Protocol Number: KY1044-CT01

Official Title: A Phase 1/2, Open-Label, Multi-Center Study of the Safety and Efficacy of KY1044 As Single Agent and in Combination with Anti-PD-L1 (Atezolizumab) in Adult Patients with Selected Advanced Malignancies

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Statistical Analysis Plan (SAP)

Protocol Title:	A Phase 1/2, open-label, multi-center study of the safety and efficacy of KY1044 as single agent and in combination with anti-PD-L1 (atezolizumab) in adult patients with selected advanced malignancies
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1.0 Table of Contents

2.0 Purpose

The statistical analysis plan (SAP) describes the statistical methods to be used during the reporting and analyses of data collected under Kymab Ltd. Protocol KY1044-CT01.

3.0 Scope

The SAP outlines the following:

- Study Objectives
- Study Design
- Study Endpoints
- Applicable Study Definitions
- Statistical Methods for analysis of all endpoints

4.0 Introduction

This SAP describes the statistical methods to be used during the reporting and analyses of data collected under Kymab Ltd Protocol KY1044-C01. It should be read in conjunction with the current study protocol and case report form (CRF). This version of the plan has been developed using protocol version 7.0 dated 18-Nov-2021 and CRF version 4.1 dated 06-Jul-2021. Any changes to the protocol or CRF may necessitate updates to the SAP.

Changes following approval of the first version of the SAP will be tracked in the Document History section of this document and a final version of the updated SAP will be approved prior to database lock.

5.0 Study Objectives

5.1 Primary Objectives

Phase 1:

To characterize the safety and tolerability of KY1044 as single agent and in combination with atezolizumab and to identify recommended doses for future studies.

Phase 2:

To estimate the anti-tumor efficacy of KY1044 as single agent and in combination with atezolizumab.

5.2 Secondary Objectives

- To evaluate the preliminary anti-tumor activity of KY1044 as single agent and in combination with atezolizumab (Phase 1 only).
- To characterize the safety and tolerability of KY1044 as single agent and in combination with atezolizumab (Phase 2 only).
- To characterize the pharmacokinetic (PK) profile of KY1044 as single agent and in combination with atezolizumab.
- To assess emergence of anti-KY1044 and anti-atezolizumab antibodies following one or more intravenous (i.v). infusions of KY1044 as single agent and/or in combination with atezolizumab, respectively.
- To assess changes in biomarkers from baseline in tumor tissue as potential predictors of efficacy of KY1044 as single agent and in combination with atezolizumab.
- To describe the survival rate at 12 and 24 months of patients treated with KY1044 as single agent and in combination with atezolizumab for each disease group.

5.3 Exploratory Objectives

- To assess the pharmacodynamics (PD) effect of KY1044 as single agent and in combination with atezolizumab in tumor tissue.
- To assess the PD effect of KY1044 as single agent and in combination with atezolizumab in peripheral blood.
- To determine the level of target occupancy in response to KY1044 as single agent (Phase 1 only).

6.0 Study Design

This study is a first in human, open-label, Phase 1/2, multi-center study consisting of a Phase 1 dose escalation component with KY1044 as single agent and a dose escalation of KY1044 in combination with atezolizumab that will start after at least two cohorts of KY1044 as single agent have been considered to be safe and tolerable.

KY1044 will be administered i.v. every 3 weeks (Q3W). Atezolizumab will be administered according to dosing instructions given in the approved label for marketing (1200 mg i.v. Q3W) until the patient discontinues the study for up to 48 months.

Patients should not discontinue treatment based on progressive disease per response evaluation criteria in solid tumors version 1.1 (RECIST 1.1) (study discontinuation due to progressive disease as per iRECIST) unless clinical deterioration or increase in tumor markers is observed.

Phase 1:

In Phase 1, patients with advanced/metastatic malignancies (all comers) and with preferred indications will be enrolled. Preferred indications are: head and neck squamous cell carcinoma (HNSCC), gastric/esophageal cancer, hepatocellular carcinoma (HCC), non-small cell lung cancer (NSCLC), melanoma, cervical cancer, renal cell cancer, pancreatic cancer and triple negative BC.

Dose escalation part - KY1044 single agent

In the Phase 1 part of the study, cohorts of patients with advanced/metastatic malignancies, preferentially those with indications which are expected to have a high expression of inducible T cell costimulator (ICOS), will be treated with KY1044 as single agent Q3W until the maximal tolerated dose (MTD) is reached or a lower recommended phase 2 dose (RP2D) is established. It is expected that a RP2D based on safety, PK, and PD data may be established before the MTD is reached, as this has been the case with other checkpoint inhibitors.

The dose escalation will be guided by the Modified Toxicity Probability Interval Design (mTPI-2 design, Guo et al 2017 (1)), which is an adaptive dose-finding method that allows dose escalation and de-escalation according to the pre-calculated decision table in Appendix 14.1 of the SAP. The maximum sample size for dose escalation in each Phase 1 component (single agent and combination therapy) will be 36 patients, using cohorts of a minimum of three patients (Section 4.1.1 of the protocol).

Dose escalation part – KY1044 in combination with atezolizumab

The combination part of the study will commence after at least two cohorts of KY1044 as single agent have been considered to be safe and tolerable and the data suggest that it is reasonable to begin treatment in combination. The combination dose escalation will follow a Q3W dosing schedule. Treatment in combination will escalate until the MTD is reached or a lower RP2D is established based on safety, PK and available PD data. The dose escalation will be guided by the mTPI-2 design, which is an adaptive dose-finding method that allows dose escalation and de-escalation according to the pre-calculated decision table. The maximum sample size for dose escalation will be 36 patients using cohorts of a minimum of three patients.

Phase 1: Enrichment cohorts (optional)

An optional enrichment part may include the testing of additional patients at one or more dose levels to better understand the safety, tolerability, biomarkers, PK, preliminary anti-tumor efficacy and /or PK/PD relationships of KY1044 as single agent and/or in combination with atezolizumab.

The enrichment part of the study will only use doses that have already been explored in the Phase 1 dose escalation part of the study, and have been determined to be safe.

Total number of patients in Phase 1

The total number of patients included across all cohorts in the Phase 1 dose escalation and enrichment parts will be approximately 150.

Phase 2:

In Phase 2, patients will be enrolled

- in one or more specific indication(s), in which efficacy has been observed in Phase 1 to support definition of the RP2D for future indications and
- in tumor indications, where signs of anti-tumor activities were detected during Phase 1 (indications, where complete response (CR), partial response (PR) or durable stable disease (SD) with tumor shrinkage that does not qualify for PR have been observed) and
- in selected indications, HNSCC, NSCLC, gastric/esophageal cancer, cervical cancer,

In the absence of identifying an MTD or single efficacious dose in Phase 1, an initial Phase 2 dose assessment part in one or more specific indication(s) will be opened to compare the efficacy and biomarker readouts of two biologically relevant dose levels of KY1044 (as single agent or in combination with atezolizumab) in a more homogeneous population. Up to 20 patients (i.e. 15 anti-programmed cell death ligand 1 [PD-(L)1] naïve patients and where feasible five anti-PD-(L)1 pre-treated patients) will be included at each dose level and indication. Together with safety, efficacy and biomarker data from Phase 1, data from this part will assist with the selection of the RP2D. Once the MTD and/or RP2D has been identified, Phase 2 may be extended to explore efficacy at the RP2D in additional selected indications as described below.

KY1044 as Single Agent

A Phase 2 part will be opened should signs of anti-tumor activity (defined as CR, PR or SD with tumor shrinkage that does not qualify for PR) be seen in at least one subject in the Phase 1 dose escalation parts in any indication (in either anti-PD-(L)1 naïve or pre-treated patients). Initially up to 15 anti-PD-(L)1 naïve patients will be enrolled and depending on early efficacy additionally up to 30 patients will be enrolled per each indication. In the anti-PD-(L)1 pre-treated group of patients, initially five patients will be enrolled per indication and depending on early efficacy in these patients, additionally up to 15 patients will be enrolled in certain indications.

KY1044 in Combination with Atezolizumab

Patients will be enrolled in the Phase 2 part in selected indications (HNSCC, NSCLC, TNBC, gastric/esophageal and cervical cancers and any indication showing activity in the Phase 1 dose escalation of the combination) in order to assess preliminary anti-tumor efficacy. These patients will either be

- anti-PD-(L)1 treatment naïve or
- pre-treated with anti-PD-(L)1

In the anti-PD-(L)1 treatment naïve group, initially approximately 15 patients will be enrolled in a defined indication and depending on response rates, certain indications may be further expanded to up to 30 patients.

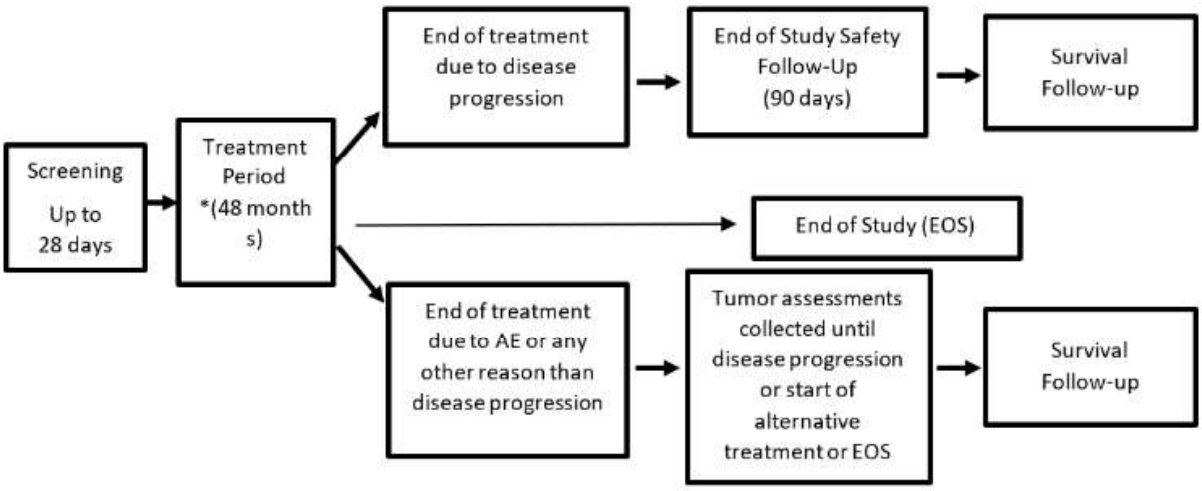
In the anti-PD-(L)1 pre-treated group, initially a minimum of five patients will be enrolled in each of the defined indications which may be further expanded to up to 15 patients, depending on emerging efficacy data.

Should enrolment for any of these disease indications not be feasible, or if the early response assessment (see below) suggests that there is only limited benefit in one or more of these indications, then enrolment to that group may be closed before the target is met.

Early Response Assessment in Phase 2:

The early assessment of objective response rate (ORR) will compare observed response rates to historical controls, to define a minimum number of objective responses (CR, PR or durable SD with tumor shrinkage that does not qualify for PR) per RECIST 1.1 per each indication in the initial Phase 2 phase, in order to decide if enrolment should be further extended up to 40 patients.

6.1 Study Flow Chart



*Note: Additional provisions may be made for patients who are ongoing on treatment and are still receiving clinical benefit at 48 months for continuation of treatment.

6.2 Sample Size Considerations

Phase 1:

A maximum of 36 patients will be used for each Phase 1 dose escalation component (single agent and combination therapy). The total number of patients included across all cohorts in the Phase 1 dose escalation and enrichment parts will be approximately 150.

Phase 2:

The initial Phase 2 dose assessment part in one or more specific indication(s) (Section 3.1.4 in the protocol) will include approximately 20 patients (that is 15 anti-PD-(L)1 naïve and where feasible five anti-PD-(L)1 pre-treated patients) at each of two dose levels of KY1044 (as single agent or in combination with atezolizumab).

Once the RP2D is established, Phase 2 may be extended and approximately 15 patients will be enrolled initially in each tumor type in the anti-PD-(L)1 naïve subgroup per each indication in either the single agent cohort or the combination cohort.

The full sample size of specific indications in Phase 2 of the study will be based on early evaluation of ORRs and only indications with promising response rates will be expanded further (up to 40 per subgroup). The Go-no-go decision criteria for cohort expansion will be based on historical ORR and a target ORR for KY1044 treatment. No formal statistical testing will be performed. Instead confidence intervals will be constructed around the ORR observed in each cohort, and this will enable decisions to be made around the likely success of future studies.

Historical ORR for monotherapy with immune checkpoint inhibitors in the second line metastatic setting are in the region of 15% to 25% for anti-PD-(L)1 inhibitors as monotherapy across the different indications and will be even lower in more advanced stages of disease (≥3 lines of anti-cancer treatment in the metastatic setting).

In order to illustrate the impact of sample sizes of 15 or expansion to 40 on the width of the confidence intervals, example evaluations are given for these 3 situations (ORR of 13% (3 and more lines of prior therapies in the advanced metastatic setting and 20% and 33% ORR for 2nd line metastatic setting) for cohort sizes of either 15 or 30 patients are given below:

- If the observed response rate is 13% (2/15), the 2-sided 80% confidence interval will be (4%, 32%).
- If the observed response rate is 20% (3/15), the 2-sided 80% confidence interval will be (8%, 39%).
- If the observed response rate is 33% (5/15), the 2-sided 80% confidence interval will be (17%, 53%).
- If the observed response rate is 13% (5/40), the 2-sided 80% confidence interval will be (6%, 22%).
- If the observed response rate is 20% (8/40), the 2-sided 80% confidence interval will be (12%, 30%).
- If the observed response rate is 33% (13/40), the 2-sided 80% confidence interval will be (23%, 44%).

In the anti-PD-(L)1 pre-treated subgroup, initially five patients will be recruited in each indication in either the single agent cohort or the combination cohort. These patients will have already progressed on previous immunotherapy; hence any individual response would indicate a proof of mechanism in these subject groups. If signs of efficacy have been observed in at least one subject any of these anti-PD-(L)1 pre-treated indications a further expansion up to 15 patients per cohort will be considered.

This number of patients, also offers the opportunity to evaluate further the safety and PK/PD of the chosen MTD/RP2D of KY1044 as single agent or in combination with Atezolizumab.

Overall a maximum of 412 patients may be enrolled into the study (Phases 1 and 2).

6.3 Randomization and Blinding

Not applicable. This is an open-label study without randomization.

7.0 Study Endpoints

7.1 Endpoint Attributes

Objectives	Endpoints
Primary	Primary Endpoints
Phase 1: To characterize the safety and tolerability of KY1044 as single agent and in combination with atezolizumab and to identify recommended doses for future studies. **Phase 2:** To estimate the anti-tumor efficacy of KY1044 as single agent and in combination with atezolizumab.	**Phase 1:** • Safety: Incidence and severity of adverse events (AEs) and serious AEs (SAEs), including changes in laboratory parameters, vital signs and electrocardiograms (ECGs). • Tolerability: Dose interruptions, reductions and dose intensity. • The incidence of dose limiting toxicities (DLTs) with KY1044 as single agent during the first 21 days of treatment. • The incidence of DLTs with KY1044 in combination with atezolizumab during the first 21 days of treatment. **Phase 2:** • ORR per RECIST 1.1.
Secondary	Secondary Endpoints
• To evaluate the preliminary anti-tumor activity of KY1044 as single agent and in combination with atezolizumab (Phase 1 only). • To characterize the safety and tolerability of KY1044 as single agent and in combination with atezolizumab (Phase 2 only). • To characterize the PK profile of KY1044 as single agent and in combination with atezolizumab. • To assess emergence of anti-KY1044 and anti-atezolizumab antibodies following one or more i.v. infusions of KY1044 single agent and/or in combination with atezolizumab. • To assess changes in biomarkers from baseline in tumor tissue as potential	**Efficacy:** • Best overall response (BOR), Progression free Survival (PFS) and Duration of Response (DOR) per RECIST 1.1. • ORR and PFS per immune-related (i) RECIST (Phase 1 and Phase 2). • ORR per RECIST 1.1 (Phase 1 only). • Survival rate at 12 and 24 months. **Safety:** • Safety: Incidence and severity of AEs and SAEs, including changes in laboratory parameters, vital signs and ECGs (Phase 2). • Tolerability: Dose interruptions, reductions and dose intensity (Phase 2). **PK measures:**

predictors of efficacy of KY1044 as single agent and in combination with atezolizumab. • To describe the survival rate at 12 and 24 months of patients treated with KY1044 as single agent and in combination with atezolizumab for each disease group.	• KY1044 PK measures; Serum concentration vs. time profiles. **Anti-drug antibodies:** • Presence and/or concentration of anti-KY1044 and anti-atezolizumab antibodies. **Biomarkers:** • Presence of tumor-infiltrating lymphocytes (TILs) as determined by expression of ICOS, forkhead box P3 (FOXP3) and cluster of differentiation (CD) 8 cells (immunohistochemistry [IHC]).
Exploratory	Exploratory Endpoints
• To assess the PD effect of KY1044 as single agent and in combination with atezolizumab in tumor tissue • To assess the PD effect of KY1044 as single agent and in combination with atezolizumab in peripheral blood • To determine the level of target occupancy in response to KY1044 as single agent (Phase 1 only)	**Tumor tissue:** • Expression of immune- and response related markers such as (but not limited to) PD-L1, CD163, CD68 by IHC. • Messenger Ribonucleic Acid (mRNA) gene signature (transcriptomics/ Nanostring) with special interest in IFN gene signature (PanInflammatory panel and/or IO360 panel) **Peripheral blood:** • Peripheral, soluble ligands and cytokine levels (e.g., interferon gamma [IFNγ] tumor necrosis factor alpha [TNFα], granulocyte-macrophage colony-stimulating factor (GM-CSF)) contingent on availability of assay (i.e. SIMOA). • Phenotype and markers of immune cells (IC) activation in peripheral blood . • Plasma and peripheral blood mononuclear cells (PBMCs) gene signature (ribonucleic acid, RNA) (transcriptomics/Nanostring). • ICOS receptor occupancy (RO) in PBMCs (KY1044 as single agent in Phase 1 only)

7.2 Analysis Sets

The following analysis sets will be used for presentation of the data.

For each analysis set, the number and percentage of patients eligible for inclusion will be summarized. A listing of reasons for exclusion from analysis sets will be provided by subject.

A subject data-listing of subject analysis set will be provided.

7.2.1 Screened Set

The patients who have signed informed consent form will be considered as screened subject.

7.2.2 Enrolled Analysis Set

The patients from screened set who have been allocated to study drug regardless of whether the study drug was received or not will be included in enrolled set.

7.2.3 Full Analysis Set

The full analysis set (FAS) will consist of all patients who are allocated to study drug, regardless of treatment ultimately received. Patients will be grouped according to the study drug they will be allocated to. The FAS will be the primary analysis set for efficacy endpoints.

7.2.4 Safety Analysis Set

The safety set will consist of all patients who take at least one dose of study drug within the relevant phase. Patients will be grouped according to the study drug received at cycle 1 day 1. The safety set will be the analysis set used for safety endpoints.

7.2.5 Dose Limiting Toxicity Evaluable Set

The DLT evaluable set will be patients who have been on study for 1 full cycle (21 days) and have received adequate treatment with KY1044 as single agent or in combination with atezolizumab (i.e. have had full infusion of planned doses of KY1044 and Atezolizumab if appropriate) or have experienced a DLT in Cycle 1. The evaluation of DLTs in Phase 1 of the study will occur in this population.

7.2.6 Pharmacokinetic Evaluable Set

The PK evaluable set will consist of all patients who had sufficient concentration-time data within the relevant phase to permit calculation of PK parameters for KY1044. For patients who were noncompliant with respect to administration of KY1044, or for patients with incomplete data, a decision as to their inclusion in the PK analysis will be made on a case-by-case basis. The PK evaluable set will be used for evaluation of PK parameters.

7.2.7 Anti-Drug Antibody Evaluable Set

The anti-drug antibody (ADA) evaluable set will consist of all patients who receive at least one dose of KY1044 or atezolizumab and have ADA results available for analysis within the relevant phase. This population will be used for the analyses of anti-KY1044 and anti-Atezolizumab antibodies.

7.2.8 Biomarker Evaluable Set

The biomarker evaluable set will consist of all patients who receive at least one dose of study drug and have at least one of ICOS, FOXP3 and CD8 cells results available for analysis within the relevant phase. This population will be used for the analyses of ICOS, FOXP3 and CD8 cells biomarkers.

8.0 Conventions and Derivations

8.1 Baseline Values

Baseline is defined as the last measurement prior to first study drug administration.

8.2 Change from Baseline

Change from baseline (CFB) will be calculated as (post-baseline value – baseline value). Change from baseline will be calculated for patient who have both a baseline and post-baseline value as applicable.

8.3 Prior and Concomitant Medication

Medications administered to patients during the study are captured on a log CRF page. Medications are considered prior medications if they have a start date prior to the date of first dose of study medication or a partial start date which indicates the medication was begun prior to the first dose of study treatment.

Concomitant medications are defined as medications administered to patients on or after the first dose of study medication and before the last dose of study medication.

The medication taken after the last dose of study medication will be considered as post-study and will be included in subject data listings.

The medication with start date prior to first dose of study medication and ongoing in the study will be included in subject data listing and will be flagged as prior and concomitant.

Collected prior and concomitant medications will be coded using the World Health Organization (WHO) medical dictionary.

8.4 End of Study for Individual Patient

The end of study for each patient will be either:

- At the end of the 90 day safety follow-up period after stopping treatment, for the last patient in the study.
- At the overall end of the study for all patients, who are still in follow-up for PFS and or survival as determined by the Sponsor.

The end of the study recorded in the CRF will be used to count patients who complete the overall study.

8.5 Time since Initial Diagnosis

The time since initial diagnosis in years will be derived as (date of informed consent – date of initial diagnosis)/365.25. In case of missing or partial date of diagnosis the time since initial diagnosis will be missing.

8.6 Efficacy Analysis

8.6.1 Best Overall Response

The BOR for each patient is defined as the best response per RECIST 1.1 or iRECIST among all responses recorded from start of treatment until progressive disease, initiation of new anti-cancer therapy, death, or analysis cut-off date, whichever comes first, with a response of CR or iCR, PR or iPR, SD or iSD, progressive disease or immune-unconfirmed progressive disease (iUPD) or immune-confirmed progressive disease (iCPD) and then not evaluable (NE).

For confirmed responses, an equal or superior response must be observed at a subsequent time point at least 4 weeks after the initial assessment. In the case of SD, measurements must have met the SD criteria

at least once no less than 7 weeks after first study drug administration, regardless of whether the endpoint is confirmed or unconfirmed responses.

8.6.2 Objective Response Rate

Patients' tumor imaging results will be assessed by the Investigator in screening and periodically after start of treatment in each study phase for response per RECIST 1.1 and iRECIST. Response categories by RECIST as indicated by Investigator will be CR, PR, SD, PD, or NE and by iRECIST will be iCR, iPR, iSD, iUPD, iCPD, or NE.

ORR accordingly to RECIST 1.1 is defined as the proportion of patients with a measurable disease at baseline and with BOR of CR or PR. The response of CR or PR must be confirmed by a later scan conducted at least 4 weeks after the initial response is observed. In case of SD, measurements must have met the SD criteria at least once no less than 7 weeks after first study treatment administration.

The ORR for iRECIST is defined as the proportion of patients with a measurable disease at baseline and having achieved complete immune-response (iCR) or partial immune-response (iPR) by iRECIST.

8.6.3 Duration of Response

DOR is defined as the time in months from date of the first documentation of objective response (CR or PR) per RESIST 1.1 to the first documentation of progression of disease or to death due to any cause in the absence of documented progression of disease (i.e., min [progression of disease date, death date] – date of the first observation of objective response +1) divided 30.4375. DOR will only be calculated for the subgroup of patients achieving a BOR of CR or PR.

The censoring rules to be applied to DOR are the same as for PFS.

8.6.4 Progression Free Survival

PFS is defined as the time from the first dose of study drug to the date of progression of disease or death (event) due to any cause, whichever occurs first. PFS (in months) will be calculated as:

(first event/censored date – first dose date of study drug +1)/30.4375.

The clinical progression without further radiological assessment as corroboration will not be considered as progressive disease.

Using iRECIST, PFS is defined as the time from the first dose of study drug to the date of death or the of first documented tumor progression (iUPD) provided that iCPD is confirmed at the next assessment, whichever is earlier.

The patients who have not progressed or died at the time of analysis will be censored. Following censoring rules will be applied for PFS:

Patients with no disease assessment (or only have assessment(s) with response = NE) after first study treatment or have baseline or post-baseline assessments where the RECIST criteria cannot be applied (e.g. not all baseline lesions assessed) will have their PFS time censored on the date of first dose with duration of 1 day unless they die within 2 tumor assessments of baseline, then they will be treated as an event with date of death as the event date.

Event time will be censored on the date of the last evaluable assessment documenting absence of progression of disease for:

- Patients on-study and progression-free at the time of analysis;
- Patients who have progression of disease or death on study after ≥2 consecutive missed tumor assessments;
- Patients given alternative cancer treatment prior to progression of disease or death on-study.

8.6.5 Overall Survival

The overall survival (OS) is defined as the time from first dose of study drug to the date of death due to any cause. OS (in months) is calculated as (date of death − date of first dose of study drug +1) divided by 30.4375. Patients who are continuing on study at the time of an analysis, are lost to follow-up or who withdraw consent, will have their event time censored on the last date that they were known to be alive. The last date that patients are known to be alive can be derived from the clinical database and may include the latest Visit date for patients still on study or the latest Date of Contact on the Long-Term Follow-Up/Survival Status CRF page, whichever occurs latest. For patients with no follow-up after first dose of study drug, OS will be censored at the date of first dose.

8.7 Study Drug Exposure Variables

The exposure for KY1044 and Atezolizumab will generally be presented separately but in addition, the study treatment duration will be presented combining both treatments (please see below).

8.7.1 Study Treatment Duration

Study treatment duration (weeks) for each study drug separately is defined as ((last dose date+21 days – first dose date)+1)/7. For patients in the combination arm, an additional duration of study treatment will be calculated using the same formula but which takes the latest KY1044 or Atezolizumab administration for the last dose date, and the earliest of either drug for the first dose date.

8.7.2 Dose Interruption

A dose interruption is defined as any interruption during the administration (infusion) of a dose of study drug. Dose interruptions are recorded on the Exposure KY1044- IV/Infusion Administration or the Exposure Atezolizumab- IV/Infusion Administration CRF pages in time units of minutes, hours, or days.

8.7.3 Dose Reduction

A dose reduction is defined as any reduction in the dose assigned for infusion and are recorded along with the actual dose administered (infused) on the Exposure KY1044- IV/Infusion Administration. Dose reductions for Atezolizumab are not permitted.

8.7.4 Cumulative Dose Received

Cumulative dose received (mg) is defined as the total amount of study drug received as recorded on the Exposure KY1044- IV/Infusion Administration or the Exposure Atezolizumab- IV/Infusion Administration CRF pages, i.e., the sum of actual dose per administration.

8.7.5 Dose Intensity

Absolute dose intensity (mg/week) is calculated as cumulative dose received (mg) / study treatment duration (weeks).

Relative dose intensity is calculated as the cumulative dose received (mg) / initial planned cumulative dose (mg). Initial planned cumulative dose is calculated as the starting dose (Cycle 1 Day 1 dose) multiplied by the scheduled number of administrations within the study treatment duration.

8.8 Safety Variables

8.8.1 Baseline Signs and Symptoms

Signs and symptoms of the patient’s cancer diagnosis and/or comorbidities present prior to Day 1 of study treatment dosing are recorded in the CRF as medical history.

8.8.2 Treatment Emergent Adverse Events

A treatment emergent adverse event (TEAE) is defined as an AE observed after starting administration of the specific treatment. If a patient experiences an event both prior to and after starting administration of a treatment, the event will be considered a TEAE (of the treatment) only if it has worsened in severity (i.e., it is reported with a new start date) after starting administration of the specific treatment, and prior to the start of another treatment (if any) or up to 21 days after the last dose.

8.8.3 Post-Treatment Adverse Events

A post treatment adverse event is defined as an AE with start date being up to 21 days after the last study dose.

8.8.4 Immune-Related Adverse Events

The Immune-related AEs (irAEs) are defined as follows:

Infusion reactions, Hematological, Cardiological, GI, Renal, Pulmonary, Hepatic, Endocrinopathy, Dermatological, Neurological, Ophthalmological, and Rheumatological AEs.

8.8.5 Adverse Events of Special Interest

Adverse events of special interest (AESI) will be determined during the conduct according to protocol Section 16.3 of the study and will be recorded on CRF.

8.8.6 Related Adverse Events

The related adverse events are defined as those having relationship as “Possibly Related” or “Related”.

8.9 Handling of Missing or Partial Dates

Below are rules for imputing missing or partial dates for analyses of medical history, AEs, and concomitant medications. Though imputed for analyses, actual dates (missing or partial) will be reflected in listings. Otherwise, there will be no imputation of missing data values. Data on patients who withdraw early will be summarized up until the time of withdrawal.

Missing or partial dates for medical history will be imputed as follows:

- If only the day is missing, it will be imputed with the 1st day of the month.
- If both the day and month are missing, the month and day will be imputed with January 1st.
- If the date is completely missing, no imputation will be performed.

Missing or partial dates for AEs and concomitant medications will be imputed as follows:

- Start Date
    - If only the day is missing and the month and year are the same as the month and year of the first dose date, then the day will be imputed with the day of the first dose date. Otherwise the day will be imputed with the first day of the event month.
    - If both the day and month are missing and the year is the same as the year of the first dose date then they will be imputed with the month and day of the first dose date. Otherwise they will be imputed with the January 1st.
    - If the start date is completely missing, the date will be imputed with the first dose date.
    - If the stop date is complete and the imputed start date is after the stop date, then the imputed start date will be set to the stop date.
- Stop Date

- If only the day is missing and the month and year are the same as the month and year of the study discontinuation date, then the day will be imputed with the day of the study discontinuation date. Otherwise the day will be imputed with the last day of the event month.
- If both the day and month are missing and the year is the same as the year of the study discontinuation then they will be imputed with the month and day of the study discontinuation date. Otherwise they will be imputed with the December 31st.
- If the stop date is completely missing, then it will be imputed with the study discontinuation date.

Note that stop date imputation will not be applied to ongoing AEs. If the imputed stop date is greater than last the contact date, then the imputed stop date will be set to last contact date

9.0 Interim Analyses

A preliminary analysis of the study data will be performed and reported based on all patients' data up to the time when all patients from the Phase 1 part have completed at least six cycles of treatment or discontinued the study and the initial patients from the Phase 2 part have had at least one tumor assessment after six months of treatment or discontinued the study.

10.0 Statistical Methods

There will be no formal statistical testing in this study. Statistical analyses will be limited to descriptive summaries.

In general, continuous variables will be summarized by number of patients, mean, standard deviation (STD), median, minimum, and maximum. The mean and median will be presented to one more and the STD to 2 more decimal places than the precision of the variable, while the minimum and maximum will be presented at the same precision. Categorical variables will be summarized by frequency counts and percentages. Percentages will be presented to one decimal place. Where relevant, estimates will be presented with 95% two-sided confidence intervals (CI).

All tables, figures and listing will be presented separately for Phase 1 and Phase 2 portion of the study.

The Phase 1 summaries will be reported by dose levels within KY1044 single agent and KY1044 with atezolizumab combination groups.

The Phase 2 of the study will be reported by indication within KY1044 single agent and KY1044 in combination with atezolizumab, split by anti-PD-(L)1 naïve and pre-treated groups, and dose levels as appropriate.

Wherever possible, patients with the same tumor type who have received the recommended dose/schedule of KY1044 as single agent or in combination with atezolizumab will be pooled for analysis, respectively.

All analyses will be performed using SAS version 9.4 or higher.

10.1 Subject Disposition

The number and percentage of patients who completed the study, completed the 24 months survival follow-up, discontinued the study and a breakdown of the corresponding reasons for discontinuation.

The number and percentage of patients who discontinued the treatment prior to 48 months and a breakdown of the corresponding reasons for withdrawal from the treatment will be presented.

The subject disposition will be listed.

10.2 Demographic and Baseline Characteristics

The demographic characteristics will be summarized on the FAS and safety analysis set.

The demographic variables include age at screening (years), age groups in years (≥ 18 – 64, ≥ 65 – 84 and ≥ 85), sex, ethnicity, race, weight (kg), height (m), body mass index (BMI) (kg/m^2), and Eastern Cooperative Oncology Group (ECOG) status.

The following baseline characteristics will be summarized in the safety analysis set in both study phases:

- Medical history (coded by medical dictionary for regulatory activities [MedDRA] dictionary version 21.0 or higher and summarized by system organ class (SOC) and preferred term (PT))
- Tumor history
- Prior anti-cancer therapies
- Prior radiotherapies

Listings of the demographic characteristics, medical history, tumor history, prior anti-cancer therapy, prior cancer surgery, and prior radiotherapy will be presented.

10.3 Treatments

10.3.1 Extent of Study Drug Exposure

Exposure to study drug will be summarized for all patients in the safety analysis set. Descriptive statistics will be provided for study treatment duration (weeks), the total number of cycles started, number of infusions received, cumulative dose received (mg), absolute dose intensity (mg/week), and relative dose intensity.

The number and percentage of patients with at least 1 dose not administered, dose reduction or increase and at least 1 dose interruption will be presented along with a summary of the reasons for dose not administered, dose reductions and interruptions.

The bar plot of time to treatment will be presented for subject in FAS population.

A listing of study drug exposure will also be created. These data can be found on the Exposure KY1044- IV/Infusion Administration or the Exposure Atezolizumab- IV/Infusion Administration CRF pages.

10.3.2 Concomitant Medications

The medications received concomitantly with study drug, categorized by medication group and subgroup according to WHO Drug Enhanced [Version March 2016], will be summarized. The number and percentage of patients using each medication will be displayed together with the number and percentage of patients using at least one medication with each anatomical therapeutic chemical (ATC) and preferred term (PT).

Prior, concomitant and post study medications will be listed.

10.4 Important Protocol Deviations

Per PRA processes, important protocol deviations data will be entered into our clinical trials management system (CTMS). The study team and the Sponsor will conduct on-going reviews of the deviation data from CTMS and the resulting set of evaluable patients throughout the study, adjusting the deviation criteria as seems appropriate. The evaluable patients set must be finalized at the post-freeze data review meeting (or earlier), prior to database lock.

For each study phase, important protocol deviations for patients in the FAS will be reported by deviation category. Important protocol deviations will also be listed.

A separate listing of all COVID-19 related protocol deviations will be provided.

10.5 Efficacy Analyses

10.5.1 Hypothesis Testing Strategy and Multiplicity

No formal hypothesis testing and no measures will be employed to adjust the primary analysis and key secondary analysis for multiplicity are applicable for this study.

10.5.2 Primary Endpoint

Phase 1

- Safety: Incidence and severity of AEs and SAEs, including changes in laboratory parameters, vital signs and ECGs.
- Tolerability: Dose interruptions, reductions and dose intensity
- The incidence of DLTs with KY1044 as single agent during the first 21 days of treatment
- The incidence of DLTs with KY1044 in combination with atezolizumab during the first 21 days of treatment

Phase 2

- ORR per RECIST 1.1.

10.5.2.1 Imputation Methods

There will be no imputation of missing data values. Data on patients who withdraw early will be summarized up until the time of withdrawal.

10.5.2.2 Primary Analysis

The primary endpoints in Phase 1 are safety endpoints (see SAP Section 12.3 and 12.7).

The number and percentage of patients with confirmed CR or PR per RECIST 1.1 will be presented for all patients in FAS. The ORR will be accompanied by the 2-sided exact 95% Clopper-Pearson CI.

The waterfall plots of best percent change from baseline and maximum tumor size reduction from baseline as assessed by the investigator according to RECIST 1.1 will be provided for the FAS population.

The spider plot for percent change from baseline in tumor size will be provided for the FAS population.

Lesions assessed by the investigator (target, non-target, and new lesions) and investigator-reported overall tumor response assessment as per RECIST 1.1 will be presented in listings.

The subject-data listing will be provided for tumor assessment and tumor response.

10.5.2.3 Sensitivity Analyses

No sensitivity analyses is planned for the study.

10.5.2.4 Supplementary Analyses

No supplementary analyses is planned for the study.

10.5.3 Secondary Endpoints

Efficacy measures:

- BOR, PFS and DOR per RECIST 1.1
- ORR and PFS per immune-related iRECIST (Phase 1 and Phase 2)
- ORR per RECIST 1.1 (Phase 1 only)

- Survival rate at 12 and 24 months

Safety measures:

- Safety: Incidence and severity of AEs and SAEs, including changes in laboratory parameters, vital signs and ECGs (Phase 2).
- Tolerability: Dose interruptions, reductions and dose intensity (Phase 2).

PK measures:

- KY1044 PK measures (e.g., C_{max}, half-life); Serum concentration versus. time profiles.

Anti-drug antibodies:

- Presence and/or concentration of anti-KY1044 and anti-atezolizumab antibodies.

Biomarkers:

- Presence of tumor-infiltrating lymphocytes (TILs) as determined by expression of ICOS, FOXP3 and CD8 cells (IHC).

10.5.3.1 Best Overall Response

The counts and percentages of subject with BOR of CR, PR, SD and PD per RECIST 1.1 will be presented for Phase 1 and Phase 2 study phases for all patients in the FAS.

The overall response assessment by investigatory per RECIST 1.1 will be presented for Phase 1 and Phase 2 study phases for all patients in the FAS.

10.5.3.2 Progression Free Survival

PFS will be summarized using the Kaplan-Meier method. Estimated PFS rates and 95% CIs using complementary log-log transformation method will be presented at 12 and 24 months. The median, 25th, and 75th percentile of PFS and their two-sided 95% CIs using the Brookmeyer-Crowley method will also be presented. Kaplan-Meier curves of the estimated PFS function will also be presented.

This analysis will be performed according to RECIST 1.1 and iRECIST 1.1 in the FAS for both the study phases.

The PFS will be presented in subject-data listing.

10.5.3.3 Duration of Response

DOR per RECIST 1.1 will be summarized with the same approach used for PFS for both the study phases.

The DOR will be presented in subject-data listing.

10.5.3.4 Objective Response Rate

ORR per iRECIST for both the study phases and ORR per RECIST 1.1 for Phase 1 patients in FAS will be summarized with the same approach described in SAP section 12.5.2.2.

The subject-data listing will be provided for tumor assessment and tumor response.

10.5.3.5 Survival rate at 12 and 24 months

The OS will be summarized using the Kaplan-Meier method. Estimated OS rates and 95% CIs using the complementary log-log transformation method will be presented at 12 and 24 months. Median, 25th, and 75th percentile of OS and their 95% CIs using the Brookmeyer-Crowley method will also be presented. Kaplan-Meier curves of the estimated OS function will also be presented.

This analysis will be performed in the FAS of both study phases.

The OS will be presented in subject-data listing.

The analysis of secondary safety endpoints in Phase 2 is detailed in Section 12.7 of the SAP.

The PK and anti-drug antibodies analysis is detailed in Section 12.6 of the SAP.

10.5.4 Exploratory Endpoints

The following exploratory endpoints will be evaluated:

Tumor tissue:

- Expression of immune- and response-related markers such as (but not limited to) PD-L1, CD163, CD68 by IHC.
- mRNA gene signature (transcriptomics/ Nanostring) with special interest in IFN gene signature (PanInflammatory panel and/or IO360 panel).

Peripheral blood:

- Peripheral, soluble ligands and cytokine levels (e.g., IFNγ, TNFα, GM-CSF) contingent on availability of assay (i.e. SIMOA).
- Phenotype and markers of IC activation in peripheral blood (e.g., CD3, CD8, CD4, T_{Regs}, CD4 memory cells, CD25, FOXP3, CD45RA, ICOS, CD14. CD45, CD56, CD19 and ICOSLG) (FACS or ChipCytometry).
- PBMCs gene signature (ribonucleic acid [RNA]) (transcriptomics Nanostring).
- ICOS RO in PBMCs (KY1044 as single agent in Phase 1 only).

All exploratory endpoints will be presented graphically as appropriate.

10.6 Pharmacokinetic and Anti-drug Antibody Analyses

10.6.1 Pharmacokinetic Analyses

The serum PK of KY1044 as a single agent and in combination with atezolizumab will be characterized using non-compartmental analysis (NCA). Nominal times of sample collections will be used for the noncompartmental analysis (NCA). All BLQ values will be set to 0 units.

The following PK measures will be calculated, whenever possible, from serum concentrations:

C_{max}: Maximum concentration (for atezolizumab – only one time point of serum concentration at the end of infusion)

t_{max}: Time of the maximum concentration (obtained without interpolation)

Ctrough: Trough concentrations

λ_z: Terminal elimination rate constant (whenever possible) using Linear Up Log Down method of determination and Best Fit setting.

$AUC_{0\text{-last}}$: Area under the concentration-time curve calculated using linear trapezoidal summation from time 0 to time last, where “last” is the time of the last measurable concentration

$AUC_{0\text{-inf}}$: Area under the concentration-time curve from 0 to infinity, calculated using the formula: $AUC_{0\text{-inf}} = AUC_{0\text{-last}} + C_{last}/ \lambda_z$, where λ_z is the apparent terminal elimination rate constant

Clearance

Volumes of distribution

$t_{½}$: Half-life

The following diagnostic criteria will be used to flag individual data in Listings:

- %AUCextrap is 30% (criteria for exclusion of parameters: AUCinf, t-half, CL, CLss, Vz, Vss)
- Rsq < 0.7
- half-life calculated over a period of < 2 times the resultant half-life (Span)

For KY1044, all peak (end-of-infusion) and trough (pre-infusion) concentrations will be tabulated. For KY1044 peak and trough concentrations will be tabulated separately for use as a single agent and for combination with atezolizumab.

Besides listings of pharmacokinetic measures for individual patients, all measures will be summarized by descriptive statistics (N, Mean, SD, SE, Min, Median, Max, CV%, and Geometric Mean (only for ratios). The summaries will include estimates of not only central tendency but variability such as Standard Error (SE). For t_{max} median (and range) and for half-lives, arithmetic means will be provided. Besides listings of concentrations, NCA Mean parameter tables, charts illustrating the mean concentration-time profiles will be generated.

10.6.2 Anti-drug Antibody Analysis

The anti-drug antibody analysis will be performed on anti-drug antibody evaluable set.

The anti-drug antibody results will be analyzed descriptively for patients who develop detectable anti-KY1044 and anti-atezolizumab antibodies. The titer of anti-KY1044 and anti-atezolizumab antibodies will be summarized using summary statistics (n, mean, STD, median, minimum and maximum values). The presence of anti-KY1044 and anti-atezolizumab antibodies will be summarized using frequency counts and percentage.

The mean (±STD) plot of titer values of anti-KY1044 and anti- atezolizumab antibodies will be presented.

The summary of anti-KY1044 antibodies incidence will be presented.

The by-subject data listing will be presented.

10.6.3 Biomarker Analysis

The biomarker analysis will be performed on all patients in biomarker evaluable set.

The descriptive summary of change in following marker will be presented:

- number of ICOS positive regulatory T cells (ICOS+FOXP3+) per mm^2 in the tumor microenvironment.
- number of CD8 positive cells per mm^2 in the tumor
- number of CD8 positive cells per mm^2 in the invasive margin
- ratio of CD8 T cells per mm^2 to the number of ICOS positive regulatory T cells per mm^2
- CD8 to Regulatory T-cells ratio
- ChipCytometry Assay

The biomarkers data will be listed in subject data listing.

10.7 Safety Analyses

Unless otherwise specified all safety analysis will be based on safety analysis set.

10.7.1 Adverse Events

AEs will be coded using the MedDRA Version 21.0 or higher.

The analysis described in this section will be based on TEAEs and will be tabulated by SOC and/or PT. The number and percentage of patients experiencing each event at least once will be summarized.

A summary of AEs, including the number of events reported, the number of DLTs reported within 21 days of treatment (Phase 1 only), and the number and percentage of

- patients reporting at least one TEAE by SOC and PT,
- patients with at least one CTCAE grade ≥3 TEAE by SOC and PT,
- patients with at least one TEAE by SOC, PT and maximum CTCAE grade
- patients with at least one TEAE by PT,
- patients with at least one TEAE related to KY1044 by PT,
- patients with at least one TEAE related to KY1044 TEAE by SOC and PT,LLOQ
- patients with at least one TEAE related to Atezolizumab by SOC and PT,
- patients with at least one TEAE related to either study drug by SOC and PT,
- patients with at least one greater than or equal to CTCAE grade 3 TEAE related to KY-1044 by SOC and PT,
- patients with at least one greater than or equal to CTCAE grade 3 TEAE related to Atezolizumab by SOC and PT,
- patients with at least one KY1044-related TEAE by SOC, PT and maximum CTCAE grade,
- patients with at least one Atezolizumab-related TEAE by SOC, PT and maximum CTCAE grade,
- patients with an TEAE leading to study discontinuation of either study drug by SOC and PT,
- patients with an TEAE leading to discontinuation of KY1044 by SOC and PT,
- patients with an TEAE leading to discontinuation of Atezolizumab by SOC and PT,
- patients with an TEAE leading to interruption of KY1044 by SOC and PT,
- patients with an TEAE leading to interruption of Atezolizumab by SOC and PT,
- patients with an TEAE leading to interruption of either study drug by SOC and PT,
- patients with an TEAE leading to reduction of KY1044 by SOC and PT,
- patients with at least one TEAE of special interest by SOC and PT
- patients with at least one irAE by SOC and PT

will be presented. In the summary by worst CTCAE grade, the TEAE with the highest or most severe grade will be counted when patients have multiple TEAEs, overall, in a SOC or in a PT as appropriate.

A breakdown of the number and percentage of patients reporting each kind of TEAE above, categorized by SOC and PT, will be also presented. This breakdown will be sorted by decreasing frequency of PT within SOC. Note that counting will be by subject and not by event and patients are only counted once within each SOC or PT. This breakdown will be repeated and sorted by decreasing frequency of PTs in the KY1044 group for patients reporting at least one TEAE and patients reporting at least one CTCAE grade 3 and above TEAE. This breakdown will also be repeated by worst CTCAE grade for patients reporting at least one TEAE and patients reporting at least one CTCAE grade 3 and above TEAE, sorted by PT within SOC.

All adverse events (including non-treatment-emergent events) recorded on the CRF will be listed.

10.7.2 Deaths and Serious Adverse Events

A summary of TEAEs, including the number of events reported, the number and percentage of patients reporting at least one SAE and deaths will be presented.

The following summaries of AEs will be provided for each treatment group by MedDRA primary SOC and PT:

- Serious TEAEs
- Serious TEAEs related to KY1044
- Serious TEAEs related to Atezolizumab
- Serious TEAEs of special interest
- TEAEs with an outcome of death
- TEAEs related to KY1044 with an outcome of death
- Post treatment AEs with an outcome of death

The listings of all SAEs and AEs with outcome of death will be provided. A separate listing of all deaths during treatment will be provided.

10.7.3 Laboratory Data

Actual values, based on central laboratory results, at each planned visit and change in values from baseline at each post-baseline planned visit will be summarized. Nominal visits will be used for these summaries but unscheduled visits will also be considered when looking at potentially clinically important (PCI) results across the entire treatment period.

For parameters that were graded, the worst grade (in the appropriate direction(s)) post-baseline (including from unscheduled assessments) and shifts in grade from baseline to worst will be summarized. All laboratory results over time will be presented in a listing, including reference ranges and indications of out of range values, grading (if done), and an assessment of clinical significance by the Investigator.

Baseline is defined as the last measurement prior to first study drug administration. If the assessment is made on the same day as first study drug administration and there are no times to indicate that it was after administration, it will be assumed to be prior and therefore qualify as the baseline measurement.

Potential Hepatotoxicity will be summarized by time point.

To address the impact of global pandemic of COVID-19, the local laboratory results for all assessment time points will be considered where central laboratory results cannot be obtained. The CRF page “Unscheduled Local Laboratory Results” will be completed in rare circumstances if no central laboratory samples are collected at a visit due to COVID-19 where local laboratory is collected instead. The separate listing will be presented for all local laboratory results obtained from the unscheduled CRF page.

Local laboratory results collected at Screening will be listed separately.

10.7.4 Vital Signs

Vital signs at each scheduled visit will be summarized along with the change from baseline to post-baseline visits. A summary of abnormal vital signs will also be presented, where abnormal vital signs are systolic blood pressure >140 mmHg, diastolic blood pressure >90 mmHg, heart rate <60 beats/min or >100 beats/min, or temperature >37.5°C.

Baseline is defined as the last measurement prior to first study drug administration. If the assessment is made on the same day as first study drug administration and there are no times to indicate that it was after administration, it will be assumed to be prior and therefore qualify as the baseline measurement.

A listing of vital signs over time will also be presented, including an indicator of abnormal assessments as defined above and as indicated on the Vital Signs CRFs (both abnormal and clinically significant).

10.7.5 Physical Examination, ECGs, and Other Observations Related to Safety

10.7.5.1 Physical Examination

Full physical examination at Screening and EOT will be summarized.

A listing of physical examination findings during the study will be presented, including an indication of abnormal and clinically significant findings as entered on the Physical Examination CRFs.

10.7.5.2 Electrocardiograms

The mean QTcF (msec) from ECGs performed in triplicate periodically over the study period will be summarized at scheduled time points/visits. Change in QTcF from baseline at all scheduled post-baseline time points/visits will also be summarized.

A listing of QTcF over time will also be presented, including an indicator of clinically significant assessments as indicated on the ECG 1 and ECG 2 CRFs.

Baseline is defined as the last measurement prior to first study drug administration. If the assessment is made on the same day as first study drug administration and there are no times to indicate that it was after administration, it will be assumed to be prior and therefore qualify as the baseline measurement.

The number and percentage of patients with ECG abnormalities will be presented. Abnormality criteria to be used in the determination of ECG abnormalities are defined as follows.

Parameter	**Abnormality Criteria**
QTcF (msec)	Maximum value at any post visit baseline visit: ≥ 450 - < 480 msec, ≥ 480 - < 500 msec and ≥ 500 msec
	Maximum change from baseline: ≥ 30 to < 60 msec and ≥ 60 msec

All ECG parameter values will be listed for patients meeting any abnormality criteria. A subject data listing will be provided that identifies patients with abnormal findings as assessed by the investigator/cardiologist after the first dose of study treatment for each type of ECG abnormality.

11.0 References

1. Guo W, Wang S-J, Yang S, Lynn H, Ji Y. A Bayesian interval dose-finding design addressing Ockham's razor: mTPI-2. Contemporary Clinical Trials. 2017 Jul; 58:23–33.

2. Ji Y, Wang S-J. Modified Toxicity Probability Interval Design: A Safer and More Reliable Method Than the 3 + 3 Design for Practical Phase I Trials. Journal of Clinical Oncology. 2013 May 10;31(14):1785–91.

12.0 Appendix

12.1 Example mTPI-2 Decision Table

Number of Patients

Number of DLTs	1		2		3		4		5		6		7		8		9		10	
	mTPI	mTPI2	mTPI	mTPI2	mTPI	mTPI2	mTPI	mTPI2	mTPI	mTPI2	mTPI	mTPI2	mTPI	mTPI2	mTPI	mTPI2	mTPI	mTPI2	mTPI	mTPI2
0	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E
1	D	D	S	D	S	S	S	S	S	E	E	E	E	E	E	E	E	E	E	E
2			DU	DU	D	D	S	D	S	D	S	S	S	S	S	S	S	E	S	E
3					DU	DU	DU	DU	D	D	S	D	S	D	S	D	S	S	S	S
4							DU	DU	DU	DU	DU	DU	D	D	D	D	S	D	S	D
5									DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	D	D
6											DU	DU	DU	DU	DU	DU	DU	DU	DU	DU
7													DU	DU	DU	DU	DU	DU	DU	DU
8															DU	DU	DU	DU	DU	DU
9																	DU	DU	DU	DU
10																			DU	DU

E: Escalate to the next higher dose; S: Stay at the same dose; D: De-escalate to the previous lower dose; DU: De-escalate to the previous lower dose and the current dose will never be used again in the trial;

Column indicates the number of patients treated. **Row** indicates the number of patients with DLTs. Decisions for both mTPI and mTPI-2. For each column (the number of patients treated), there are two sub-columns listing the decisions of mTPI and mTPI-2 side by side. Here, the target toxicity probability p_T=0.30, e_1=0.05 and e_2=0.05.

13.0 Glossary of Abbreviations

Glossary of Abbreviations:	
ADA	Anti-drug Antibody
AE	Adverse event
AESI	Adverse Events of Special Interest
ATC	Anatomic Therapeutic Classification
AUC	Area under the Concentration-Time Curve
$AUC_{0\text{-infinity}}$	Area under the Concentration-Time curve from 0 to infinity
$AUC_{0\text{-last}}$	Area under the Concentration-Time curve from 0 to last measurable concentration
BMI	Body Mass Index
BOR	Best Overall Response
CD	Cluster of Differentiation
CFB	Change from baseline
CI	Confidence Interval
C_{max}	Minimum Concentration
C_{min}	Maximum Concentration
CR	Complete Response
CRF	Case Report Form
CSR	Clinical Study Report
CTMS	Clinical Trials Management System
DMC	Data Monitoring Committee
DOR	Duration of Response
DLT	Dose Limiting Toxicity
DSMB	Data Safety Monitoring Board
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
FAS	Full Analysis Set
FOXP3	Forkhead box P3
HCC	Hepatocellular Carcinoma
HNSCC	Head and Neck Squamous Cell Carcinoma
IC	Immune Cells
iCR	immune-Confirmed Response
ICOS	Inducible T cell Costimulator

iCPD	immune-Unconfirmed Progressive Disease
IFNγ	Interferon Gamma
IgG	Immunoglobulin G
IHC	Immunohistochemistry
iPR	immune-Partial Response
irAEs	Immune-related Adverse Events
iRECIST	immune- Response Evaluation Criteria in Solid Tumors
iSD	immune-Stable Disease
iUPD	immune-Unconfirmed Progressive Disease
i.v	Intravenous
IVRS	Interactive Voice Response System
MedDRA	Medical Dictionary for Regulatory Activities
mRNA	Messenger Ribonucleic Acid
MTD	Maximal Tolerated Dose
mTPI-2	Modified Toxicity Probability Interval Design No 2
NCA	Non- Compartmental Analysis
NE	Not Evaluable
NSCLC	Non-Small Cell Lung Cancer
ORR	Objective Response Rate
OS	Overall Survival
PBMCs	Plasma and peripheral blood mononuclear cells
PD	Pharmacodynamics
PD-1	Programmed Cell Death Protein-1
PD-L1	Programmed Cell Death-Ligand 1
PFS	Progression Free Survival
PK	Pharmacokinetic
PP	Per Protocol
PR	Partial Response
PT	Preferred Term
Q3W	Every 3 Weeks
R2PD	Recommended Phase 2 Dose
RECIST 1.1	Response Evaluation Criteria in Solid Tumors Version 1.1
RNA	Ribonucleic Acid
RO	Receptor Occupancy

SAP	Statistical Analysis Plan
SAE	Serious Adverse Event
SD	Stable Disease
SOC	System Organ Class
STD	Standard Deviation
$t_{1/2}$	Half-life
t_{max}	Time to maximum observed serum concentration
TEAE	Treatment Emergent Adverse Events
TCR	T Cell Receptor
TILs	Tumor-Infiltrating Lymphocytes
TNFα	Tumor Necrosis Factor alpha
WHO	World Health Organization

14.0 Approvals

Sponsor	
Sponsor Name:	Sanofi
Representative/ Title:	[redacted] / Study Statistician
Signature /Date:	[redacted]
ICON	
Biostatistician / Title:	[redacted] / Principal Biostatistician
Signature /Date:	[redacted]

15.0 Document History

Version/Date	Change Log
1.0/08-Nov-2019	Created as new
2.0/17-Aug-2021	• As the new template of SAP is used. Hence, the section number and corresponding section description is updated. • Sections updated as per Protocol Version 6.0.

	• Additional approvers from Kymab are added in. • In the entire document the text “Estimands” is replaced with “Endpoints”. • In the entire document the text “Overall Response Rate” is replaced with “Objective Response Rate”. **Section 8.0 Study Design** • The treatment duration is updated to 48 months as per protocol amendment version 6.0. • The figure of study design is added. • Enrollment for patients in Phase 1 and Phase 2 is detailed as in protocol. **Section 9.2 Analysis Sets** • The screened subject and enrolled subject are defined separately. **Section10.3 Prior and Concomitant Medications** • The medication taken post-study are defined. • The medication that can be flagged as “Prior and Concomitant” are defined. • Section 10.4 End of Study for Individual Patient is included. • The definition of Time since Initial Diagnosis is included in Section 10.5. **Section 10.6 Efficacy Analysis** • The derivation of Duration of Response and Progression-free Survival by iRECIST is included. • The confirmatory Stable Disease response criteria is considered of 7 weeks. **Section 10.8.2 Treatment Emergent Adverse Events** • The below text in the definition “Plus 21 days” is rephrased as “up to 21 days after the last dose”. **Section 12.0 Statistical Analysis Method** • The tables, figures and listings for the Phase II part of the study will be presented by indication and dose group(s) within KY1044 single agent and KY1044 combination groups, split by anti-PD-(L)1 naïve and pre-treated groups. **Section 12.4 Protocol Deviations** • The listing of protocol deviation for all deviations related to COVID-19 is included. **Section 12.5 Efficacy Analyses** • In this section the endpoints and analysis is separated by primary, secondary and exploratory endpoints. • The confidence interval of median, 25th and 75th percentile of progression-free survival and overall survival is updated to use Brookmeyer-Crowley method. • The confidence interval for 12 and 24 months’ survival rates of progression-free survival and overall survival is updated to use complementary log-log transformation method. **Section 12.7 Safety Analysis** • The definition of treatment emergent adverse is updated to match the protocol. • The definitions of adverse events, dose limiting toxicity are removed as they are not need for the analysis. **Section 13 Reference** • The references for Bayesian interval dose-finding design and Modified Toxicity Probability Interval Design is added in.

	Section 14 Appendix • The example of mTPI-2 decision table is included. **Section 15 Glossary of Abbreviations** • The list abbreviation is updated to include all abbreviations used in this document.
3.0/xx-Mar-2024	Update the definition of safety analysis set in section 7.2.4 Update the definition of BOR in section 8.6.1 Update the PK section 10.6.1 Update the SAP template per IOD harmonized processes