Statistical Analysis Plan: AM0010 – 201 (J1L-AM-JZGD) (v3)

An Open-label Randomized Phase 2 Trial of AM0010 in Combination with Nivolumab vs Nivolumab Alone as Second-Line Therapy in Subjects with Stage IV/Metastatic Wild-Type (WT) Non-Small Cell Lung Cancer and Low Tumor Expression of PD-L1

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1. Statistical Analysis Plan: J1L-AM-JZGD: An Open-label Randomized Phase 2 Trial of AM0010 in Combination with Nivolumab vs Nivolumab Alone as Second-Line Therapy in Subjects with Stage IV/Metastatic Wild-Type (WT) Non-Small Cell Lung Cancer and Low Tumor Expression of PD-L1

(AM0010, pegilodecakin, LY3500518) Indication Studied

This study is a US only, open-label, randomized, multicenter, Phase 2 second-line trial in adult male and female patients with Stage IV/metastatic NSCLC whose tumors have negative or low expression (0% to 49%) of PD-L1 (without known EGFR mutation or ALK rearrangement) randomized to receive AM0010 in combination with nivolumab or nivolumab alone.

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Protocol J1L-AM-JZGD
Phase 2

Statistical Analysis Plan Version 1 electronically signed and approved by Lilly: 20 March 2019.
Statistical Analysis Plan Version 2 electronically signed and approved by Lilly on date provided below.

Approval Date: 10-Sep-2019 GMT

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3. Revision History

Statistical Analysis Plan Version 1 was approved prior to the first interim analysis. The first interim analysis was conducted based on data cut-off date: 18 March, 2019

Statistical Analysis Plan Version 2 was approved prior to the first interim analysis. The overall changes and rationale for the changes incorporated in Version 2 are as follows:

- updated to include providing descriptive statistics for the efficacy data at the interim analysis without performing any formal statistical test
- clarified the primary analysis for the primary endpoint objective response rate (ORR) to be based on response assessed per RECIST v1.1; analysis based on confirmed response is added as additional sensitivity analysis for ORR.
- added additional analysis on ORR

Statistical Analysis Plan Version 3 was approved prior to the primary endpoint ORR data lock. The overall changes and rationale for changes incorporated in Version 3 are as follows:

- updated to clarify that the data cut off for the primary analysis of the study will occur at 6 months after the last patient randomized
- clarified that corrected QT interval (QTc) will be calculated based on Fridericia formula

4. Study Objectives

4.1. Primary Objective

The primary objective of Study J1L-AM-JZGD (JZGD) is to evaluate objective response rate (based on RECIST v1.1) in AM0010 plus nivolumab and nivolumab alone in patients diagnosed with metastatic non-small cell lung cancer (NSCLC) who have been exposed to 1 prior systemic therapy, not containing anti-PD-1/PD-L1 treatment alone, in combination with an anti-CTLA-4 treatment or in combination with platinum-based chemotherapy, and whose tumors have negative or low PD-L1 expression. AM0010 is also known as pegilodecakin and LY3500518 and hereafter is referred to only as AM0010.

4.2. Secondary Objectives

The secondary objectives of the study are to estimate AM0010 plus nivolumab versus nivolumab alone with respect to each of the following:

- progression-free survival (PFS)
- overall survival (OS)
- disease control rate (DCR)
- duration of response (DOR)
- safety and tolerability profile

4.3. Exploratory Objectives

- To characterize AM0010 pharmacokinetics (PK) in combination with nivolumab
- To explore biomarkers including immune activation markers that may correlate with efficacy outcome measures

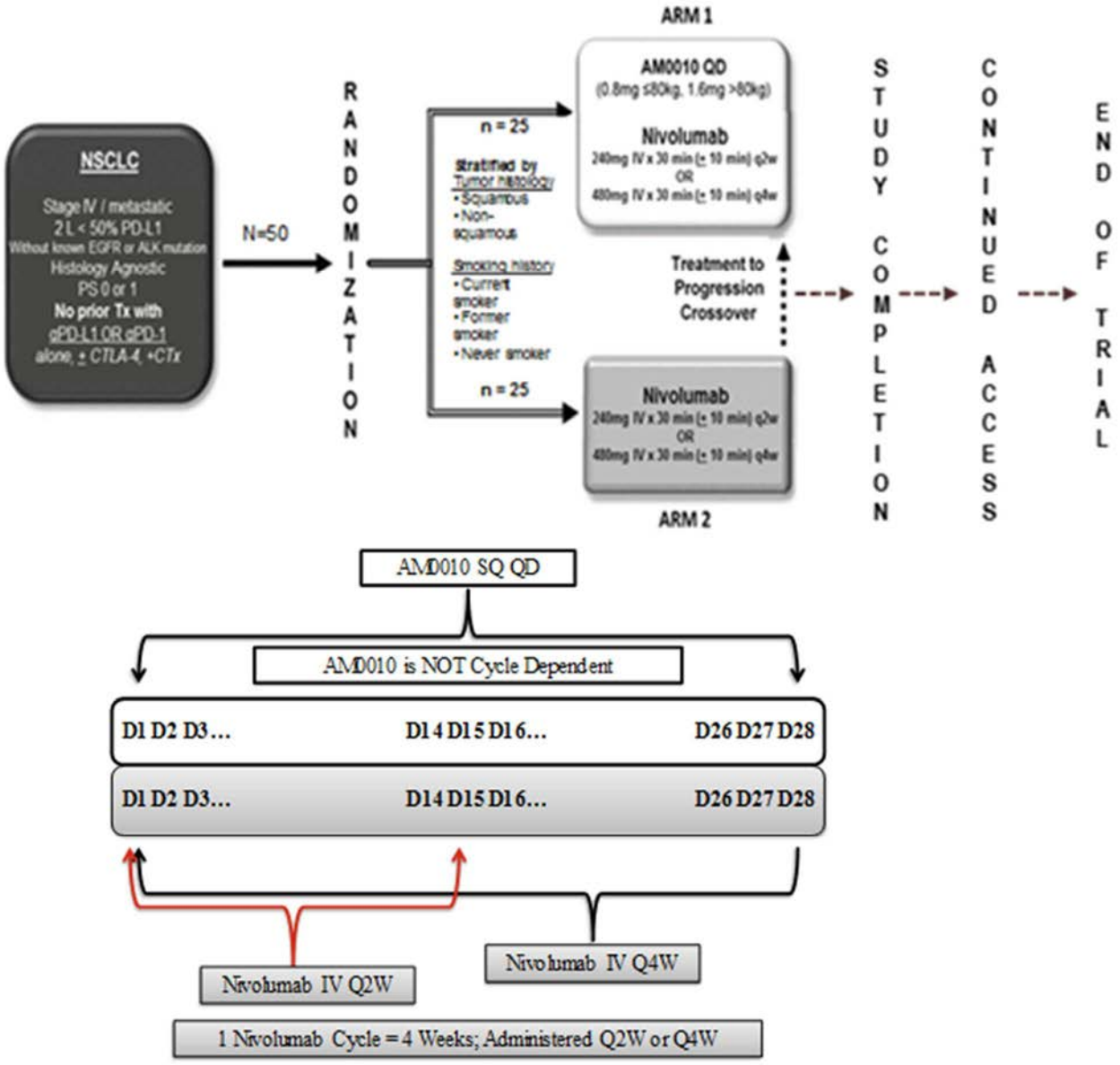
5. Study Design

5.1. Summary of Study Design

This is an open-label, randomized, multicenter, Phase 2 second-line trial in adult male and female patients with Stage IV/metastatic NSCLC whose tumors have negative or low expression (0% to 49%) of PD-L1 (without known EGFR mutation or ALK rearrangement). PD-L1 will be determined with any FDA-approved assay detecting PD-L1.

Patients will be stratified according to tumor histology (squamous vs non-squamous) and smoking history (current smoker, former smoker, and never smoker). Current smokers will include subjects with any tobacco use, former smokers will include subjects with a history of tobacco use who do not currently use any tobacco, and never smokers will include subjects who have never used any tobacco products.

- Arm 1: Patients will receive AM0010 and nivolumab
- Arm 2: Patients will receive nivolumab alone



Note: AM0010 is NOT cycle-dependent for either schedule of nivolumab.

Abbreviations: NSCLC = non-small cell lung cancer; PD-L1 = programmed death-ligand 1; Q2W = every 2 weeks; Q4W = every 4 weeks.

Figure JZGD.5.1. Trial and treatment design.

5.2. Determination of Sample Size

Approximately 50 patients will be randomized to the 2 treatment arms in a 1:1 ratio. With a total of 50 patients, 25 patients each arm would enable evaluating ORR for each treatment arm. With 25 patients in each treatment arm, the 90% confidence interval (CI) for an objective response rate would be (3%, 28%) if 3 patients (12%) had a response; (11%, 42%) if 6 patients (24%) had a response; and (17%, 50%) if 8 patients (32%) had a response.

6. A Priori Statistical Methods

6.1. General Considerations

6.1.1. Population

Enrolled Population: all patients who signed the informed consent form and were registered into the interactive web response system (IWRS).

Intent-to-Treat (ITT) population: all randomized patients per the IWRS.

Unless otherwise noted, all disposition analyses will be performed on the ITT population, all patient characteristic and efficacy analyses will be performed on the ITT population and all safety and exposure analyses will be performed on the safety population.

All analyses will be performed descriptively by treatment arm. Unless otherwise noted, all summary statistics on the ITT population will be performed by assigned treatment arm and all summary statistics on the safety population will be performed by actual treatment received.

Per-Protocol Population: all patients who are in the safety population and have no important protocol deviations.

The important protocol deviations which will result in exclusion from the Per-Protocol population are listed below. This is not an exhaustive list and may be amended over the course of the trial.

- patients with disease histology other than NSCLC
- patients with European Cooperative Oncology Group (ECOG) >1 at baseline
- patients who received more than one prior regimen in metastatic setting
- patients who do not have measurable disease at baseline
- patients receiving the incorrect randomized treatment assignment (any amount of duration)

Response Evaluable Population: all patients who are randomized and received any amount of study medication, have baseline adequate tumor assessment, and at least 1 post-baseline adequate tumor assessment.

Safety Population: all randomized patients who received any amount of study medication, AM0010 or nivolumab.

PK Population: all patients who are treated and with available serum time-concentration data from randomized patients.

Biomarker Population: all patients who are treated and with available biomarker data from randomized patients.

ADA Evaluable Population: all patients who are treated (in safety population), have baseline ADA (Anti-Drug Antibody) result, and at least one post-baseline ADA result.

6.1.2. Definitions and Conventions

Study treatment refers to AM0010 + nivolumab or nivolumab.

The date of randomization is the date the patient was randomly assigned to AM0010 + nivolumab arm or nivolumab arm using the IWRS.

The date of **first** dose is the date of the first dose of any study treatments.

The baseline value of a safety assessment is the last value observed prior to the date of first dose.

The study day of a safety event or assessment will be calculated as:

- The difference between the date of the event or assessment and the date of first study dose plus 1 for all events or assessments occurring on or after the day of first dose. For example, if an event occurs on 08 June 2018 and the date of first dose was 06 June 2018, the study day of the event is 3.
- The difference between the date of the event or assessment and the date of first dose for all events or assessments occurring before the day of first dose. For example, if an event occurs on 05 June 2018 and the date of first dose was 06 June 2018, the study day of the event is -1.

The study day of an efficacy event or assessment will be calculated as:

- the difference between the date of the event or assessment and the date of randomization plus 1 for all events or assessments occurring on or after the date of randomization.
- the difference between the date of the event or assessment and the date of randomization for all events or assessments occurring before the date of randomization.
- 1 month = 30.4375 days
- 1 year = 365.25 days

Unless otherwise noted, summaries of continuous variables will include a mean, median, standard deviation (SD), minimum, and maximum.

Unless otherwise noted, summaries of categorical variables will include the frequency and percentage (relative to the population being analyzed) of each category.

6.2. Handling of Dropouts or Missing Data

With the exception of dates, missing data will not be imputed. The method of imputation for any dates that are imputed is described in the relevant section.

6.3. Patient Disposition

A detailed description of patient disposition will be provided. It will include a summary of the number and percentage of patients enrolled in the study, randomized in the study, treated in the study, reasons for discontinuation from study treatment, and reasons for discontinuation from study. If the reason for discontinuation is adverse event (AE), the associated AE term will be reported. Patients who cross over from nivolumab to AM0010 in combination with nivolumab following progressive disease will be summarized as well.

Protocol violation will be summarized by treatment arm.

6.4. Patient Characteristics

6.4.1. Demographics and Performance Status

Patient demographics will be summarized. Patient demographics will include the following:

- sex
- race
- ethnicity
- age
- height
- weight
- body mass index

6.4.2. Baseline Disease characteristics

Disease characteristics will be summarized. Variable of disease characteristics will include the following:

- time from initial diagnosis to randomization (months)
- initial diagnosis
- stage at initial diagnosis
- time from metastatic disease diagnosed date to randomization (months)
- PD-L1 tumor proportion score (%)
- tumor mutational burden
- smoking status
- baseline ECOG Performance Status

6.4.3. Medical History

Medical history terms will be coded using the Medical dictionary for Regulatory Activities[MedDRA].

A summary for medical history will be presented including the count and percent of patients with any medical history record and also by body system and preferred term.

6.4.4. Prior Therapies

Prior anti-cancer therapy and radiotherapy will be summarized. Line of prior anti-cancer therapy, prior anti-cancer therapy regimen, duration of the regimen, and the best response of the regimen will be summarized.

Prior radiotherapy, site, and duration of prior radiotherapy will be summarized.

Duration of the anti-cancer therapy and duration of the radiotherapy will be calculated as (therapy stop date – therapy start date + 1). If only month and year of a therapy is available, the day will be imputed using the 15th.

6.4.5. Subsequent Anti-Cancer Therapies

Therapies received following study treatment discontinuation will be summarized by treatment arm.

6.4.6. Concomitant Medications

All medications will be coded to the generic preferred name according to the current World Health Organization (WHO) drug dictionary. All concomitant medications will be summarized for the ITT population using the preferred name.

Selected concomitant medication such as steroid use will be summarized separately.

6.5. Efficacy Analyses

6.5.1. General Considerations

6.5.1.1. Population

Unless otherwise noted, all efficacy analyses will be performed on the ITT population.

6.5.1.2. Stratification Factors

The stratification factor for the analysis of primary and secondary analyses are:

- histology type (squamous versus non-squamous)
- smoking history (current smoker, former smoker, and never smoker)

The stratification factors are captured in the IWRS and on electronic case report forms (eCRFs). Unless otherwise specified, all stratified analyses will be based on the stratification factor per IWRS. A cross tabulation of the frequency of each level of the stratification factor, histology type, per IWRS, and eCRF will be produced.

6.5.2. Primary Endpoint: Objective Response Rate

6.5.2.1. Definition

The primary efficacy measure is ORR as defined by RECIST version 1.1 and determined by the investigator.

The ORR is defined as the number of patients with a complete response (CR) or partial response (PR) divided by the number of randomized patients recorded between the date of randomization and the date of objectively documented progression or the date of subsequent anti-cancer therapy, whichever occurs first. For patients without documented progression or subsequent anti-cancer therapy, all available response designations will contribute to the ORR

determination. For patients who continue treatment beyond progression due to suspected pseudoprogression is described in the protocol Section 7.6.

Rates and their corresponding 95% exact CI will be calculated by Clooper-Pearson method for each randomized treatment arm.

6.5.2.2. Additional Analysis of ORR

Objective response rate Analysis 1 (ORR1): the same primary analysis on the primary endpoint ORR will be performed on the response evaluable population.

Objective response rate Analysis 2 (ORR2): If the stratification factor, squamous versus non-squamous, at the IWRS and at baseline (CRF) disagrees for at least 10% for the randomized patients, similar analysis of ORR as primary analysis will be performed using the strata determined at baseline based on CRF.

Objective response rate Analysis 3 (ORR3): the same primary analysis on the confirmed ORR will be performed.

Objective response rate Analysis 3 (ORR4): the same primary analysis on the ORR including response observed beyond pseudoprogression will be performed.

6.5.3. Secondary Endpoints

6.5.3.1. Progression-Free Survival

6.5.3.1.1. Definition

Progression-free survival (PFS) is defined as the time from randomization to the date of documented progression (per scan or clinical progression as determined by the investigator) or the date of death due to any cause, whichever is earlier.

The detailed censoring rules are described in Table JZGD.6.1.

Table JZGD.6.1. Rules for Determining Date of Progression or Censor for Progression-Free Survival (PFS)

Rule	Situation	Date of Progression or Censor	Outcome
1	No baseline tumor assessments	Date of Randomization	Censored
2	No post baseline assessments and no death	Date of Randomization	Censored
3	No documented progression and no death (with a post-baseline tumor assessment)	Date of last adequate tumor assessment	Censored
4	Patient lost to follow-up (or withdrew consent from study participation) before documented progression or death	Date of last adequate tumor assessment	Censored
5	Progression per scan	Date of documented progression. If a tumor assessment was done on multiple days, use the earliest date for that assessment	Progressed
6	Clinical progression	Date of clinical progression	Progressed
6	Death without documented progression	Date of death	Progressed
7	Documented progression or death after missing ≥ two consecutive post-baseline tumor assessments	Date of last adequate tumor assessment before missed assessment or date of randomization, whichever is later	Censored
8	New anti-cancer therapy started without a prior documented progression or death	Date of last adequate tumor assessment before the start of new anti-cancer therapy	Censored
9	Documented progression or death after missing ≥ two consecutive post-baseline tumor assessments	Date of last adequate tumor assessment before the start of new anti-cancer therapy	Censored

Note: Progression-free survival and associated outcome is determined by the earliest of the dates above, if more than one situation applies. Two consecutive post-baseline tumor assessments refers to the next 2 protocol scheduled tumor assessments. Time is measured from the last adequate tumor assessment date. The window of the tumor assessment is also considered (that is, the weeks for the scheduled tumor assessments plus the window allowed for each scan is 7 days, for example a patient who goes more than (2*7*8+7) =119 days is considered missing 2 consecutive assessments) in the first year.

The PFS curves for each treatment arm will be estimated using the Kaplan-Meier product-limit method. Two-sided, 95% CI for the first quartile, median, and third quartile of PFS will be provided. Progression-free survival rates at fixed time points (every 3 months) will be estimated using Kaplan-Meier estimates on the PFS curve for each randomized arm provided minimum follow-up is longer than time point to generate the rate. Two-sided 95% Cis for the PFS rates will be calculated.

Restricted mean difference in PFS will be calculated. Following the suggestion of Karrison (1997), the restriction time T will be chosen as largest time point t such that the standard error (SE) of the survival estimate at time t in each treatment group is no more than 0.075. For this purpose, we will use the simple, albeit conservative, formula proposed by Peto et al. (1977) for calculating the SE of S(t) as:

$$SE\big(S(t)\big) = S(t)\sqrt{1 - S(t)/n(t)}$$

where n(t) is the number of patients still at risk at time t.

6.5.3.2. Overall Survival

Overall survival is defined as the time from the date of randomization to the date of death due to any cause. Patients who are alive will be censored at the date last known to be alive.

Overall survival will be analyzed in a similar manner as PFS. Duration of follow-up will be summarized.

6.5.3.3. Disease Control Rate

Disease control rate is defined as the proportion of patients who achieve SD plus CRs and PRs.

Disease control rate will be calculated for each randomized treatment arm and corresponding 95% CI will be provided.

6.5.3.4. Duration of Response

Duration of response is defined as the time from the date of first documentation of objective tumor response criteria for CR or PR (whichever is first recorded) to the date of the first documentation of tumor progression (clinical progression or progression per scans) or death due to any cause, whichever occurs first. If a patient does not progress following a response, then their duration of response will use the PFS censoring time.

The analysis of response duration will only include ITT patients with CR or PR. Duration of response will be summarized with descriptive statistics (median and 95% CI) for each treatment arm using the Kaplan-Meier method.

Duration of CR is defined as the time from the date of first documentation of objective response criteria for CR to the date of documentation of tumor progression (clinical progression or progression per scans) or death, whichever occurs first.

Duration of SD is defined as the time from randomization until the criteria for progression are met (clinical progression or progression per scans or death, whichever occurs first).

6.5.4. Other Efficacy Analyses

6.5.4.1. Best Objective Response Rate

Best objective response is calculated based on the overall visit response from each tumor assessment. It is the best response a patient has had following randomization but prior to starting any subsequent cancer therapy, prior to documented progression (clinical progression or

progression per scan) or the last tumor assessment in the absence of documented progression and subsequent cancer therapy.

Best objective response will be summarized using the following response categories: CR, PR, SD, progressive disease, and not evaluable.

6.5.4.2. Time to Response

Summary statistics of time to objective response will be provided for patients who achieve PR or CR. Time to response is defined as the time from the date of randomization and the date of first documentation of objective tumor response, CR or PR (whichever status is recorded first). No censoring observation will occur by definition.

6.5.4.3. Change in Tumor Burden

Percentage change from baseline in tumor burden will be calculated at each tumor assessment. Best percentage change from baseline in tumor burden will be calculated as the biggest decrease or the smallest increase in tumor burden from baseline.

Tumor burden is defined as the sum of the longest diameters of the target lesions (the measurable tumor lesions).

The percentage change from baseline in tumor burden is calculated as:

- (Sum of target lesions at week x – sum of target lesions at baseline) / sum of target lesions at baseline *100

6.5.5. Sensitivity Analyses

6.5.5.1. Progression Free Survival

Progression-Free Survival Sensitivity Analysis 1 (PFS event is disease progression per scan or death): clinical progression will not be considered as a progression event.

Progression-Free Survival Sensitivity Analysis 2: (PFS event is the earlier of disease progression per scan, clinical progression, or death): pseudoprogression without confirmation is not an event (progressive disease).

Progression-Free Survival Sensitivity Analysis 3 (PFS event is the earlier of disease progression per scan, clinical progression, death, or initiation of subsequent anti-cancer therapy): patient initiates subsequent anti-cancer therapy will be considered as a progression event at the date of initiation of subsequent anti-cancer therapy – 1 day.

6.5.5.2. Overall Survival

Overall Survival Sensitivity Analysis: Patients who crossover will be censored on the first dose date of crossover – 1 day.

6.6. Safety Analysis

6.6.1. Study Treatments

6.6.1.1. Extent of Exposure

Extent of exposure will be summarized, variables include: duration of treatment, number of cycles, total dose administered, dose intensity, and relative dose intensity for the entire treatment duration as well as for cycles if appropriate. Relative dose intensity (%) will be summarized using the following categories: <50%; 50% to <80%, 80% to <100%, ≥100%. Number and percentage of patients experiencing dose modification for each treatment arm and reasons will be provided.

The key parameters used to calculate dosing are shown in Table JZGD.6.2.

Table JZGD.6.2. Study Treatment Administration: Definition of Parameters

	AM0010	Nivolumab
Dosing schedule per protocol	0.8 mg for ≤80 kg body weight 1.6 mg for >80 kg body weight Daily dosing	240 mg Q2W or 480 mg Q4W
Duration of treatment (months)	(last dose date – first dose date + 1) / 30.4375	
Number of Cycles	see cycle definition for Nivolumab	When nivolumab administered If on Q2W schedule, every two doses count as a cycle If on Q4W schedule, every dose is a cycle
Cumulative Dose (mg)	Sum of the actual doses administered to a patient during the treatment period (not including cross over period)	Sum of the actual doses administered to a patient during the treatment period (not including cross over period).
Dose Intensity	mg received in a week (mg/week) cumulative dose / (duration of treatment / 7)	mg received in a cycle (mg/cycle) cumulative dose / total number of cycles
Relative Dose Intensity (%)	Actual dose intensity / planned dose intensity	

6.6.1.2. Dose Modifications

6.6.1.2.1. AM0010

Dose schedule of AM0010 may be modified for toxicity. Dose schedule reductions are defined in the protocol as follows:

Dose Schedule	Schedule Modification Criteria	AM0010
SC QD (continuous daily dosing)	-	Starting dose schedule
5 Days on/2 days off	First Grade 3 or 4 event(s)	First dose schedule reduction
4 Days on/3 days off	Second Grade 3 or 4 event(s)	Second dose schedule reduction
2 Days on/5 days off	Third Grade 3 or 4 event(s)	Third dose schedule reduction

Parameters summarized include number and percentage of patient with at least 1 dose schedule reduction and reason for dose schedule reduction, number and percentage of patients with a dose schedule reduction to 5 days on / 2 days off, number and percentage of patients with a dose schedule reduction to 4 days on / 3 days off, and number and percentage of patients with a dose schedule reduction to 2 days on / 5 days off.

Number and percentage of patients with at least 1 dose withhold and reason for dose withhold will be summarized. Number of dose withhold per patient will be summarized as well.

6.6.1.2.2. Nivolumab

Nivolumab dose reductions are not permitted. A dose will be considered as actually delayed if the delay is exceeding 2 days (i.e., ≥3 days from scheduled dosing date). Number of dose delays per patient, length of delay, and reason for delay will be summarized.

6.6.2. Adverse Events

Adverse event (AE) terms will be mapped using the Medical Dictionary for Regulatory Activities (MedDRA). Adverse events will be graded according to the National Cancer Institute (NCI) – A Common Terminology Criteria for Adverse Events (CTCAE) v 4.03.

Pre-existing conditions are defined as AEs that begin prior to the first dose of study drug.

A treatment emergent adverse event (TEAE) is defined as any AE that begins between the day of first dose and 30 days after treatment discontinuation (or up to any time if serious and related to study treatment), or any pre-existing condition that increases in CTCAE grade between the day of first dose and 30 days after treatment discontinuation (or up to any time if serious and related to study treatment).

Related AEs in patients treated with AM0010 in combination with nivolumab are defined as either related to AM0010 or related to nivolumab or both AM0010 and nivolumab.

The following TEAE/serious adverse events (SAE) outputs will be produced:

a. overview of TEAEs
b. summary of TEAEs by Preferred Terms (PTs) (all grade and grade ≥ 3)
c. summary of TEAEs by System Organ Class (SOC) and PT (all grade and grade ≥3)
d. summary of TEAEs by PT and Maximum Grade
e. listing of SAEs
f. summary of SAEs by SOC and PT (all grade and grade ≥3)
g. listing of TEAEs leading to study treatment discontinuation

Summaries b, c, d, and f will be produced for the related TEAEs/SAEs.

6.6.3. Deaths

All deaths on study will be listed along with the cause for death.

6.6.4. Consolidated AEs

Given the high level of granularity of the MedDRA dictionary, clinically identical or synonymous PTs reported under different terms in the database, in addition to being reported separately, will also be consolidated in a separate summary. The list of consolidated AE categories will be reported in the clinical study report.

6.6.5. Immune mediated AE

Potential immune mediated AE, such as colitis, pneumontitis, endocrine and hepatic events will be summarized.

6.6.6. AE of Special Interest

Adverse events of special interest (AESIs) are AEs thought to be potentially associated with the study treatment or the underlying disease per protocol. Therefore, aggregate or single AE terms for including additional medical interventions for identifying AEs possibly associated or possibly associated with the study drug were developed.

Adverse events of special interest are listed in the Investigator's Brochure. The Medical Dictionary for Regulatory Activities (MedDRA™) preferred terms (PTs) that are grouped under each of the AESI terms will be provided.

6.6.7. Clinical Laboratory Evaluation

Summary and change from baseline by cycle will be provided for selected hematology, chemistry, coagulation tests, and thyroid function parameters.

Hematology and chemistry laboratory values will be graded according to CTCAE v4.03. The laboratory grade will be summarized by cycle and maximum post-baseline grade. Shift tables from baseline to worst post-baseline CTCAE grade will be generated.

Listing of abnormal laboratory events will be presented.

6.6.8. Vital Signs

Vital signs (blood pressure, heart rate, temperature, and oxygen saturation), and weight will be summarized by cycle.

6.6.9. Electrocardiogram

Electrocardiogram parameters including QTc and change from baseline will be summarized by cycle and by treatment arm. QTc will be calculated based on Fridericia's formula (QTcF). Number and percent of patients for each QTc parameter for the following categories will be summarized:

- Absolute QTc<450, 450 to <480, 480 to 500, and >500 ms
- QTc change from baseline 30 to <60 ms and ≥60 ms.

6.6.10. ECOG Performance Status

European Cooperative Oncology Group performance status will be summarized by cycle.

6.6.11. Utilization

Utilization data will be summarized by category across arms. The following categories will be described:

- transfusions (on study treatment and during short-term follow up)
- hospitalizations (on study treatment and during short-term follow up)

For categorical variables, frequency and the corresponding proportions will be calculated.

6.7. Exploratory Analysis

6.7.1. Pharmacokinetic Analysis

Serum concentration data will be summarized. Descriptive statics will include mean, median, range, and SD, as appropriate.

Additional PK and/or PK/pharmacodynamic (PD) analyses may be conducted at interim as well as on final data. These will be specified in a separate PK/PD analysis plan.

6.7.2. Biomarker Analysis

Biomarker analyses will be described separately.

6.7.3. Immunogenicity Analysis

The Treatment Emergent (TE) ADA evaluable population will be defined within the Safety Population as those patients with both a baseline ADA test result and a postbaseline ADA test result. As a proportion of the TE ADA evaluable population, the number and frequency of the following will be tabulated by treatment group: TE ADA+ patients, and TE ADA+ patients with

detected higher-tier assay results. Included in the same tabulation will be, as a proportion of the TE ADA evaluable population, the number and frequency of patients with ADA present at baseline, as well as patients with detected higher-tier assay results at baseline.

A summary will be provided of the number and percentage of patients who receive AM0010 reporting specific TEAEs (overall and by PT) by patient TE ADA status (TE ADA+, TE ADA-, TE ADA Inconclusive, Patient not evaluable for TE ADA). The PT will be ordered by decreasing frequency in the TE ADA+ status group. The specific TEAE of interest are events in any one of the MedDRA Anaphylactic reactions Standardized MedDRA Query (SMQ), Hypersensitivity SMQ, Angioedema SMQ, Injection site reactions High Level Term (HLT), or Infusion site reactions HLT.

Additional immunogenicity analyses, to be presented in a standalone immunogenicity report in context with other studies of AM0010, will be described in a separate SAP.

6.7.4. Crossover Patients

Patients in Arm 2 (nivolumab) who crossover to Arm 1 (AM0010 in combination with nivolumab) following documented disease progression will be analyzed accordingly if data warrants.

For patients who crossover to Arm 1 after documented disease progression on nivolumab, time to progression while on nivolumab and time to progression following progression will be estimated, where the time to progression following crossover is defined as the time from time of crossover to the earliest documented disease progression. The last available tumor assessment before crossover will serve as the baseline for disease assessment post crossover. If the number of events permits, time to progression before and after crossover will be summarized descriptively using the Kaplan-Meier method

Patients who crossover to the AM0010 in combination with nivolumab are censored at time of crossover (i.e., AEs occurring during treatment with AM0010+nivolumab are excluded for control arm (nivolumab) patients). An exploratory safety analysis may be conducted for the crossover patients including all adverse events starting from the date of first dose of AM0010+nivolumab.

6.8. Timing of Planned Analyses

Interim analysis may be conducted to evaluate patient's safety. Efficacy data will be described without performing any formal statistical test. The primary analysis (data cut off) will occur 6 months after the last patient randomized.

7. References

Karrison TG. Use of Irwin's restricted mean as an index for comparing survival in different treatment groups-- interpretation and power considerations. *Control Clin Trials.* 1997;(18):151-167.

Peto R, Pike MC, Armitage P, Breslow NE, Cox DR, Howard SV, Mantel N, McPherson K, Peto J, Smith PG. Design and analysis of randomized clinical trials requiring prolonged observation of each patient. II. analysis and examples. *Br J Cancer.* 1977;35(1):1-39.

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