs first; SAEs and adverse events of special interest will continue to be reported until 90 days after the last dose of study drug or until initiation of new anticancer therapy, whichever occurs first. Any and treatment related SAEs and AESIs will be reported until study completion.

The above AEs reporting rules may be used to select AEs to be summarized if significant among of AEs are reported outside of the protocol defined AE reporting period.

4.6.3 Laboratory Data

Laboratory data collected during study treatment and for 30 days after the last dose of study drug were classified according to NCI CTCAE grade and following analysis will be performed.

1) Summary of Laboratory Values over Time, including descriptive statistics for change from baseline.
2) Listing and summary of lab values above or below the normal range and above or below the marked laboratory abnormalities.
3) Clinically relevant shifts in laboratory parameters defined as shifts from Grade 0, 1, or 2 at baseline to Grade 3 or 4 post baseline.

4.6.4 Vital Signs

Vital sign (heart rate, respiratory rate, blood pressures, and temperature) data will be summarized by time and by NCI CTCAE grade, where appropriate.

4.6.5 Medications and Other Treatments

Previous and concurrent medical conditions, previous and concomitant medications, and other anti-cancer treatment will be summarized. .

4.7 Biomarker Analyses

Biomarker analysis will be based on Biomarker analysis population, which is all patients who receive at least one dose of study drug and have evaluable baseline biomarker assessment, as defined in section 4.2.

The blood tumor mutational burden (bTMB) assay is a blood-based, circulating tumor DNA (ctDNA) next generation sequencing (NGS) test that will be used as an aid in the identification of non-small cell lung cancer (NSCLC) patients most likely to respond to atezolizumab, a

programmed death-ligand (PD-L1) blocking antibody. The NGS-based assay counts the total number of somatic mutations (single nucleotide variants (SNVs) excluding driver mutations) over a 1.25 megabase (Mb) region of coding DNA in ctDNA isolated from fresh plasma derived from whole blood. bTMB is reported as a whole integer score.

The bTMB assay has been analytically validated and clinically validated retrospectively (ESMO 2017 Gandara presentation and Fabrizio poster and manuscript in review). The assay detects SNVs down to 0.5% allele frequency across 394 genes from as little as 1% tumor content in a cell free DNA (cfDNA) sample. Tumor content is estimated by determining the maximum somatic allele frequency (MSAF). All samples in the biomarker evaluable population have MSAF >=1%. The FDA approved the IDE for the bTMB assay in 2017, and the assay is now being used to prospectively enroll 1L NSCLC patients in the BFAST trial.

4.7.1 Primary Biomarker Analyses

K-M curves and a log-rank test will be used to evaluate the differences in PFS between bTMB high versus low groups at 16 and 10 two different cutoff points (i.e. bTMB ≥16 vs <16, and bTMB ≥10 vs <10). The Gatekeeping testing procedures will be used to test PFS differences at these two primary bTMB cut off points. PFS difference at cutoff point 16 will be tested first. If there is statistically significance in PFS difference bTMB ≥16 vs <16 groups, we will claim statistical significant difference in PFS between bTMB ≥16 vs <16 groups, and we will further test PFS difference at cutoff 10. We can only claim PFS difference between bTMB ≥10 vs <10 groups if both tests for cutoff point 16 and cut off point 10 are statistically significant.

The statistical tests for primary analysis as well as for other analyses comparing efficacy differences between bTMB high group vs low group will be two-sided at a significance level of 0.10. he corresponding bTMB group differences will be estimated and two-sided 90% confidence interval will be provided. All other statistical tests used in the study will be two-sided at level of 0.05. Their corresponding point estimators will be estimated and two-sided 95% confidence interval will be provided.

4.7.2 Secondary Biomarker Analyses

K-M curves and a log-rank test will be used to evaluate the differences in PFS between bTMB mutation high versus low groups as measured by an NGS-based mutation burden assay in blood at various cutoff points other than the primary cut off points 16 and 10. These cutoff points are defined as range 4 to 24 by twos and quartiles.

Descriptive statistics for PFS curves including median PFS time and 6-, 9-, and 12-month PFS probabilities will be estimated for various bTMB cutoff points. OS will be analyzed in a similar way as PFS. ORR and DCR will also be summarized by various bTMB cutoff points. The Brookmeyer-Crowley methodology will be used to construct the CI for the median. Greenwood's formula will be used to construct the CI for the landmark PFS.

4.7.3 Exploratory Biomarker Analyses

Change in blood-based mutational load after immunotherapy will be analyzed.

The relationship between PBMCs and PFS may be analyzed in a similar way similar as bTMB and PFS, in order to explore whether higher expression of an immune-related gene signature in blood PBMCs predict improved PFS with atezolizumab.

Status of additional circulating biomarkers related to immunotherapy in NSCLC at pre-specified timepoints and outcomes with the study drug will also be summarized in a similar way as bTMB.

The relationship between blood-based mutation load and tissue-based mutation load may also be explored.

5. REFRENCES

Brookmeyer R, Crowley J. A confidence interval for the median survival time. Biometrics 1982;38:29−41.