Official Title: A Single Arm, Phase II Study of Atezolizumab (MPDL3280A, Anti-PD-L1 Antibody) in Combination With Bevacizumab in Patients With EGFR Mutation Positive Stage IIIB-IV Non-Squamous Non-Small Cell Lung Cancer Pretreated With Epidermal Growth Factor Receptor Tyrosine-Kinase Inhibitors

NCT Number: NCT04426825

Document Dates: SAP Version 1: 19-August-2021

STATISTICAL ANALYSIS PLAN

TITLE: **A SINGLE ARM, PHASE II STUDY OF ATEZOLIZUMAB (MPDL3280A, ANTI-PD-L1 ANTIBODY) IN COMBINATION WITH BEVACIZUMAB IN PATIENTS WITH EGFR MUTATION POSITIVE STAGE IIIB-IV NON-SQUAMOUS NON-SMALL CELL LUNG CANCER PRETREATED WITH EPIDERMAL GROWTH FACTOR RECEPTOR TYROSINE-KINASE INHIBITORS**

PROTOCOL NUMBER: ML41256

STUDY DRUG: Atezolizumab (RO5541267)
Bevacizumab（RO4876646）

VERSION NUMBER: Final 1.0

IND NUMBER: Not Applicable

EUDRACT NUMBER: Not Applicable

SPONSOR: F. Hoffmann-La Roche Ltd

PLAN PREPARED BY: [redacted]
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DATE FINAL: 2021-08-19

DATE(S) AMENDED:

STATISTICAL ANALYSIS PLAN APPROVAL

STATISTICAL ANALYSIS PLAN AMENDMENT

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Abbreviation

Abbreviation	Definition
AE	Adverse event
AESI	Adverse event of special interest
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
CI	Confidence interval
CNS	Central nervous system
CR	Complete response
CRF	Case Report Form
CTCAE	Common Terminology Criteria for Adverse Events
DI	Dose Intensity
DOR	Duration of response
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
EORTC	European Organisation for Research and Treatment of Cancer
HRQoL	Health-Related Quality of Life
irAE	Immune-Related Adverse Event
ITT	Intention-To-Treat
LDH	Lactate dehydrogenase
MedDRA	Medical Dictionary for Regulatory Affairs
NCI	National Cancer Institute
NSCLC	Non-Small Cell Lung Cancer
ORR	Objective Response Rate
OS	Overall survival
PD	Progressive disease
PFS	Progression free survival
PR	Partial response
PRO	Patient-Reported Outcome
PT	Preferred Term
QLQ-C30	Quality-of-Life Questionnaire for Cancer
RDI	Relative Dose Intensity
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	Serious adverse event
SOC	System Organ Class
TTR	Time to Response
ULN	Upper limit of normal
WHO	World Health Organization

1. BACKGROUND

Genotype-directed therapy has the potential to dramatically improve the balance of benefit and toxicity for selected patients with NSCLC (mainly non-squamous histology) characterized by alterations of driver oncogenes, including sensitizing EGFR mutations and ALK rearrangements. Randomized Phase III trials of the EGFR inhibitors gefitinib, erlotinib, and afatinib showed significant improvement of PFS and objective response rate (ORR) compared with platinum doublet chemotherapy(Fukuoka et al.2011; Rosell et al.2012； Yang et al.2012).

Despite the high initial response rate, patients treated with first line EGFR TKIs develop acquired resistance after 9–14 months. Salvage treatment with platinum-based doublet chemotherapy gives response rate of ~10-20% only (Yang CJ et al 2016, Tseng Y-H et al 2016). Hence novel treatment strategies are urgently warranted.

Atezolizumab is a humanized IgG1 monoclonal antibody that targets PD-L1 and inhibits the interaction between PD-L1 and its receptors, PD-1 and B7-1 (also known as CD80), both of which function as inhibitory receptors expressed on T cells.

Atezolizumab shows anti-tumor activity in both nonclinical models and cancer patients and is being investigated as a potential therapy in a wide variety of malignancies. Atezolizumab is being studied as a single agent in the advanced cancer and adjuvant therapy settings, as well as in combination with chemotherapy, targeted therapy, and cancer immunotherapy.

Atezolizumab is approved for the treatment of urothelial carcinoma, the treatment of non-small cell lung cancer, the treatment of Triple-Negative Breast Cancer and for small cell lung cancer.

Vascular endothelial growth factor (VEGF) is the most important pro-angiogenic factor and a key regulator of physiological angiogenesis. It is also implicated in pathological angiogenesis such as that associated with tumor growth.

AVASTIN® (bevacizumab) is a recombinant humanized monoclonal antibody to VEGF that recognizes all isoforms of VEGF. It may exert a direct anti-angiogenic effect by binding to and clearing VEGF from the tumor environment. Bevacizumab has been tested in Phase II and III studies in a variety of solid tumors in combination with chemotherapy. Bevacizumab is registered in over 40 countries worldwide for the first-line treatment of metastatic colorectal cancer (CRC) in combination with chemotherapy, as second-line CRC treatment, and first-line treatment of advanced NSCLC, metastatic breast cancer, advanced renal cell carcinoma (RCC), ovarian cancer, and glioblastoma (Reck and Crino 2009).

Some immunosuppressive activities of VEGF can be reversed by inhibition of VEGF signaling. Thus, mice exposed to pathophysiologic levels of VEGF exhibited impaired dendritic cell function, which could be restored by blockade of VEGFR2 (Huang et al. 2007). In a murine melanoma model, VEGF blockade synergized with adoptive immunotherapy, as evidenced by improved anti-tumor activity, prolonged survival, and increased trafficking of T cells into tumors (Shrimali et al. 2010).

Synergistic effects have also been observed in a clinical study of melanoma patients combining an immunomodulatory antibody (anti−CTLA-4; ipilimumab) and bevacizumab (Hodi et al. 2011).

Therefore, the combined treatment with atezolizumab and bevacizumab may augment the antitumor immune response, resulting in improved and more durable clinical benefit.

The IMmotion 151 was the front-line, phase III trial of the atezolizumab combination with bevacizumab in RCC. The result of IMmotion 151 showed atezolizumab + bevacizumab demonstrated a clinically meaningful and statistically significant improvement in PFS (as evaluated by the investigators) versus sunitinib in the PD-L1+ population (HR = 0.74 [95% CI: 0.57, 0.96]). (Brian I Rini et al.2019)

In the analysis of safety data from Study GO30140 (clinical cutoff date of 7 June 2017) in 20 patients with HCC (median treatment duration of 2.8 months [range: 1-11 months]), the combination of atezolizumab +bevacizumab was generally safe and well tolerated; no new safety signals related to the combination therapy were identified beyond the established safety profile for each individual agent. There is a global phase III YO40245 is ongoing, which evaluate the efficacy and safety of atezolizumab + bevacizumab versus sorafenib in patients with locally advanced or metastatic HCC who have received no prior systemic treatment.

2. STUDY DESIGN

2.1 PROTOCOL SYNOPSIS

The Protocol Synopsis is in Appendix 1. For additional details, see the Schedule of Assessments in Appendix 2.

2.2 OUTCOME MEASURES

2.2.1 Primary Efficacy Outcome Measures

The primary effectiveness objective of this study is as follows:

- Objective response rate (ORR).

2.2.2 Secondary Efficacy Outcome Measures

The secondary effectiveness objectives of this study are as follows:

- Duration of objective response (DOR).
- Time to response (TTR).
- Disease control rate (DCR).
- Overall survival (OS).
- Progression-free survival (PFS).
- PFS rate at 6 and 12 months.
- OS rate at 1 and 2 years.
- Expression of PD-L1 defined by the SP142 and SP263 assay

2.2.3 Exploratory Efficacy Outcome Measures

- Exploratory analyses ORR, DOR, PFS, PFS rate at 12m, by investigator according to Modified RECIST V1.1(iRECIST).

2.2.4 Safety Outcome Measures

The safety objectives for this study are as follows:

- Incidence and severity of adverse events, with severity determined according to NCI CTCAE v5.0.
- Incidence of serious and non-serious immune- mediated adverse events (irAEs) related to atezolizumab treatment.

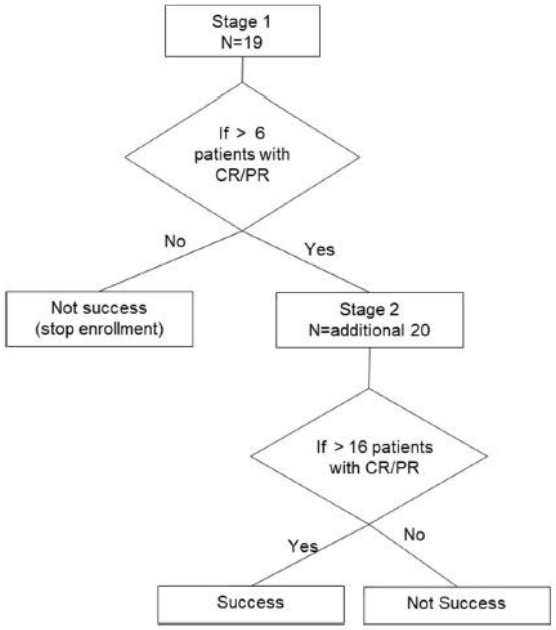
2.2.5 Health Status Utility Measures

- PROs of lung cancer symptoms, patient functioning, and health-related quality of life (HRQoL) as measured by the European Organization for Research and treatment of Cancer (EORTC) Quality-of-life Questionnaire Core 30 (QLQ C30) and its Lung Cancer Module (QLQ LC13).

2.3 DETERMINATION OF SAMPLE SIZE

The sample size estimation is based on having sufficient sample in the FAS population to show that the ORR is higher than 20%. Simon's minimax two-stage design will be used. The null hypothesis that the true ORR is at least 50% will be tested against a one-sided alternative.
The sample size calculation was based on a Simon two-stage design, and the primary end point was ORR (H0 = 30%, H1 = 50%). Two-sided alpha is set to be 0.1 and statistical power is set to be 80%.
19 fully evaluable patients will be included at the first stage. If there are 6 for fewer responders (CR/PR) in these 19 patients, enrollment will be stopped. Otherwise, additional 20 fully evaluable patients will be included in the second stage. Finally, if we have more than 16 patients in 39 patients have objective response, the endpoint is reached. Thus, considering a drop-out rate of 10%, a total number of 22 patients (if stops at the first stage) or 44 patients (if runs into the second stage) will need to be finally enrolled in this study.
Figure 1 presents an overview of the sample size allocation.

Figure 1 Sample size allocation



3. STATISTICAL METHODS

The following represents an overview of the planned statistical analysis. Additional analyses could be performed if deemed appropriate.

3.1 GENERAL RULE

Continuous data will be summarized using n, mean, standard deviation, median, minimum and maximum. The minimum and maximum values will be presented to the same number of decimal places as recorded in the CRF, mean and median will be presented to one more decimal place than the raw data, standard deviation will be presented to two more decimal places than the raw data. And each of them will be presented no more than three decimals.

Categorical variables will be expressed as absolute and relative number and 95% CI. Percentages will be rounded to one decimal place, with the denominator being the number of patients in the relevant population with non-missing data, unless otherwise stated. For category of Unable to evaluate, Not evaluable, Not applicable, Unknown, Not done will be uniformly summarized as Missing.

Time to event variables will be assessed with median survival time, lower quartile, upper quartile and its corresponding 95% CI using Kaplan-Meier method, these statistical will be presented to two decimal places. Besides, Kaplan-Meier product-limit plot will be produced. No formal hypothesis testing is planned. All effectiveness and safety variables documented in this study will be analyzed by means of descriptive analyses.

Statistical programming and analyses will be performed using SAS® Software (SAS Institute Inc., Cary, NC) Version 9.4 or higher.

3.2 DEFINITIONS AND CONVENTIONS FOR DATA HANDLING

3.2.1 Baseline Definitions

The baseline value is defined as the last non-missing value prior to start of study treatment. Since at each treatment cycle, assessments should be performed before study drug infusion unless otherwise noted, baseline could include the first dose date. When the date of the assessment is the same as the first administration date of study drug, if it is not confirmed that the assessment occurred after the first administration of the study drug, the result of the assessment shall be considered as the baseline value. However, for adverse events, concomitant medications/ therapies etc. is considered to have occurred after baseline, when the onset date is the same as the first administration date of study drug.

3.2.2 Study Day

The first dose date is considered as Day 1, patients' time on study will be determined in study days. Study day is defined as follows:

Study Day = the current date – Day 1 + 1, if the current date ≥ date of Day 1;

Study Day = the current date – Day 1, if current date < date of Day 1.

3.2.3 Last Known Alive Date

The last known alive date will be derived for patients known to be alive at the analysis cut-off date using the latest date among the following data:

- All assessment dates (e.g. vital signs assessment, ECOG performance status assessment, and also assessment date of tumor imaging etc.).
- Medication dates including study medication, concomitant medications, anticancer therapies administered after study treatment discontinuation.

- Medical history dates including clinically significant diseases, surgeries, cancer history (including prior cancer therapies and procedures, autoimmune diseases).
- Adverse events onset and end dates
- Date at which subjects were confirmed to be still alive during follow-up

The last known alive date will be used for censoring of patients in the analysis of overall survival.

3.2.4 Visit Windows

The analysis visit will be based on the nominal visits in CRF. The visit window is not applicable.

3.2.5 Pooling Center

This is a multi-center study and centers will be pooled for analysis.

3.3 ANALYSIS POPULATIONS

3.3.1 Full Analysis Set

Full analysis set (FAS): defined as all enrolled patients who receive any amount at least one dose of any study treatment. All efficacy analysis except for primary analysis of ORR will use FAS, and patients without post-baseline radiologic assessment will be regarded as non-responder.

3.3.2 Safety Analysis Set

Safety Analysis Set (SAF): defined as all enrolled patients who receive any amount at least one dose of any study treatment. The safety analysis will be performed on the safety population.

3.3.3 ITT Population

ITT population: defined as all enrolled patients regardless of whether they receive any assigned study drug. The ITT population will be used for other analyses (Demography, Baseline Characteristics, PROs, etc.).

3.3.4 Evaluable Population

Evaluable population: defined as all enrolled patients who receive any amount of study treatment, have baseline and at least one post-baseline efficacy measurement. Evaluable population will be used for primary analysis of ORR.

3.4 ANALYSIS OF STUDY CONDUCT

Analysis of study conduct will be based on ITT population.

The patient's distribution of the analysis population will be provided in study treatment. The number of patients enrolled, discontinued from Atezolizumab and Bevacizumab, discontinued from study will be summarized. Treatment and study discontinuation will be summarized according to the reasons of discontinuation as documented in the Case Report Form (CRF). Based on ITT population, the number and percentage of subjects in FAS, SAF and evaluable population, and the reasons for subjects who are excluded from specific population will be summarized.

Disposition information will be displayed by patients in listing.

In order to evaluate whether the protocol is well executed, all protocol deviations will be determined according to data contents, combined protocol requirements before database lock, and the major protocol deviations will be summarized as the frequency and percentage of patients in each type.

All protocol deviations will be listed by patients.

3.5 ANALYSIS OF SUBJECT AND TREATMENT INFORMATION

Analyses will be conducted in ITT population, and treatment compliance will be conducted on full analysis set.

3.5.1 Demographics and Baseline Characteristics

Subject demographics and baseline disease characteristics will be summarized using descriptive statistics. Continuous variables will be summarized using n, mean, standard deviation, median, minimum, and maximum. Categorical variables will be summarized as the frequency and percentage of patients in each category. Details as below:

- **Demographics**

Quantitative index:

- Age (Years), where age (Years)= (date of informed consent-date of birth)/365.25, round down.
- Weight (Kg),
- Height (cm),
- BMI(Kg/m^2), where BMI(Kg/m2) = Weight (Kg)/Height$(m)^2$, keep two decimals.

Qualitative index:

- Sex (Female, Male)
- Age group(＜65,≥65)
- Ethnicity (Asian, Other)
- Smoking history (Never, Current, Previous), if current, number of years of smoking will be summarized
- LVEF (Normal, Abnormal, not clinically significant, Abnormal, clinically significant)
- ECOG (0,1,2,3,4,5)

- **Baseline Disease Characteristics**

Quantitative index:

- Months from first diagnosis date to first dose date = (The first dose date- date of initial diagnosis+1)/ 30.4375, keep two decimals.
- Months from last recurrence date to first dose date = (The first dose date- date of last recurrence +1)/ 30.4375, keep two decimals.

Qualitative index:

- Brain MRI/CT Status
  - Brain metastasis (Yes, No)
- Bone Scan
  - Bone metastasis (Yes, No)
- Histology at time of initial diagnosis (Squamous, Non-squamous), If Non-Squamous, select one option (Adenocarcinoma, Large cell, Large cell with neuroendocrine differentiation, Poorly differentiated, Mixed (not including small cell), NSCLC/NOS, Other)
- Initial diagnosis staging (Occult, Stage 0, Stage I (including Stage IA, Stage IB), Stage II (including Stage IIA, Stage IIB), Stage IIIA, Stage IIIB, Stage IIIC, Stage IV)
- Primary tumor location (Left lung, Right lung, Double-lung, Other)
- Status of disease (Locally recurrent disease, Locally advanced unresectable disease, Metastatic disease)
- Anatomical locations of metastatic disease at time of study enrollment (Bone, Brain)
- EGFR mutation (L858R or Ex.19 deletion, Other EGFR mutation, No mutation)

- PD-L1 expression (Yes,No)
- Stage of NSCLC at Study entry (Stage IIIB, Stage IIIC, Stage IV)

Demographics and baseline disease characteristics will also be listed by patients.

3.5.2 Medical History

Medical history, including clinically significant diseases, surgeries, cancer history (including autoimmune diseases) and reproductive status will be recorded at baseline.

The following information will be presented in frequency tables by system organ class (SOC) and preferred terms (PT) based on Medical dictionary for regulatory affairs (MedDRA) version xx or the latest version before database lock.

- General medical history and baseline conditions (non- NSCLC related);
- Surgery and procedure history (non-NSCLC related)
- History of autoimmune diseases

A patient data listing of medical history will also be presented.

3.5.3 Prior and Concomitant Medication

Concomitant therapy consists of any medication (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by a patient in addition to protocol-mandated treatment from 7 days prior to initiation of study treatment to the treatment discontinuation visit. All such medications should be reported to the investigator and recorded on the Concomitant Medications eCRF.

For summarization purposes, medications other than study medications will be coded to a generic term based on the World Health Organization (WHO) dictionary version xx or the latest version before database lock. Prior medications will be defined as all medications that stopped prior to the first dose of study drug.

Concomitant medications will be defined as follows:

all medications that started on or after the first dose of study medication, or

all medications that started before the first dose date and stopped after the first dose date.

Prior and concomitant medication will be listed by patients.

3.5.4 Prior/On-Study/Post-Study Treatment

3.5.4.1 Prior NSCLC Treatment

Prior NSCLC treatment including NSCLC Therapy, Radiotherapy and Surgeries/Procedures.

For summarization purposes, prior NSCLC therapy will be coded to a generic term based on the World Health Organization (WHO) dictionary version xx or the latest version before database lock.

3.5.4.2 On-Study Treatment

On-Study treatment including surgery and procedure as well as radiotherapy.

On-Study Surgery and Procedure will be presented in frequency tables by System Organ Class (SOC) and preferred terms (PT) based on Medical Dictionary for Regulatory Affairs (MedDRA) version xx or the latest version before database lock.

A patient data listing of on-study treatment will also be presented.

3.5.4.3 Post-Study Treatment

Post-study treatment including NSCLC therapy and radiotherapy.

For summarization purposes, Post-study treatment NSCLC Therapy will be coded to a generic term based on the World Health Organization (WHO) dictionary version xx or the latest version before database lock.

Post-Study treatment will be listed by patients.

3.5.5 Treatment Compliance

The compliance will be summarized with descriptive statistics and the categorical variable of compliance (>100%, 75%~100%, 50%~75%, <50%) will also be summarized.

For Atezolizumab, treatment compliance=Total Atezolizumab dose (mg)/(1200*Number of cycles) *100%;

For Bevacizumab, treatment compliance=Total Bevacizumab actual dose (mg)/Total Bevacizumab planned dose (mg) *100%.

3.6 EFFICACY ANALYSIS

The efficacy analyses and sensitivity analysis of ORR will be performed on the FAS, Primary analysis of ORR will be analyzed using evaluable population, DOR will be assessed in patients who have an objective response. All effectiveness variables documented in this study will be analyzed by means of descriptive analyses. All interval estimation will be reported using 2-sided 95% confidence intervals, unless otherwise specified. Tumor assessment will be listed at each visit point by patients.

3.6.1 Primary Efficacy Endpoint

The best overall response (BOR) is the best response recorded from the start of the study treatment until disease progression or subsequent anti-tumor therapies started. For subjects without disease progression or subsequent anti-tumor therapies, BOR will be determined based on all available tumor assessments. Complete response (CR) or partial response (PR) should be confirmed on two consecutive occasions ≥4 weeks apart during the study treatment. When SD is believed to be best response, it must also meet the interval between the first dose of study drug and the determination of SD was at least 39 days. If the interval is not met when SD is otherwise the best time point response, the patient's best response depends on the subsequent assessments. The same patient lost to follow-up after the first SD assessment would be considered not evaluable. PD will not to be confirmed, and NE will be determined as BOR if there are no evidence of CR/PR or SD or PD.

The detailed BOR after confirmation is clarified in below **Error! Reference source not found.**.

Table 1 CR and PR confirmation rule for Best Overall Response

Overall response First time point	Overall response Subsequent time point[a]	Best overall response
CR	CR	CR
CR	PR	SD if SD duration of no less than 39 days from first administration date of study drug was met, otherwise, PD
CR	SD	SD if SD duration of no less than 39 days from first administration date of study drug was met, otherwise, PD
CR	PD	SD if SD duration of no less than 39 days from first administration date of study drug was met, otherwise, PD
CR	NE	SD if SD duration of no less than 39 days from first administration date of study drug was met, otherwise NE

CR		SD if SD duration of no less than 39 days from first administration date of study drug was met, otherwise NE
PR	CR	PR
PR	PR	PR
PR	SD	SD
PR	PD	SD if SD duration of no less than 39 days from first administration date of study drug was met, otherwise, PD
PR	NE	SD if SD duration of no less than 39 days from first administration date of study drug was met, otherwise NE
PR		SD if SD duration of no less than 39 days from first administration date of study drug was met, otherwise NE
NE	NE	NE

[a] Subsequent confirmed tumor response should be at least 4 weeks after previous tumor response. In the case where a patient has two non-consecutive visit responses of PR, then, as long as the time between the 2 visits of PR is greater than 4 weeks and there is no PD between the PR visits, the patient will be defined as a responder. Similarly, if a patient has visit responses of CR, NE, CR, then, as long as the time between the 2 visits of CR is greater than 4 weeks, then a best response of CR will be assigned.

Objective response rate (ORR), defined as the proportion of patients with a complete response (CR) or partial response (PR) on two consecutive occasions ≥4 weeks apart, as determined by the investigator according to RECIST v1.1.

Patients without any post-baseline tumor assessments will be considered non-responders.

Number and percentage of responders with corresponding Clopper-Pearson 90% and 95% confidence intervals will be provided.

The ORR will be the basis for decision whether the study would be continued when Stage 1 is completed.

The frequency and percent for the responders and non-responders will be summarized as well.

Sample SAS code as following:

```
proc freq data = dd;
    table response / alpha=0.05;
    exact binomial;
run;
```

3.6.2 Secondary Efficacy Endpoints

The secondary efficacy objective for this study is to evaluate the efficacy of atezolizumab plus bevacizumab in the evaluable population on the basis of the following endpoints and the analysis will be performed in FAS population.

3.6.2.1 Duration of Response (DOR)

For patients who have experienced an objective response (CR or PR) during the study, duration of objective response (DOR) is defined as the time from the first occurrence of a documented objective response to disease progression or death from any cause whichever occurs first, as determined by the investigator according to RECIST v1.1.

Patients who are alive and who have not experienced disease progression at the time of analysis will be censored at the time of the last tumor assessment date. If no tumor assessments were performed after the date of the first occurrence of a complete or partial response, DOR will be censored at the date of the first occurrence of a complete or partial response plus 1 day.

The analysis population will be FAS that have experienced an objective response (CR or PR).

The DOR will be derived based on imaging dates, not visit or RECIST response assessment dates.

RECIST imaging contributing towards a particular visit may be performed on different dates. The following rules will be applied to determine the progression or censoring date:

• For progressions patients, progression date will be determined based on the earliest of the dates contribution to a particular overall visit tumor assessment.

• For censoring patients, censored date will be determined at the latest of the dates contributing to a particular overall visit assessment.

If progression or death happened, DoR (months) = (date of progression or death –date of first documented response (CR or PR) +1) /30.4375,

If censored, DoR (months) = (censoring date –date of first documented response (CR or PR) +1) /30.4375.

Censoring rules are displayed in **Error! Reference source not found.**.

Table 2 Censoring Rules for DOR Analysis

Sequence	Category	Situation	Date of Progression or Censoring	Outcome
1	No tumor assessments after the date of the first occurrence of CR or PR	No tumor assessments after the date of the first occurrence of CR or PR(without death or death reported without 2 visit/tumor assessment from the date of first occurrence of CR or PR)	Date of the first occurrence of a CR or PR+1	Censored
2	Progression	Progression documented between scheduled visits(all conditions are met: a. progression reported within 2 visit/tumor assessment from previous adequate tumor assessment, or from the date of first occurrence of a CR or PR if no adequate tumor assessment before progression; b no new anticancer treatment or new anticancer treatment is after than PD date)	Date of first radiologic PD assessment	Progressed
3	No progression	No progression(have tumor assessments after the date of first occurrence of CR or PR, without PD, death, new anticancer treatment)	Date of last adequate radiologic assessment	Censored
4	Received another kind of anti-cancer therapy before progression/death	New anticancer treatment started(any of the following conditions are met :a. no progression/death missed 2 visit/tumor assessment or progression/death missed 2 scan intervals and new anticancer treatment started earlier than date of last adequate radiologic assessment before missed tumor assessments; b. no	Date of last adequate radiologic assessment prior to or on date of new anticancer treatment(If no adequate radiologic assessment prior to or on date of new anticancer treatment, censor to the date of the first	Censored

		progression/death or progression/death within 2 visit/tumor assessment and new anticancer treatment started earlier than PD date, if progressed)	occurrence of a CR or PR +1)	
5	Death	No tumor assessments after the date of the first occurrence of CR or PR and death within 2 visit/tumor assessment [1] (no tumor assessments after the date of the first occurrence of CR or PR and death reported within 2 visit/tumor assessment from the date of first occurrence of CR or PR, without new anticancer treatment)	Date of death	Progressed
6	Death	Death between adequate assessment visits(death reported within 2 visit/tumor assessment from previous adequate tumor assessment, and without new anticancer treatment and no PD)	Date of death	Progressed
7	Death or progression after more than two missed visit/tumor assessment	Death or progression after more than two missed visit/tumor assessment [2] (without new anticancer treatment or new anticancer treatment date is after than the date of last adequate radiologic assessment before missed tumor assessments)	Date of last adequate radiologic assessment before missed tumor assessments(If no adequate radiologic assessment before death or progression, censor to the date of the first occurrence of a CR or PR +1)	Censored
Note: Adequate assessment including the tumor evaluations are the followings: CR, PR, SD, PD. [1] Refers to date of death from the first dose date of study drug is less than or equal to 12 weeks+7 days. [2] If death or progression is before or on 36th week, it refers to the date of death or progression is larger or equal to 12 weeks +7 days from the last adequate tumor assessment , if there are no adequate radiologic assessment before death or progression, will compare with the first dose date of study drug. If death or progression is after 36th week, it refers to the date of death or progression larger or equal to 18 weeks +7 days from the last adequate tumor assessment.				

The median for DOR will be calculated using the Kaplan- Meier product-limit method, and presented with two-sided 95% CI, and the Kaplan-Meier plot will be produced by time.

3.6.2.2 Time to Response (TTR)

Time to response (TTR), defined as the time from the start of the treatment to the first objective tumor response observed for patients who achieved CR or PR (which must be confirmed subsequently), as determined by the investigator according to RECIST v1.1.

TTR will be analyzed for patients who achieved CR or PR, for non-responders will be excluded from the TTR analysis population.

TTR (months) = (date of first documented response (CR or PR) – the first administration date of study medication +1) /30.4375.

TTR will be summarized using n, mean, standard deviation, median, minimum and maximum.

3.6.2.3 Disease Control Rate (DCR)

DCR, defined as the proportion of patients who have a best overall response of CR or PR or SD, as determined by the investigator according to RECIST v1.1.
Number and percentage of patients with DCR with corresponding Clopper-Pearson 95% confidence intervals will be provided.

3.6.2.4 Overall Survival (OS)

Overall survival (OS) after enrollment, defined as the time from enrollment to death from any cause.

Patients who do not have post-baseline information will be censored at the date of initiation of study treatment + 1 day. Patients who are alive at the time of analysis will be censored at the last known survival date + 1 day, and will be categorized as off-study:(lost to follow-up, withdrew consent, other) and still on-study at the time of analysis.

The median for overall survival, and the survival rates will be calculated using the Kaplan- Meier product-limit method, and presented with two-sided 95% CI, and the Kaplan-Meier plot will be produced by time.

3.6.2.5 Progression-free Survival (PFS)

Progression-free survival (PFS), defined as the time from enrollment to the first occurrence of disease progression or death from any cause, whichever occurs first, as determined by the investigator according to RECIST v1.1.

PFS will be summarized descriptively using the Kaplan-Meier (KM) product-limit method. Median values of PFS, if available, along with two-sided 95% CIs (based on the log-log transformation), will also be calculated. The source of progression (death vs. progression) will be summarized. KM curve of PFS will be generated.

Patients who are alive and have not experienced disease progression at the time of analysis will be censored at the time of the last tumor assessment.

The PFS will be derived based on imaging dates, not visit or RECIST response assessment dates.

RECIST imaging contributing towards a particular visit may be performed on different dates. The following rules will be applied to determine the progression or censoring date:

- For progressions patients, progression date will be determined based on the earliest of the dates contribution to a particular overall visit tumor assessment.
- For censoring patients, censored date will be determined at the latest of the dates contributing to a particular overall visit assessment.

If progression or death happened, PFS (months) = (date of progression or death –date of first dose of trial treatment +1) /30.4375,

If censored, PFS (months) = (censoring date –date of first dose of trial treatment+1) /30.4375.

The PFS censoring rules are displayed in **Error! Reference source not found.**.

Table 3Censoring Rules for PFS Analysis

Sequence	Category	Situation	Date of Progression or Censoring	Outcome
1	No baseline or post-baseline tumor assessments	No baseline or post-baseline tumor assessments (without death or death reported without 2 visit/tumor assessment from the first dose date of study drug)	Date of first dose date of study drug+1	Censored

2	Progression	Progression documented between scheduled visits (all conditions are met: a. progression reported within 2 visit/tumor assessment from previous adequate tumor assessment, or from first dose date of study drug if no adequate tumor assessment before progression; b no new anticancer treatment or new anticancer treatment started is after than PD date)	Date of first radiologic PD assessment	Progressed
3	No progression	No progression(have baseline and post-baseline tumor assessments, without PD, death, new anticancer treatment)	Date of last adequate radiologic assessment	Censored
4	Received another kind of anti-cancer therapy before progression/death	New anticancer treatment started(any of the following conditions are met : a. no progression/death missed 2 visit/tumor assessment or progression/death missed 2 scan intervals and new anticancer treatment started earlier than date of last adequate radiologic assessment before missed tumor assessments; b. no progression/death or progression/death within 2 scan intervals and new anticancer treatment started earlier than PD date, if progressed)	Date of last adequate radiologic assessment prior to or on date of new anticancer treatment (If no adequate radiologic assessment prior to or on date of new anticancer treatment, censor to the first dose date of study drug+1)	Censored
5	Death	No post-baseline and death within 2 visit/tumor assessment [1] (no post-baseline tumor assessments and death reported within 2 visit/tumor assessment from first dose date of study drug, without new anticancer treatment)	Date of death	Progressed
6	Death	Death between adequate assessment visits(death reported within 2 visit/tumor assessment from previous adequate tumor assessment, and without new anticancer treatment and no PD)	Date of death	Progressed
7	Death or progression after more than two missed visit/tumor assessment	Death or progression after more than two missed visit/tumor assessment [2] (without new anticancer treatment or new anticancer treatment date is after than the date of last adequate	Date of last adequate radiologic assessment before missed tumor assessments (If no adequate radiologic assessment before	Censored

		radiologic assessment before missed tumor assessments)	death or progression, censor to the first dose date of study drug+1)	
Note: Adequate assessment including the tumor evaluations are the followings: CR, PR, SD, PD. [1] Refers to date of death from the first dose date of study drug is less than or equal to 12 weeks+7 days. [2] If death or progression is before or on 36th week, it refers to the date of death or progression is larger or equal to 12 weeks +7 days from the last adequate tumor assessment, if there are no adequate radiologic assessment before death or progression, will compare with the first dose date of study drug. If death or progression is after 36th week, it refers to the date of death or progression larger or equal to 18 weeks +7 days from the last adequate tumor assessment.				

3.6.2.6 PFS rate at 6 and 12 months

PFS rate at 6 and 12 months, defined as the proportion of patients who have not experienced disease progression or death from any cause at 6 and 12 months, as determined by the investigator according to RECIST v1.1.

The PFS rates at 6 months and 1 year after initiation of treatment will be estimated using Kaplan-Meier methodology, along with 95% CIs calculated using the standard error derived from Greenwood's formula.

3.6.2.7 OS rate at 12 and 24 months

OS rate at 12 and 24 months, defined as the proportion of patients who have not experienced death from any cause at 12 and 24 months. The analysis method is similar with PFS rate at 6 and 12 months.

3.6.2.8 Expression of PD-L1 defined by the SP142 and SP263 assay.

Expression of PD-L1 defined by the SP142 and SP263 IHC assay will be investigated. The proportions of the patients with PD-L1+ tested by SP142 and SP263 in all patients will be presented respectively, with their 95% Clopper-Pearson CI. The consistency between SP142 and SP263 IHC assay will be investigated using chisq-square test.

3.6.2.9 Sum of target lesion diameters (SLD)

The SLD is the sum of all target lesion diameters (including longest for non-nodal lesions, short axis for nodal lesions).

The best percentage change of the SLD from baseline is defined as the minimum value of the percentage change from the baseline to the SLD in all visits after the study treatment. The specific calculation formulas are as follow:

The best change of the SLD from baseline = the minimum value of SLD at post-baseline – baseline SLD;

The best percentage change of the SLD from baseline = (the minimum value of SLD at post-baseline – baseline SLD)/ baseline SLD*100%.

The best percentage change of the SLD from baseline will be summarized using n, mean, standard deviation, median, minimum, and maximum.

Waterfall plot of the best percentage change of the SLD from baseline will be generated.

Tumor assessment will be listed for each subject.

3.6.3 Exploratory Efficacy Endpoints

Exploratory analyses ORR, DOR, PFS, PFS rate at 12m, by investigator according to Modified RECIST V1.1(iRECIST). And the following points for iRECIST require to be noted:

(1) Immune-Modified RECIST Response

Since immune-modified RECIST response assessment collected in CRF does not correspond with iRECIST, especially for progressive disease. For CR/PR/SD will be derived as iCR/iPR/iSD respectively by adding 'i'. For PD, will be derived as iUPD or iCPD according to the following rules from iRECIST V1.1:

iRECIST defines iUPD on the basis of RECIST 1.1 principles; however, iUPD requires confirmation, which is done on the basis of observing either a further increase in size (or in the number of new lesions) in the lesion category in which progression was first identified in (ie, target or non-target disease), or progression (defined by RECIST 1.1) in lesion categories that had not previously met RECIST 1.1 progression criteria. However, if progression is not confirmed, but instead tumour shrinkage occurs (compared with baseline), which meets the criteria of iCR, iPR, or iSD, then the bar is reset so that iUPD needs to occur again (compared with nadir values) and then be confirmed (by further growth) at the next assessment for iCPD to be assigned. If no change in tumour size or extent from iUPD occurs, then the timepoint response would again be iUPD.

Each timepoint response is based on the assessment of target lesions, non-target lesions, and new lesions.

Progression is confirmed in the target lesion category if the next imaging assessment after iUPD (4–8 weeks later) confirms a further increase in sum of measures of target disease from iUPD, with an increase of at least 5 mm. However, the criteria for iCPD (after iUPD) are not considered to have been met if complete response, partial response, or stable disease criteria (compared with baseline and as defined by RECIST 1.1) are met at the next assessment after iUPD.

Progressive disease in the non-target lesion category is confirmed if subsequent imaging, done 4–8 weeks after iUPD, shows a further increase from iUPD.

If a new lesion is identified (thus meeting the criteria for iUPD) and the patient is clinically stable, treatment should be continued. New lesions should be assessed and categorised as measurable or non-measurable using RECIST 1.1 principles. Five lesions (no more than two per organ) should be measured and recorded as a new lesion target, but should not be included in the sum of measures of the original target lesions identified at baseline. Other measurable and non-measurable lesions are recorded as new lesion non-target. New lesions do not need to meet the criteria for new lesion target to result in iUPD (or iCPD); new lesion non-target can also drive iUPD or iCPD. Progressive disease is confirmed (iCPD) in the new lesion category if the next imaging assessment, done at 4–8 weeks after iUPD, confirms additional new lesions or a further increase in new lesion size from iUPD (sum of measures increase in new lesion target ≥5 mm, any increase for new lesion non-target). Notably, if iUPD criteria were met on the basis of progression in the target or non-target disease, or the appearance of new lesions, then RECIST 1.1-assigned progression in another lesion category in the confirmatory scan also confirms iCPD.

(2) Best Overall Response (iBOR)

For iRECIST, the best overall response (iBOR) is the best timepoint response recorded from the start of the study treatment until confirmed disease progression(iCPD) or subsequent anti-tumor therapies started, taking into account any requirement for confirmation.

Confirmation of response which required in RECIST 1.1 is also recommended for iRECIST. The duration of iCR and iPR is from the timepoint when the criteria for iCR or iPR are first met, whereas the duration of iSD is still calculated from baseline. Specific rules are as follows:

Table 4 iCR and iPR confirmation rule for Best Overall Response(iBOR)

Overall response First time point	Overall response Subsequent time point[a]	Best overall response
iCR	iCR	iCR
iCR	iPR	iSD if iSD duration of no less than 39 days from

		first administration date of study drug was met, otherwise, iUPD
iCR	iSD	iSD if iSD duration of no less than 39 days from first administration date of study drug was met, otherwise, iUPD
iCR	iUPD	iSD if iSD duration of no less than 39 days from first administration date of study drug was met, otherwise, iUPD
iCR	NE	iSD if iSD duration of no less than 39 days from first administration date of study drug was met, otherwise NE
iCR		iSD if iSD duration of no less than 39 days from first administration date of study drug was met, otherwise NE
iPR	iCR	iPR
iPR	iPR	iPR
iPR	iSD	iSD
iPR	iUPD	iSD if iSD duration of no less than 39 days from first administration date of study drug was met, otherwise, iUPD
iPR	NE	iSD if iSD duration of no less than 39 days from first administration date of study drug was met, otherwise NE
iPR		iSD if iSD duration of no less than 39 days from first administration date of study drug was met, otherwise NE
NE	NE	NE

[a] Subsequent confirmed tumor response should be at least 4 weeks after previous tumor response. In the case where a patient has two non-consecutive visit responses of iPR, then, as long as the time between the 2 visits of iPR is greater than 4 weeks and there is no iUPD between the iPR visits, the patient will be defined as a responder. Similarly, if a patient has visit responses of iCR, NE, iCR, then, as long as the time between the 2 visits of iCR is greater than 4 weeks, then a best response of iCR will be assigned.

iBOR will be assigned as iCPD if iUPD is confirmed at the next imaging assessment after 4–8 weeks later and there are no evidence of iCR/iPR or iSD. For the situation of assessments that are not done or are not evaluable should be disregarded, for example, an iUPD followed by an assessment that was not done or not evaluable, and then another unconfirmed progressive disease, would be indicative of iCPD.

iUPD will be determined as iBOR if there are evaluable response assessment and no evidence of iCR/iPR or iSD or iCPD.

NE will be determined as iBOR if there are no evidence of iCR/iPR or iSD or iUPD/ iCPD .

(3) Event Date

The event date to be used for calculation of progression date should be the first date at which progression criteria are met (ie, the date of iUPD) provided that iCPD is confirmed at the next assessment. If iUPD occurs, but is disregarded because of later iSD, iPR, or iCR, that iUPD date should not be used as the progression event date.

If progression is not confirmed and there is no subsequent iSD, iPR, or iCR, then the iUPD date should still be used in the following scenarios: if the patient stops study treatment, or no further response assessments are done; the next timepoint responses are all iUPD, and iCPD never occurs; or the patient dies from disease progression.

3.7 SAFETY ANALYSES

Safety analysis will be based on safety analysis set. Descriptive statistics will be used to summarize all safety data.

3.7.1 Exposure of Study Medication

For administration of Atezolizumab and Bevacizumab, details information will be provided as below:

- Number of cycles (actual number of the administrations)
- Duration of exposure (week) = (min (date of last dose +21 days, date of death, date of subject discontinued the Atezolizumab/ Bevacizumab, subsequent anti-tumor treatment-1day) – date of first dose)/7;
- Cumulative dose (mg)
- Mean Dose Per Cycle(mg/cycle) = cumulative dose (mg)/number of cycles
- For atezolizumab, dose intensity (DI) (mg/week) = cumulative dose (mg)/ duration of exposure (week);
  For bevacizumab, DI (mg/kg/week) = sum of the actual dose per cycle (mg/kg)/ duration of exposure (week), where, sum of the actual dose per cycle (mg/kg) = sum(dose actual administered(mg) per cycle /weight(kg) per cycle)
- For atezolizumab, relative dose intensity (RDI)(%) = 100*(DI (mg/week)/ planned dose intensity(mg/week)), planned dose intensity(mg/week) = (1200* number of cycles)/ duration of exposure (week);
  For bevacizumab, RDI (%) = 100*(DI (mg/kg/week)/ planned dose intensity(mg/kg/week)), planned dose intensity(mg/kg/week) = sum of the planned dose per cycle(mg/kg)/ duration of exposure (week), where sum of the planned dose per cycle(mg/kg)= sum(dose planned administered(mg) per cycle /weight(kg) per cycle)
- Premedication given? (Yes, No)
- Injection/infusion modified (Yes, No)
  - Reason for injection/infusion modification (including Adverse Event, Medication error, Other)
- Treatment modification (Infusion Stopped and Restarted at the same rate, Infusion Stopped and Restarted at a lower rate, Prematurely stopped and not restarted)

The exposure of study medication will be descriptively summarized. The number and percentage of patients with dose modification and the reasons will be summarized.

Administration of Atezolizumab and Bevacizumab will be displayed by patients.

3.7.2 Adverse Events

Verbatim adverse event terms will be mapped to Medical Dictionary for Regulatory Activities (MedDRA) thesaurus terms, and adverse event severity will be graded according to NCI CTCAE v5.0. Adverse events will be coded to primary System Organ Class (SOC) and preferred term (PT) using MedDRA, Version xx or the latest version before database lock.

The adverse event severity grading scale for the NCI CTCAE (V5.0) will be used for assessing adverse event severity.

A treatment-emergent adverse event(TEAE) is defined as any adverse event reported, or worsening of an existing condition, on or after the first dose of study drug. AE analysis will be based on TEAEs, all AEs will be listed regardless of whether they are a TEAEs.

An overview table, all AEs occurring after the initiation of treatment will be summarized. Summaries of AEs by grade, seriousness, and relationship to Atezolizumab or Bevacizumab will be presented, as well as summaries of adverse events of special interest (AESI) for this study, AESI related to Atezolizumab, AESI related to Bevacizumab, irAE, serious irAE related to Atezolizumab, Non- serious irAE related to Atezolizumab, infusion-related reaction (IRR), AEs leading to death, drug interrupted, drug withdrawn, study discontinuation from study.

The number (percent) of patients with AEs will also be summarized by SOC, PT and maximum grade according to CTCAE, Version 5.0. If a MedDRA term is reported more than once for a subject, that subject will be counted only once in the incidence count for that MedDRA term with closest relationship to study treatment.

The number (percent) of patients with AEs will also be summarized by highest grade (≥ Grade 3) according to CTCAE, Version 5.0.

AEs includes:

- TEAE
- Most Common(Incidence rate≥10%) TEAE
- TEAEs related to Atezolizumab
- TEAEs related to Bevacizumab
- TEAEs lead to drug interrupted (Atezolizumab)
- TEAEs lead to drug interrupted (Bevacizumab)
- TEAEs lead to drug withdrawn (Atezolizumab)
- TEAEs lead to drug withdrawn (Bevacizumab)
- TEAEs related to Atezolizumab lead to study discontinuation
- TEAEs related to Bevacizumab lead to study discontinuation
- Serious adverse events (SAE)
- ≥ Grade 3 adverse events
- AESI
- AESI related to Atezolizumab
- AESI related to Bevacizumab
- TEAEs lead to death

3.7.3 Laboratory Data

Laboratory results will be converted into System International (SI) units. For quantitative parameters (hematology, chemistry, coagulation, thyroid), descriptive statistics will be performed on the results and their changes from baseline of the scheduled visits. If the laboratory test result is ">" or "<", the lower limit or upper limit of the test result will be used as the analysis value. For example, if the result is'>100', the analysis value will be assigned as 100.

For qualitative parameters (urinalysis) will be summarized base on reference range (normal, high, low) by visit.

In order to further evaluate the laboratory test results of potential clinical significance, some specific parameters of hematology, chemistry and coagulation will be graded with CTCAE (version 5.0) if applicable. And shift table from baseline to maximum toxicity grade during treatment period will be summarized (based on all visits, including unscheduled visits).

All grades will be based on lab values (direct or some derived values, or corrected values), regardless of the measures or symptoms consequences taken against them.

A severity grade of 0 will be assigned when the value is within normal limits.

In addition, some modifications to the grading system will be applied:

- Grade 5 refers to fatal outcomes, which cannot be determined solely by lab values, therefore will not appear in the grading system.
- Grade 0 would include all other lab values without corresponding grades except missing values.
- Missing results shall be graded as missing.

For some specific parameters with CTCAE grading in both high and low direction (e.g., hemoglobin, lymphocyte count), CTCAE in high and low directions will be presented separately, i.e. hyper for higher values of concern and hypo for lower values of concern.

All laboratory test, including thyroid function testing, pregnancy test and urinalysis will be performed in study and except pregnancy test, the abnormal results will be listed.

3.7.4 Vital Signs

Descriptive statistics for vital signs parameters (respiratory rate, pulse rate, systolic and diastolic blood pressure, temperature and weight) and change from baseline will be presented by visit. These vital signs will be listed for each subject by visit.

3.7.5 Physical Examination Finding

Physical examination findings are to be assessed as normal and abnormal (including Clinically Significant and Not Clinically Significant). Numbers and proportions of patients will be presented by visit and the worst findings of post-treatment (based on all visits, including unscheduled visits). And abnormal is worse than normal, abnormal, CS is worse than abnormal, NCS. A listing of physical examination findings will be provided by patients.

3.7.6 ECG Results

At each visit, the ECG result is to be assessed as being normal, abnormal, not clinically significant, abnormal and clinically significant. Numbers and proportions of patients will be presented by visit and the worst findings of post-treatment (based on all visits, including unscheduled visits). And abnormal is worse than normal, abnormal, CS is worse than abnormal, NCS. A listing of ECG findings and parameter values will be provided by patients.

3.7.7 ECOG performance status

ECOG performance status will be listed by subject.

3.8 HEALTH STATUS UTILITY ANALYSES

To more fully characterize the clinical profile of atezolizumab, PRO data will be obtained through use of the following instruments: European Organization for Research and Treatment of Cancer (EORTC) quality-of-life questionnaires for cancer (EORTC QLQ-C30) and lung cancer (EORTC QLQ-LC13).

The EORTC QLQ-C30 is an internationally validated cancer-specific HRQOL questionnaire. The 30-item EORTC QLQ-C30 version 3 is composed by five multi-item function scales (physical, role, cognitive, emotional, and social), three multi-item symptom scales (fatigue, nausea and vomiting, and pain), six single-item symptom scales (dyspnea, insomnia, appetite loss, constipation, diarrhoea, and financial impact), and a two-item global quality of life scale (QL).

For questions 1 to 28, the scores from 1 to 4 correspond to 'Not at All', 'A Little', 'Quite a Bit' and 'Very Much' respectively. For questions 29 and 30, the scores range from 1 to 7, ranging from 'Very poor' to 'Excellent'. The scoring rules state that higher scores for functional areas and general health areas indicate better functional status and quality of life, and higher scores for

symptom areas indicate more symptoms or problems (poor quality of life). Therefore, the scores in various fields are standardized as follows:

The raw score for each field is calculated by dividing the total scores of items in each field by the number of entries. Second, the raw scores in each area will be standardized. The standard formulas are as follows:

- Function scales: Standard score= $\left(1-\frac{\text{Raw score}-1}{\text{Range}}\right)\times 100$;
- Symptom scales and global quality of life scale: Standard score= $\left(\frac{\text{Raw score}-1}{\text{Range}}\right)\times 100$.

Where, the range represents the range of the entry scores, for example, if the item score range of an item is 1~4, then the range is 3. Similarly, if the item score range of an item is 1~7, then the range is 6. **Error! Reference source not found.** summarizes the scoring rules for each field.

Table 3 Summary of relevant parameters of QLQ-C30 scoring

Scales	Nature of Scales	Number of Item	Range of Item	Calculation of Raw Scores
Global quality of life	Global quality of life scale	2	6	(Q29+Q30)/2
Physical Functioning	Functional	5	3	(Q1+Q2+Q3+Q4+Q5)/5
Role functioning	Functional	2	3	(Q6+Q7)/2
Emotional functioning	Functional	4	3	(Q21+Q22+Q23+Q24)/4
Cognitive functioning	Functional	2	3	(Q20+Q25)/2
Social functioning	Functional	2	3	(Q26+Q27)/2
Fatigue	Symptom	3	3	(Q10+Q12+Q18)/3
Nausea and vomiting	Symptom	2	3	(Q14+Q15)/2
Pain	Symptom	2	3	(Q9+Q19)/2
Dyspnoea	Symptom	1	3	Q8
Insomnia	Symptom	1	3	Q11
Appetite loss	Symptom	1	3	Q13
Constipation	Symptom	1	3	Q16
Diarrhoea	Symptom	1	3	Q17
Financial difficulties	Symptom	1	3	Q28
Note：Qxx represents the score of question XX.				

EORTC QLQ-LC13 is a specific module for lung cancer. It consists of 13 items covering lung cancer symptoms (dyspnea, coughing, hemoptysis, pain in chest, pain in arm or shoulder and pain in other parts) and the side effects of chemo- and radiotherapy (alopecia, peripheral neuropathy,

sore mouth, and dysphagia), which are divided into 10 fields, all of which are symptom types. **Error! Reference source not found.** summarizes the scoring rules for each field.

Table 4 Summary of relevant parameters of QLQ-LC13 scoring

Scales	Nature of Scales	Number of Item	Range of Item	Calculation of Raw Scores
Dyspnea	Symptom	3	3	(Q33+Q34+Q35)/3
Coughing	Symptom	1	3	Q31
Hemoptysis	Symptom	1	3	Q32
Sore mouth	Symptom	1	3	Q36
Dysphagia	Symptom	1	3	Q37
Peripheral neuropathy	Symptom	1	3	Q38
Alopecia	Symptom	1	3	Q39
Pain in chest	Symptom	1	3	Q40
Pain in arm or shoulder	Symptom	1	3	Q41
Pain in other parts	Symptom	1	3	Q42
Note：Qxx represents the score of question XX.				

Summary statistics will be reported for all of the items and subscales of EORTC QLQ-C30 questionnaire and the QLQ-LC13 according to the EORTC scoring manual guidelines. The mean change of the linear transformed scores from baseline will also be assessed as well as the proportion of patients with improved, stable, or worsened outcomes. A patient will be classified as improved if a decrement of 10 points or worse is observed in the average change from baseline scores across all available timepoints; and a patient will be classified as worsened if a 10-point or greater increase is observed in the average change from baseline scores across all available timepoints. Otherwise, classified as stable.

Completion and compliance rates will be summarized at each time point will be calculated as the number of patients who completed the assessment divided by the number of patients expected to complete the assessment at each time. Reasons for missing assessments, will be summarized using frequencies and percentages.

A listing of questionnaires values will be provided by patients.

Time to Deterioration (TTD)

The analysis populations for TTD will be all enrolled patients with a non-missing baseline PRO assessment.

TTD using EORTC is defined as the time from baseline (the start of the study treatment) to the first time the patient's score shows a ≥10 points increase above baseline in any of the following EORTC-transformed symptom subscale scores (whichever occurs first):

- Cough (single item, question 31 on the EORTC QLQ-LC13),
- Dyspnea (single item, each question of 33,34,35 on the QLQ-LC13),
- Dyspnea (multi-items, questions 33-35 on the QLQ-LC13),
- Chest pain (single item, question 40 on the QLQ-LC13)
- Arm/shoulder pain (single item, question 41 on the QLQ-LC13)

In order for the symptoms to be considered "deteriorated", score increase of ≥ 10 points above baseline must be held for at least two consecutive assessment or an initial score increase of ≥ 10

points is followed by death within 3 weeks from the last assessment. A "≥10 point" change in the symptoms subscale score is perceived by patients as clinically significant.
Patients will be censored at the last time when they complete an assessment if they have not deteriorated. If no post-baseline assessment is performed, patients will be censored at the first dose date plus 1 day.
TTD using the EORTC scale will be analyzed using the same methods as for PFS.

3.9 MISSING DATA

In general, other than for partial dates, missing data will not be imputed and will be treated as missing unless specified.

3.9.1 Date of Initial Diagnosis

Partial date of initial diagnosis will be imputed as below:

- If year is missing (or completely missing), do not impute;
- 15th of the month will be imputed as the initial diagnosis date if only the day is missing;
- July 1st of the year will be imputed as the initial diagnosis date if both the day and the month are missing;

The imputed date will be compared to start date of study drug. If it is later than the study drug start date, the start date of study drug will be used to impute the incomplete date.

3.9.2 Prior and Concomitant Medications

Start date of prior and concomitant medications

- If only the day of the month is missing, use the first day of the month to replace the missing part.
- If both the day and month are missing, January 1st will be used to replace the missing part.
- If Day, Month and Year are all missing, use a date one day before the first administration date of study drug.

End date of prior and concomitant medications

- If only Day is missing, use the last day of the month.
- If Day and Month are both missing, use the last day of the year.
- If Day, Month and Year are all missing, assign 'continuing' status to stop date

If the imputed concomitant end date is after the death date or the last known alive date, then the date of the death or last known alive will be imputed as the concomitant end date.

3.9.3 Adverse Events

Onset date of AE

If the AE onset date is completely missing, the AE start date will be imputed as the first administration date of study drug;

If the AE onset date is partial missing, then

- If both the year and month are available and the year and month are the corresponding year and month of the first administration date of study drug, then the AE onset date will be imputed as the first administration date of study drug;

- If both the year and month are available and the year or the month are not equal to the corresponding year and month of the first administration date of study drug, then the AE onset date will be imputed as the 1st date of the month;
- If only the year is available and the available year is the corresponding year of the first administration date of study drug, then the AE onset date will be imputed as the first administration date of study drug;
- If only the year is available, and the available year is not equal to the corresponding year of the first administration date of study drug, then the AE onset date will be imputed as the January 1st of the year.

End date of AE

- If both the year and month are available, AE end date will be imputed as the last day of the month;
- If only the year is available, AE end date will be imputed as the December 31 of the year.
- If the imputed AE end date is after the death date or the last known alive date, then the date of the death or last known alive will be imputed as the AE end date.

For adverse events continuing at the cut-off date, the end date will not be imputed and will be reported as "ongoing".

3.9.4 Last Known Alive Date

Partial missing last known alive date will be imputed as below:

- If both the day and the month are missing, January 1st of the year will be imputed.
- If only the day of the month is missing, use the 1st of the month to impute the last known alive date.

3.9.5 Date of Death

Missing or partial missing date of death will be imputed as below:

- If the year is missing (or completely missing), death dates will be imputed as the last known alive date + 1 day.
- If both the day and the month are missing, January 1st of the year will be imputed as the death dates.
- If only the day of the month is missing, use the 1st of the month to impute the date of death.

The imputed death date will be compared with the last known alive date (date of censoring for survival). The maximum of the (imputed death date, last known alive date + 1) will be considered as the date of death.

3.9.6 Date of Subsequent Anti-tumor Therapy

Subsequent anti-tumor therapies include Post-Study Treatment NSCLC Therapy.

- If only the day of the month is missing, the subsequent therapy will be assumed to start on the first day of given month if this day is latter than the last administration date of study drug. Otherwise, the subsequent therapy will be assumed to start on the next day following the last administration date of study drug.
- If both the day and month are missing the subsequent therapy will be assumed to start on the first day of given year if this day is latter than the last administration date of study drug.

Otherwise, the subsequent therapy will be assumed to start on the next day following the last administration date of study drug.

- If the start date is totally missing, the subsequent therapy will be assumed on the next day following the last dosing date.

3.10 INTERIM ANALYSES

One interim analysis is planned. The interim analysis will be performed for futility at the time of 19 patients completing ORR evaluation. According to preplanned stopping rules of Simon 2-stage design, further testing of Atezolizumab and Bevacizumab would be halted if the number of patients that respond in the first evaluable 19 patients (stage 1) is less or equal than 6. This study has probability of 66.6% terminate at the first stage.

The 19 subjects in phase I will be determined according to the order of enrollment (according to the date of informed consent) from evaluable population.

When the study runs into the second stage, in the end of the study, if more than 16 patients out of 39 patients have responses, we can recommend this treatment in IIIB-IV Non-squamous NSCLC to go to the next step in the clinical trial phase, otherwise, the treatment is rejected.

4. SUMMARY OF MAJOR CHANGES IN THE PLANNED ANALYSES

The Statistical Analysis Plan is developed based on this version 3.0 of the protocol. Three major changes are made to SAP from the protocol Amendment 3.0. Any further analysis changes made after this SAP is finalized will be documented with a SAP amendment or described in the clinical study report (CSR).

Three major changes are as follows:

1. In the protocol, the efficacy analysis will be based on FAS, which defined as all enrolled patients who receive any amount of study treatment and evaluable for efficacy endpoints. The analysis is not conservative for efficacy, hence in the SAP, FAS is defined as all enrolled patients who receive any amount at least one dose of any study treatment. All efficacy analysis except for primary analysis of ORR will use FAS, and patients without post-baseline radiologic assessment will be regarded as non-responder.

2.For ORR analysis, the primary analysis will be based on evaluable population, which defined as all enrolled patients who receive any amount of study treatment, have baseline and at least one post-baseline efficacy measurement.

3.In protocol, TTR analysis based on FAS, In the SAP, TTR will be analyzed for patients who achieved CR or PR, for non-responders will be excluded from the TTR analysis population.

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Appendix 1
Protocol Synopsis

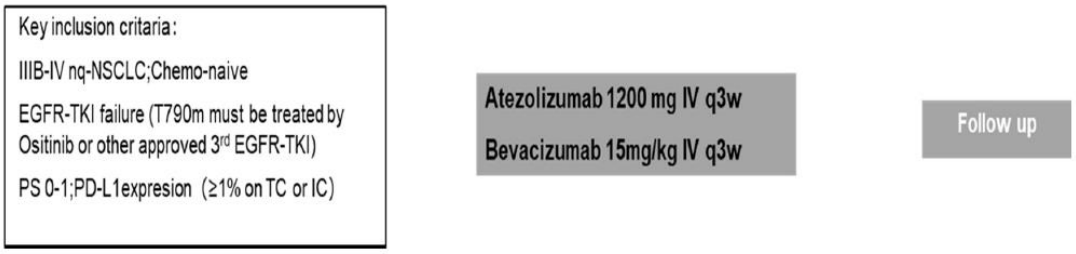
This is an open-label, single-arm, phase II, multicenter study designed to evaluated the efficacy and safety of atezolizumab in combination with bevacizumab in PD-L1-selected patients with Stage IIIB-IV Non-Squamous NSCLC harbored EGFR mutation after EGFR TKI therapy. Patients should have received at least one EGFR TKI and have disease progressed before enrollment.

This study will consist of a screening period (Day -28 to Day -1), a treatment period, a treatment discontinuation visit period (≤30 days after last dose) and a follow-up period. It is anticipated that this study will enroll about 44 patients at multiple sites in China.

At screening, tumor specimens (either fresh or archival) from each potentially eligible patient will be tested for PD-L1 expression by a central laboratory using an IHC assay. The specimens will be tested PD-L1 expression by Ventana SP142 and SP 263.The patients will be tested T790M by blood or re-biospy tissue sample. Tumor EGFR mutation status will also be confirmed by central laboratory using either tissue or blood samples.

Figure 2 presents an overview of the study design. A schedule of activities is provided in Appendix 2.

Figure 2 Study Schema



IV = intravenous; NSCLC = non-small cell lung cancer;

All eligible enrollees will receive atezolizumab by intravenous (IV) infusion at a fixed dose of 1200 mg on Day 1 of each 21-day cycle. Bevacizumab will be administered by IV infusion at 15 mg/kg on Day 1 of each 21-day cycle. Patients will continue treatment until progressive disease, unacceptable toxicity, or death. Patients may continue treatment beyond radiographic progression by RECIST v1.1, provided they are experiencing clinical benefit as assessed by investigator (i.e., in the absence of unacceptable toxicity or symptomatic deterioration attributed to disease progression as determined by the investigator after an integrated assessment of radiographic data, biopsy results (if available), and clinical status (see below). Patients who temporarily or permanently discontinue either atezolizumab or bevacizumab may continue on single-agent therapy until disease progression (i.e., patients temporarily withdrawn from bevacizumab due to adverse effects may continue atezolizumab monotherapy and vice versa). Because of the possibility of an initial increase in tumor burden caused by immune-cell infiltration in the setting of a T-cell response (termed pseudoprogression) with atezolizumab treatment, radiographic

progression per RECIST v1.1 may not be indicative of true disease progression. In the absence of unacceptable toxicity, patients who meet criteria for disease progression per RECIST v1.1 while receiving atezolizumab will be permitted to continue atezolizumab if they meet all of the following criteria:

- Evidence of clinical benefit, as determined by the investigator following a review of all available data
- Absence of symptoms and signs (including laboratory values, such as new or worsening hypercalcemia) indicating unequivocal progression of disease
- Absence of 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 will undergo tumor assessments at baseline and every 6 weeks (±7days) for the first 36 weeks following Cycle 1, Day 1, regardless of dose delays. After 36 weeks, tumor assessment will be required every 9 weeks (±7days). Patients will undergo tumor assessments until radiographic disease progression per RECIST v1.1 or loss of clinical benefit (for atezolizumab treated patients who continue treatment after radiographic disease progression according to RECIST v1.1), withdrawal of consent, study termination by Sponsor, or death, whichever occurs first. Patients who discontinue treatment for reasons other than radiographic disease progression (e.g., toxicity) will continue scheduled tumor assessments until radiographic disease progression per RECIST v1.1 or loss of clinical benefit (for atezolizumab treated patients who continue treatment after radiographic disease progression according to RECIST v1.1), withdrawal of consent, study termination by Sponsor, or death, whichever occurs first, even if patient starts another anti-cancer therapy after study treatment discontinuation, unless consent is withdrawn.

Appendix 2
Schedule of Assessments

	Screening	Treatment [a]	Treatment discontinuation	Survival follow-up
	Days-28 to -1	Every 21 days (±3 Days)	≤30 days after Final Dose or at initiation of other anti-cancer therapy (whichever occurs first)	Every 3 months after disease progression or loss of clinical benefit
Informed consent	X[b]			
Tumor tissue specimen for PD-L1 and EGFR testing (5 FFPE slides required; blocks preferred)[c] *Fresh or archival tissue can be used.*	X			
Demographic data	X			
Medical history and baseline conditions	X			
NSCLC Cancer History	X			
Vital Signs [d]	X	X	X	
Weight	X	X	X	
Height	X			
Complete physical examination	X			
Limited physical examination [e]		X	X	
ECOG Performance Status	X	X	X	
12-Lead ECG	X	X [f]	X [f]	
LVEF[g]	X			
Hematology [h]	X	X	X	
Chemistry [i]	X	X	X	
Pregnancy test[j]	X [j]	X [k]	X [k]	
Coagulation test (aPTT or INR)	X		X	
TSH, free T3, free T4	X	X [l]	X [l]	
Viral serology (HIV,HBV,HCV） [m]	X			
Urinalysis [n]	X	X	X	
Blood sample for biomarkers [o]	X			
Tumor response assessments	X [p]	X [q,r]		X [s]
Concomitant medications [t]	X	X	X	
Adverse events [u]	X	X	X	X
Study drugs infusion [v]		X		
Patient-reported outcomes		X [w]		X [x]
Survival and anti-cancer therapy follow-up			X [y]	X [y]

a. Assessments should be performed before study drug infusion unless otherwise noted.
b. Informed consent must be documented before any study-specific screening procedure is performed, and may be obtained more than 28 days before initiation of study treatment.

c. Optional biopsy at screening is the preferred method to collected the tumor specimens for PD-L1 expression at screening and T790M mutation For PD-L1 testing, if archival tissue is unavailable or is determined to be unsuitable for required testing, a pretreatment tumor biopsy is required. A pretreatment tumor biopsy may also be performed if a patient's archival tissue test results do not meet eligibility criteria. (section 4.5.6)
d. Includes respiratory rate, pulse rate, systolic and diastolic blood pressure, 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.
e. Perform a limited, symptom-directed examination at specified timepoints and as clinically indicated at other timepoints. Record new or worsened clinically significant abnormalities on the Adverse Event eCRF.
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. Baseline evaluation of left ventricular ejection fraction (LVEF) should be considered for all patients, especially in those with cardiac risk factors and/or history of coronary artery disease or where low LVEF is suspected.
h. Hematology consists of CBC, including RBC count, hemoglobin, hematocrit, WBC count with differential (neutrophils, lymphocytes, eosinophils, monocytes, basophils, and other cells), and platelet count.
i. Serum chemistry includes BUN or urea, creatinine, sodium, potassium, magnesium, chloride, bicarbonate or total CO2, calcium, phosphorus, glucose, total bilirubin, ALT, AST, alkaline phosphatase, LDH, total protein, and albumin.
j. All women of childbearing potential will have a serum pregnancy test within 14 days before Cycle 1, Day 1.
k. Urine pregnancy tests performed at each subsequent visits; if a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test.
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 four cycles thereafter
m. At screening, patients will be tested for HIV, HBsAg, 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. The patient could be enrolled if the HBV DNA is negative (below the lower detection limit of each site). 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 HCV infection.
n. Includes pH, specific gravity, glucose, protein, ketones, and blood); dipstick permitted.
o. If T790m mutation unknown and re-biopsy tissue sample unavailable，blood sample will be tested for T790M.
p. CT scans (with oral/IV contrast unless contraindicated) or MRI of the chest and abdomen. A CT or MRI scan of the pelvis is required at screening and as clinically indicated or as per local standard of care at subsequent response evaluations. A CT (with contrast) or MRI scan of the head must be done at screening to evaluate CNS metastasis in all patients. For patient with unknown bone metastases, if ALP ＞2.5xULN and ≤5x ULN and/or have symptom of suspect bone metastases，bone scan should be done at screening.
q. Patients will undergo tumor assessments at baseline and every 6 weeks (±7days) for the first 36 weeks following Cycle 1, Day 1, regardless of dose delays. After 36 weeks, tumor assessment will be required every 9 weeks (±7days). Patients will undergo tumor assessments until radiographic disease progression per RECIST v1.1 or loss of clinical benefit (for atezolizumab treated patients who continue treatment after radiographic disease progression according to RECIST v1.1), withdrawal of consent, study termination by Sponsor, or death, whichever occurs first.
r. All measurable and evaluable lesions should be re-assessed at each subsequent tumor evaluation. The same radiographic procedures used to assess disease sites at screening should be used for subsequent tumor assessments (e.g., the same contrast protocol for CT scans).
s. If a patient discontinues study treatment for any reason other than disease progression, tumor assessments will continue at the same frequency as would have been followed if the patient had remained on study treatment untilradiographic disease progression per RECIST v1.1 or loss of clinical benefit (for atezolizumab treated patients who continue treatment after radiographic disease progression according to RECIST v1.1), withdrawal of consent, study termination by Sponsor, or death, whichever occurs first., even if patient starts another anti-cancer therapy after study treatment discontinuation, unless consent is withdrawn.
t. Medication (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by a patient in addition to protocol-mandated treatment from 7 days before screening until the treatment discontinuation visit.
u. 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. After initiation of study treatment, all adverse events will be reported until 30 days after the final 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, regardless of relationship to study treatment, will be reported until 90 days after the last dose of study treatment or initiation of new non-protocol systemic anti-cancer therapy after the last dose of study treatment, whichever occurs first. After this period, all deaths, regardless of cause, should be reported. In addition, the investigator should report any serious adverse event or adverse events of special interest that is believed to be related to prior exposure to study treatment.
v. The initial infusion 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. The initial dose of

bevacizumab will be delivered over 90 (± 15) minutes. If the first infusion is tolerated without infusion associated adverse events, the second infusion may be delivered over 60 (± 10) minutes. If the 60 minute infusion is well tolerated, all subsequent infusions may be delivered over 30 (± 10) minutes. The investigator should follow each AE until the event has resolved to baseline grade or better, the event is assessed as stable by the investigator, the patient is lost to follow-up, or the patient withdraws consent. Every effort should be made to follow all SAEs considered to be related to study drug or study-related procedures until a final outcome can be reported.w. PRO assessments will be completed before the patient receives any information on disease status and prior to the performance of non-PRO assessments and the administration of study treatment. Study personnel should review all questionnaires for completeness before the patient leaves the investigational site.

x. During survival follow-up, the PRO questionnaires will be completed at 3 and 6 months following disease progression or loss of clinical benefit as determined by the investigator(for patients who continue atezolizumab after radiographic disease progression).

y. After treatment discontinuation, information on survival follow-up and new anti-cancer therapy (including targeted therapy and immunotherapy) will be collected via telephone calls, patient medical records, and/or clinic visits approximately every 3 months (unless the patient withdraws consent or the Sponsor terminates the study). If a patient requests to be withdrawn from follow-up, this request must be documented in the source documents and signed by the investigator. If the patient withdraws from the study, the study staff may use a public information source (e.g., county records) to obtain information about survival status.

Appendix 3
Preexisting Autoimmune Disease and Immune Deficiencies

Patients should be carefully questioned regarding their history of acquired or congenital immune deficiencies or autoimmune disease. Patients with any history of immune deficiencies or autoimmune disease listed in the table below are excluded from participating in the study. Possible exceptions to this exclusion could be patients with a medical history of such entities as atopic disease or childhood arthralgias where the clinical suspicion of autoimmune disease is low. Patients with a history of autoimmune-related hypothyroidism on a stable dose of thyroid replacement hormone may be eligible for this study. In addition, transient autoimmune manifestations of an acute infectious disease that resolved upon treatment of the infectious agent are not excluded (e.g., acute Lyme arthritis). Contact the Medical Monitor regarding any uncertainty over autoimmune exclusions.

Autoimmune Diseases and Immune Deficiencies

• Acute disseminated encephalomyelitis • Addison disease • Ankylosing spondylitis • Antiphospholipid antibody syndrome • Aplastic anemia • Autoimmune hemolytic anemia • Autoimmune hepatitis • Autoimmune hypoparathyroidism • Autoimmune hypophysitis • Autoimmune myocarditis • Autoimmune oophoritis • Autoimmune orchitis • Autoimmune thrombocytopenic purpura • Behçet disease • Bullous pemphigoid • Chronic fatigue syndrome • Chronic inflammatory demyelinating polyneuropathy • Churg-Strauss syndrome • Crohn disease	• Dermatomyositis • Diabetes mellitus type 1 • Dysautonomia • Epidermolysis bullosa acquisita • Gestational pemphigoid • Giant cell arteritis • Goodpasture syndrome • Graves disease • Guillain-Barré syndrome Hashimoto disease • IgA nephropathy • Inflammatory bowel disease • Interstitial cystitis • Kawasaki disease • Lambert-Eaton myasthenia syndrome • Lupus erythematosus • Lyme disease, chronic • Meniere syndrome • Mooren ulcer • Morphea • Multiple sclerosis • Myasthenia gravis	Neuromyotonia • Opsoclonus myoclonus syndrome • Optic neuritis • Ord thyroiditis • Pemphigus • Pernicious anemia • Polyarteritis nodosa • Polyarthritis • Polyglandular autoimmune syndrome • Primary biliary cirrhosis • Psoriasis • Reiter syndrome • Rheumatoid arthritis • Sarcoidosis • Scleroderma • Sjögren syndrome • Stiff-Person syndrome • Takayasu arteritis • Ulcerative colitis • Vitiligo • Vogt-Koyanagi-Harada disease • Wegener granulomatosis