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

NCT Number: NCT03829501

Document Date: 10 November 2021

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AMENDED CLINICAL TRIAL PROTOCOL 07

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**
Protocol number:	**KY1044-CT01/ TCD17370**
Amendment number:	**06**
Compound number (INN/Trademark):	**KY1044/SAR445256 (alomfilimab)**
Brief title:	**KY1044 Phase 1/2 study as single agent and in combination with atezolizumab**
Study Phase:	**1/2**
Sponsor name:	**Kymab Ltd**
Legal registered address:	**The Bennet Building (B930)** **Babraham Research Campus** **Cambridge, CB22 3AT** **United Kingdom** **Tel:** [redacted]
Monitoring team's representative name and contact information:	

Regulatory agency identifier number(s):

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NCT:	Not applicable
WHO:	Not applicable
EUDAMED:	Not applicable
Other	Not applicable

Date: 10-Nov-2021 Total number of pages: 217

PROTOCOL AMENDMENT SUMMARY OF CHANGES

DOCUMENT HISTORY

Document	Country/countries impacted by amendment	Date, version
Amended Clinical Trial Protocol 07	All	10 November 2021, version 1 (electronic 1.0)
Clinical Study Protocol Version 6.0	All	07 May 2021
Clinical Study Protocol Version 5.0	All	28 July 2020
Clinical Study Protocol Version 4.0	All	08 May 2019
Clinical Study Protocol Version 3.0	All	24 January 2019
Clinical Study Protocol Version 2.0	All	14 November 2018
Clinical Study Protocol Version 1.0 (original)	All	24 August 2018

Note: The name and numbering of the protocol is based on a new numbering system followed by the Sponsor.

Amended Clinical Trial Protocol 07 (10 November 2021)

This amended clinical trial protocol 07 (Amendment 6) is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

OVERALL RATIONALE FOR THE AMENDMENT

The primary reasons for this amendment to Protocol KY1044-CT01 are to define Triple Negative Breast Cancer (TNBC) and Head and Neck Squamous Cell Carcinoma (HNSCC) as selected indications of interest for Phase 2 and to clarify and add safety language.

Protocol amendment summary of changes table

Section # and Name	Description of Change	Brief Rationale
Whole document	New logo has been added and an update to the amendment number version, date has been made	To be compliant with company conventions
Cover page and reviewers/approvers	Update of cover page has been made	To reflect the changes resulting from the acquisition and to comply with the SOP applicable to the protocol template utilized
Section Protocol Synopsis - Statistical analysis and Section 9.4.2.1	80% has been added in the reference to confidence intervals	To maintain consistency in the CIs stated in the protocol
Section protocol synopsis - Planned study dates - Duration of study and Section 3.4	Q3 2023/ Q1 2024 has been added Approximately 70 cycles have been specified	To reflect new timelines and to provide clarity to the vendors
Section protocol synopsis - Indication: Phase 2 - Study Population Abbreviation Section 3.1 ; 3.1.2 and 3.1.4	Adding TNBC to list of indications TNBC and HNSCC selected as indications of interest for Phase 2	To specify the indications selected for Phase 2 expansion.
Section protocol synopsis: - Secondary objective And Section 2.1.2	A secondary objective has been added: "- To assess PK of atezolizumab in combination with KY1044"	To complete the secondary objectives
Section Protocol Synopsis - Secondary endpoints: PK measures And Section 2.2.2	The definition of PK measures: "KY1044 PK measures (eg, maximum concentration [C_{max}], half-life); Serum concentration vs. time profiles has been replaced by: "Serum concentrations and PK parameters (eg, Cmax, t1/2) of KY1044 and of atezolizumab if in combination."	To clarify the definition of PK measures
Section Protocol Synopsis - Study Design Figure 3.2 Section Section 3.1; 3.4; 5.3 and Table 6-1; Table 6-2 and Table 6-8	The mode of administration of KY1044 description has been modify: "for up to 48 months or until the patient discontinues the study." Has been removed and replaced by "Study treatment will be administered for up to 48 months or until the patient discontinues the study treatment" Flexibility in language has been added to up to 48 months treatment duration: will replaced by may be up to 48 months; maximum delated in max period up to 48 months	To clarify the language on duration of treatment To introduce flexibility in maximum treatment duration

Section # and Name	Description of Change	Brief Rationale
Section Protocol Synopsis - Key inclusion criteria and Section 4.2	Inclusion criteria has been defined for the HNSCC and NSCLC indications	For clarification and better understanding of HNSCC and NSCLC indications inclusion criteria
Section Protocol Synopsis - Pharmacokinetic variables	Absorption has beenreplaced by distribution in the definition of PK variables	For language accuracy
Section Protocol Synopsis - Duration of the study Section 3.1; Figure 3-1; Section 3.6 and Section 5.3	Will has been replaced by may in "provisions will be made"	To be compliant with Section 3.4 Study duration.
Section 3.1.4	n for selected indications has been updated	Statistical calculations for new cohorts
Figure 3-1	Figure of study design has been updated in view of new patient number for selected indications and Phase 2 choosed design	To be compliant with defined study design
Section 3.4	Sentence: "up to 2 years (or as long as the treatment continues if it lasts more than 2 years)" has been added to "All patients will be followed up for survival …"	For follow up duration precision
Section 9.2 Sample size determination Phase 2	The cohort expansion number has been updated to up to 40 per subgroup. The corresponding section pertaining to CIs has also been updated.	Statistical calculations for new cohorts
Section protocol synopsis and 4.3	Fridericia's formula (QTcF) specified for calculations	Protocol deviations required this clarification to be included
Table 6-1 and Table 6-2	Timeline for confirmatory scan clarified to include the language"4 to 8 weeks.	To comply with the precise language in the iRECIST guidelines and ensure consistent reporting of tumor assessments
	And a sentence: "A window of ±3 days is permissible to complete the assessments" has been added to footnote of both tables	To add flexibility in time to complete assessments
Table 6-4	A footnote has been added #*c* to Biomarker Sample Collection Plan (Tumor/Blood Samples) for Phase 1 and 2 Table 6-4	For clarification on biopsy and tumor samples
Section 7.1, Section 7.1.2 and Section 7.1.5	Clarification of language relating to AE and SAE reporting	To ensure better data collection and reporting
Section 7.1.6	Infusion related reactions, overdose and pregnacy have now been designated as the AESI for both IMPs	Consensus reached at the SMT after analysis of the AEs deemed as IRRS by the PIs

Section # and Name	Description of Change	Brief Rationale
Section 7.1.7	Language pertaining to reporting of deaths has been updated	To ensure better data collection and reporting
Section 7.2.2	Definition of symptomatic overdose for IMPs has been included in guidance for overdose section	For precision
Section 8	One reason for treatment discontinuation: "48 months of treatment" has been added And sentence "Patients will be automatically discontinued in case of death." Has been removed	For treatment discontinuation clarity and accuracy
Section 8.1	Clarification on patients follow up has been made: "(all reasons 1 to 6 listed above)"	For clarification
Section 8.2.3	End of Study for Individual Patients definition has been completed by adding: "is defined as the date […] last participant in the trial globally."	For clarification of overall end of study definition
Section 9.4.3	Section safety analysis has been completed by adding a chapter: "Actual and change from baseline […]range value will be displayed."	For clarification
Section 9.4.4	The additional pharmacokinetic section has been rephrase. Text "The estimation of area […] summarized in order to linearity of pharmacokinetics." Has been removed. And section for Exploratory and PK population analysis have been added.	Clarification of PK analysis section

In addition, other minor editorial changes (eg, grammatical, stylistic, and minor typographical corrections) were implemented throughout the protocol.

STUDY PERSONNEL

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This study will be conducted in compliance with:

- **This protocol**
- **International Conference on Harmonisation (ICH) E6(R2) Good Clinical Practice (GCP) guidelines**
- **The applicable regulatory requirement(s)**
- **The general principles of the Declaration of Helsinki**

COMPLIANCE STATEMENT

The study will be conducted in compliance with the protocol, informed consent regulations, the general principles of the Declaration of Helsinki and the ICH E6(R2) guidelines related to GCP. In addition, the study will adhere to all applicable state, regional and national regulatory requirements.

The electronic data capture systems and other applicable electronic systems used in the conduct of the study will comply with ICH E6(R2), Section 5.5.3 guidance on use of electronic trial data handling and/or remote electronic trial data systems and the Food and Drug Administration (FDA), 21 CFR Part 11, Electronic Records, Electronic Signatures, and FDA, Guidance for Industry: Computerized Systems Used in Clinical Trials.

Central safety, Pharmacokinetic (PK) and pharmacodynamic (PD) analyses will be performed in laboratories qualified in accordance with the procedures of the Sponsor or the Sponsor's contracted CRO. Local safety analysis will be performed in accordance with institutional standards applicable at the relevant Investigator site.

All episodes of non-compliance will be documented and addressed. Significant non-compliance (with potential to impact on patient safety or the integrity of data) will be notified to Sponsor promptly. Noncompliance with the protocol, SOPs, ICH GCP, and/or applicable regulatory requirement(s) will lead to prompt action by the Sponsor to secure compliance. If serious and/or persistent non-compliance is identified on the part of an investigator/institution, Sponsor will terminate the investigator's/institution's participation in the trial in accordance with ICH GCP.

The Sponsor will ensure there is appropriate oversight of any trial-related duties and functions carried out on its behalf by contracted vendors, and where applicable ensure the Sponsor's contracted CRO(s) have appropriate systems processes to provide oversight of duties subcontracted to another party by them.

PROTOCOL SYNOPSIS

Protocol identifier:	KY1044-CT01
Study 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
Sponsor:	Kymab Ltd
Phase:	1/2
Study type:	Interventional
Indication:	**Phase 1:** Advanced/metastatic malignancies, and preferred indications: head and neck squamous cell carcinoma (HNSCC), non-small cell lung cancer (NSCLC), hepatocellular carcinoma (HCC), gastric/esophageal cancer, melanoma, renal cell cancer, pancreatic cancer, cervical cancer, and triple negative breast cancer (BC) **Phase 2:** • Anti-programmed cell death protein 1 (anti-PD-1)/anti-programmed cell death-ligand 1 (anti-PD-L1) treatment naïve: HNSCC, NSCLC, triple negative breast cancer (TNBC), gastric/esophageal and cervical cancer • Anti-PD-(L)1 pre-treated: HNSCC, NSCLC, TNBC, gastric/esophageal and cervical cancer • Indications in which anti-tumor activity has been observed in Phase 1
Purpose and rationale:	The purpose of this "first-in-human" study of KY1044 is to characterize the safety, tolerability, pharmacokinetics (PK), pharmacodynamics (PD) and anti-tumor activity of KY1044 administered intravenously (IV) as single agent and in combination with atezolizumab in adult patients with advanced/metastatic malignancies
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
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 PK profile of KY1044 as single agent and in combination with atezolizumab • To assess PK of atezolizumab in combination with KY1044 • To assess emergence of anti-KY1044 and anti-atezolizumab antibodies following one or more IV 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

Exploratory objectives	• To assess the pharmacodynamic effect of KY1044 as single agent and in combination with atezolizumab in tumor tissue • To assess the pharmacodynamic 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)
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 IV every 3 weeks (Q3W) and Atezolizumab will be administered according to dosing instructions given in the approved label for marketing (1200 mg IV Q3W). Study treatment will be administered for up to 48 months or until the patient discontinues the study treatment. Patients should not discontinue treatment based on progressive disease per Response Evaluation Criteria in Solid Tumors (RECIST 1.1) unless clinical deterioration or increase in tumor markers is observed. **Phase 1 dose escalation:** The Phase 1 dose escalation part of the study will enroll cohorts of minimum three patients. To assess the safety profile of KY1044 it will be required that each cohort satisfies the following requirements: • At least two patients are anti-PD-(L)1 naïve • Only one patient has a non-preferred tumor type • All inclusion/exclusion criteria are met. **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. **Phase 2:** In the absence of identifying a maximal tolerated dose (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. Together with safety, efficacy and biomarker data from Phase 1, data from this part will assist with the selection of the recommended Phase 2 dose (RP2D). Once the MTD and/or RP2D for KY1044 as single agent or in combination with atezolizumab has been defined, a Phase 2 expansion component to assess preliminary anti-tumor efficacy in additional selected indications may commence. Patients who are either anti-PD-(L)1 treatment naïve or who have had prior treatment with anti-PD-(L)1 will be considered as separate groups. **In anti-PD-(L)1 naive patients:** In Phase 2 approximately 15 patients will be enrolled in the anti-PD-(L)1 naïve subgroup per each indication, in the single agent and the combination group. **In anti-PD-(L)1 pre-treated patients:** In the anti-PD-(L)1 pre-treated subgroup a minimum of five patients will be recruited in each indication. These patients will have already progressed on

	previous immunotherapy; hence any individual response would indicate a proof of mechanism in these patient groups. If signs of efficacy have been observed in any of these anti-PD-(L)1 pre-treated indications a further expansion to 15 patients will be considered.
Sample size:	In Phase 1, each of the dose escalations (single agent and combination therapy) will include a maximum of 36 patients, unless no dose levels are determined to be safe or the safety review committee (SRC) decides to stop the dose escalation part. If fewer than 36 patients are required to dose escalate, the remainder may be included in the enrichment part. The Phase 1 part of the study (dose escalation and enrichment cohorts) may contain approximately 150 patients. The actual number of patients recruited in the Phase 2 part of the study will depend on the number of tumor indications investigated and on the number of expansions; however the total number in Phase 2 is not anticipated to exceed 262 patients.
Study population:	• The Phase 1 dose escalation and enrichment parts of the study will be conducted in adult patients with advanced/metastatic malignancies and selected indications: NSCLC, HNSCC, HCC, gastric/esophageal cancer, melanoma, renal, cervical cancer, TNBC and pancreatic cancer. • An initial Phase 2 dose assessment part will be opened 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. • A Phase 2 KY1044 single agent part will be opened should signs of anti-tumor activity (defined as either complete response (CR), partial response (PR) or durable stable disease (SD) with tumor shrinkage that does not qualify for PR) be seen in the Phase 1 dose escalation/enrichment. • A Phase 2 KY1044 combination with atezolizumab part will enroll patients in selected indications (NSCLC, HNSCC, TNBC, cervical and gastric/esophageal cancer and any indication where KY1044 in combination with atezolizumab has shown signs of anti-tumor activity in the Phase 1 dose escalation)
Key inclusion criteria:	1. Histologically documented advanced/metastatic malignancies 2. Phase 1 and Phase 2 patients with advanced/metastatic malignancies who have measurable disease (non-measurable disease is allowed only in Phase 1) as determined by RECIST 1.1 will be eligible if, according to the NCCN guidelines, there are no available therapies known to confer a clinical benefit for their disease, or they have exhausted all such available options. Additionally, the following specific tumor indications will be enrolled: **a. Phase 1 (including enrichment part):** Patients with advanced/metastatic malignancies, and preferred indications (NSCLC, HNSCC, HCC, melanoma, cervical, gastric/esophageal, renal, pancreatic, and triple negative BC) **b. Phase 2 KY1044 single agent:** Patients with advanced/metastatic malignancies in indications in which signs of anti-tumor activity (CR, PR or durable SD with tumor shrinkage that does not qualify for PR) were seen during the dose escalation/enrichment of KY1044 as single agent. **c. Phase 2 KY1044 in combination with atezolizumab:** Patients with advanced/metastatic malignancies in the selected indications below, and/or indications which have shown promising activity in Phase 1: • NSCLC (anti-PD-(L)1 therapy naïve and pre-treated between 1 and 2 prior lines of systemic therapy for advanced disease)

	• Recurrent and/or metastatic HNSCC (anti-PD-(L)1 therapy naïve and pre-treated between 1 and 2 prior lines of systemic therapy for advanced disease) • Gastric/ Esophageal cancer (anti-PD-(L)1 therapy naïve and pre-treated) • Cervical cancer (anti-PD-(L)1 therapy naïve and pre-treated) • Indications, in which signs of anti-tumor activity has been observed in Phase 1 with KY1044 in combination with atezolizumab 3. Prior therapy with anti-PD-(L)1 inhibitors is allowed provided any toxicity attributed to prior anti-PD-(L)1-directed therapy did not lead to discontinuation of therapy. 4. Eastern Cooperative Oncology Group (ECOG) performance status 0-1. 5. Life expectancy longer than 12 weeks. 6. Must have a site of disease amendable to biopsy, and be candidate for tumor biopsy, according to the treating institution's guidelines. Patients must be willing to undergo a new tumor biopsy at screening and during therapy on the study. 7. Women of childbearing potential and men must agree to use adequate contraception prior to study entry, for the duration of study participation and for at least 5 months after discontinuing study treatment, or longer if the half-life of KY1044 is observed to exceed that of atezolizumab.
Key exclusion criteria:	1. Presence of symptomatic central nervous system (CNS) metastases unless neurologically stable (for 4 weeks) and off steroids for at least 2 weeks before the first dose of study treatment. 2. History of severe hypersensitivity reactions to other monoclonal antibodies (mAbs) and/or their excipients. 3. Known presence of neutralizing anti-atezolizumab antibodies. 4. Patients previously exposed to anti-PD-(L)1 treatment who are not adequately treated for skin rash or have no replacement therapy for endocrinopathies. 5. Known human immunodeficiency virus (HIV), active hepatitis B virus (HBV) or active hepatitis C virus (HCV) infection. Patients with HCC, whose HBV or HCV infection is controlled by antiviral therapy, should not be excluded Patients with any severe infection within 4 weeks prior to initiation of study treatment, including, but not limited to, hospitalization for complications of infection. 6. Active autoimmune disease or a documented history of autoimmune disease, including ulcerative colitis and Crohn's disease or any condition that requires systemic steroids. 7. Malignant disease, other than that being treated in this study. Exceptions to this exclusion criterion include malignancies that were treated curatively and have not recurred within 2 years prior to the first dose of study treatment; completely resected basal cell and squamous cell skin cancers; and completely resected carcinoma in situ of any type. 8. Systemic steroid therapy or any immunosuppressive therapy (≥10 mg/day prednisone or equivalent). 9. Anti-CTLA4, anti-PD-(L)1 treatment within 4 weeks of the first dose of study treatment 10. Pretreatment with anti-CTLA4 antibodies in combination with other antibodies or drugs, specifically targeting T-cell stimulation or checkpoint pathways.

	11. Systemic anti-cancer therapy (tyrosine kinase inhibitor (TKI) and/or chemotherapy) within 2 weeks of the first dose of study treatment. For cytotoxic agents that have major delayed toxicity, eg, mitomycin C and nitrosourea, 4 weeks is indicated as washout period. 12. Use of live or live attenuated vaccines against infectious diseases (examples include, but are not limited to, intranasal influenza, measles, mumps, rubella, oral polio, Bacillus Calmette-Guérin vaccine, rotavirus, varicella, yellow fever, TY21a typhoid vaccines etc) within 4 weeks of the first dose of study treatment and it should not be planned to administer such a vaccine during the course of the study. SARS-CoV-2 vaccines authorized for use by the competent local regulatory health authorities for active immunization to prevent COVID-19 are allowed (unless the vaccine is live or live attenuated) and must be given in accordance with the prevailing immunization guidelines. SARS-CoV-2 vaccination may be given at least 7 days prior to the planned first dose of study treatment. 13. Participation in an interventional, investigational study within 4 weeks of the first dose of study treatment. 14. Impaired cardiac function or clinically significant cardiac disease, including any of the following: a. Clinically significant and/or uncontrolled heart disease such as congestive heart failure requiring treatment (New York Heart Association (NYHA) Grade ≥2), uncontrolled hypertension or clinically significant arrhythmia b. QTcF >470 msec on screening electrocardiogram (ECG) using Fridericia's formula (QTcF) or congenital long QT syndrome c. Acute myocardial infarction or unstable angina pectoris <3 months prior to first dose of study treatment 15. Presence of Common Terminology Criteria for Adverse Events Version 5 (CTCAE v5) ≥Grade 2 toxicity (except alopecia, peripheral neuropathy and ototoxicity, which are excluded if CTCAE v5 ≥Grade 3) due to prior cancer therapy. 16. Radiotherapy within 2 weeks of the first dose of study treatment, except for palliative radiotherapy to a limited field, such as for the treatment of bone pain or a focally painful tumor mass. To allow evaluation for response to treatment, patients enrolled in the Phase 2 part must have remaining measurable disease that has not been irradiated.
Investigational medicinal product:	KY1044 and atezolizumab (TECENTRIQ®)
Route of administration:	IV
Treatment regimen(s):	IV infusion of KY1044 Q3W. Atezolizumab is administered IV Q3W.
Efficacy assessments:	Tumor assessment as per RECIST 1.1. and immune-related (i)RECIST
Safety assessments:	Incidence and severity of Adverse Events (AEs) and Serious Adverse Events (SAEs), including changes in laboratory values, vital signs and ECGs.
Other assessments:	PK measures (see below), Receptor Occupancy, Immunogenicity (anti-drug antibody (ADA)). Pharmacodynamic assessment on pre- and post- treatment, newly obtained tumor samples, plasma and peripheral blood mononuclear cells (PBMCs). Pharmacogenomics.

Pharmacokinetic variables:	Measures for distribution and elimination for KY1044 as single agent and in combination with atezolizumab and for atezolizumab.
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 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:** • Overall response rate (ORR) per RECIST 1.1
Secondary endpoint:	**Efficacy measures** • Best Overall Response (BOR), Progression Free Survival (PFS) and Duration of Response (DOR) per RECIST 1.1 • ORR and PFS per iRECIST (Phase 1 and Phase 2) • ORR per RECIST 1.1 (Phase 1 only) • Survival rate at 12 and 24 months **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: • Serum concentrations and PK parameters (eg, Cmax, t1/2) of KY1044 and of atezolizumab if in combination. **ADAs** • Presence and/or concentration of anti-KY1044 and anti-atezolizumab antibodies **Biomarkers:** Presence of tumor-infiltrating lymphocytes (TILs) as determined by expression of inducible T cell costimulator (ICOS), Forkhead box P3 (FOXP3) and CD8 cells (immunohistochemistry)
Exploratory endpoints:	**Tumor tissue:** • Expression of immune- and response related markers such as (but not limited to) PD-L1, CD163, CD68 by immunohistochemistry (IHC) • messenger ribonucleic acid (mRNA) gene signature (transcriptomics/ Nanostring) with special interest in interferon (IFN) gene signature (PanInflammatory panel and/or IO360 panel) **Peripheral blood:** • Peripheral, soluble ligands and cytokine levels (eg, interferon gamma (IFNγ), tumor necrosis factor alpha (TNF-α), granulocyte-macrophage colony-stimulating factor (GM-CSF) contingent on availability of assay (ie, Single Molecule Array SIMOA) • Phenotype and markers of immune cells (ICs) activation in peripheral blood (eg, CD3, CD8, CD4, regulatory T cells (T_{Regs}), CD4 memory cells, CD25, FOXP3, CD45RA, ICOS, CD14, CD45, CD56, CD19 and inducible T-cell Costimulator Ligand (ICOSLG) fluorescence-activated cell sorting (FACS) or ChipCytometry)

	• PBMCs gene signature (RNA) (transcriptomics/Nanostring) • ICOS Receptor Occupancy (RO) in PBMCs (KY1044 as single agent in Phase 1 only)
Statistical analysis:	**Primary endpoints: Phase 1** Treatment-related AEs/SAEs coded by primary System Organ Class (SOC) and Preferred Term (PT) will be summarized in those receiving at least one infusion of KY1044. Additional summaries by severity of AEs/SAEs will also be produced. Actual and change from baseline data for vital signs, ECG parameters and clinical laboratory values will be reported using summary statistics. The number of dose interruption, reductions and incidence of DLTs will be summarized. **Primary endpoint: Phase 2** ORR per RECIST 1.1 will be presented for each indication along with exact 80% and 95% confidence intervals Phase 1 will be reported by dose group(s) within KY1044 single agent and KY1044 combination groups. Phase 2 of the study will be reported 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. Wherever possible, patients with the same tumor type who have received the recommended dose(s)/schedule(s) of KY1044 as single agent or in combination will be pooled for analysis. No formal statistical testing will be performed during Phase 2. Instead confidence intervals will be constructed around the objective response rate observed in each cohort, and this will enable decisions to be made around the likely success of future studies. A Go-no-go decision grid for Phase 2 cohort expansion will be developed for each indication.-- Final data analysis will be performed at the end of the study.
Planned study dates: **Start of clinical phase** **End of clinical phase**	Q1 2019 Q3 2023 / Q1 2024
Duration of the study:	The duration of the study for each patient will consist of up to 28 days of screening, up to 48 months of treatment (approximately 70 cycles) and 90 days of safety follow-up. The completion of the study is defined as the last visit for end of safety follow-up for the last patient on treatment. Survival data will be reported and censored at the completion of the study for all patients. Additional provisions may be made for patients who are ongoing on treatment and having clinical benefit at 48 months for continuation of treatment.
Key words:	Phase 1/2, KY1044, atezolizumab, immunotherapy, cancer

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
Abs	Antibodies
ADA	Anti-drug Antibody
ADCC	Antibody-Dependent Cellular Cytotoxicity
ADCP	Antibody-Dependent Cellular Phagocytosis
AE	Adverse Event
AESI	Adverse Events of Special Interest
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
ANC	Absolute Neutrophil Count
APAC	Asia Pacific
APCs	Antigen Presenting Cells
aPTT	Activated Partial Thromboplastin Time
AST	Aspartate Aminotransferase
AUC	Area under the concentration time curve
AUC_{inf}	Area under the concentration time curve to infinity
BMI	Body Mass Index
BOR	Best Objective Response
BP	Blood Pressure
BUN	Blood Urea Nitrogen
CD	Cluster of Differentiation
CEA	Carcinoembryonic Antigen
CFR	Code of Federal Regulations
C-G	Cockroft-Gault
CK	Creatine Kinase
CK-MB	Creatine Kinase-Muscle/Brain
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
C_{max}	Maximum Concentration
C_{min}	Trough Concentration
CNA	Copy Number Alterations
CNS	Central Nervous System
COVID-19	Coronavirus disease 2019
CR	Complete Response
CRO	Contract Research Organization

Abbreviation	Definition
CT	Computed Tomography
CTCAE v5	Common Terminology Criteria for Adverse Events version 5
CTFG	Clinical Trial Facilitation Group
CTLA-4	Cytotoxic T lymphocyte Antigen-4
DLT	Dose Limiting Toxicity
dMMR	Mismatch-repair deficiency
DNA	Deoxyribonucleic Acid
DOR	Duration of Response
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
EDTA	Ethylenediaminetetraacetic acid
EEA	European Economic Area
EOS	End of Study
EOT	End of Treatment
eTMF	Electronic Trial Master File
EU	European Union
FACS	Fluorescence-Activated Cell Sorting
FAS	Full Analysis Set
FCγ	Fragment crystallizable gamma
FDA	Food and Drug Administration
FFPE	Formalin-Fixed Paraffin Embedded
FIH	First In Human
FOXP3	Forkhead box P3
GCP	Good Clinical Practice
G-CSF	Granulocyte-Colony Stimulating Factor
GGT	GammaGlutamyl Transferase
GI	Gastrointestinal
GMP	Good Manufacturing Practice
GM-CSF	Granulocyte-Macrophage Colony-Stimulating Factor
HBV	Hepatitis B Virus
HCC	Hepatocellular Carcinoma
hCG	Human Chorionic Gonadotropin
Hct	Hematocrit

Abbreviation	Definition
HCV	Hepatitis C virus
HDL	High Density Lipoprotein
HED	Human Equivalent Dose
Hgb	Hemoglobin
HIV	Human Immunodeficiency Virus
HNSCC	Head and Neck Squamous Cell Carcinoma
IB	Investigator's Brochure
IC	Immune cells
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
ICI	Immune Checkpoint Inhibitors
ICOS	Inducible T cell Costimulator
ICOSLG	Inducible T-cell Costimulator Ligand
IEC	Independent Ethics Committee
IFNγ	Interferon Gamma
IgG	Immunoglobulin G
IHC	Immunohistochemistry
IL	Interleukin
IMP	Investigational Medical Product
IND	Investigational New Drug
irAE	Immune-related Adverse Events
IRB	Independent Review Board
iRECIST	Immune-Related Response Evaluation Criteria in Solid Tumors
irPD	Immune-Related Progressive Disease
ISF	Investigator Site File
IV	Intravenous
IXRS	Interactive X=Voice/Web Response System
K_D	Equilibrium dissociation constant
LDH	Lactate Dehydrogenase
LDL	Low-Density Lipoprotein
LFT	Liver Function Test
LPS	Lipopolysaccharide
mAbs	Monoclonal Antibodies
Max	Maximum

Abbreviation	Definition
MCH	Mean Cell Hemoglobin
MCHC	Mean Cell Hemoglobin Concentration
MCV	Mean Cell Volume
MedDRA	Medical Dictionary for Regulatory Activities
MFI	Mean Fluorescence Intensity
Min	Minimum
Mins	Minutes
MMR	Measles, Mumps, Rubella
MoA	Mechanism of Action
mPFS	Median Progression Free Survival
MRI	Magnetic Resonance Imaging
mRNA	Messenger Ribonucleic Acid
MRSD	Maximum Recommended Starting Dose
MSI	Microsatellite Instability
MTD	Maximal tolerated dose
mTPI2	Modified Toxicity Probability Interval Design No 2
N, No., n	Number
NCA	Noncompartmental Analysis
NL	New Lesion
NOAEL	No Observed Adverse Effect Level
NSCLC	Non-Small Cell Lung Cancer
NTLs	Non-Target Lesions
NYHA	New York Heart Association
ORR	Overall Response Rate
OS	Overall Survival
PBMC	Peripheral Blood Mononuclear Cells
PD	Pharmacodynamic
PD-1	Programmed Cell Death Protein-1
PD-L1	Programmed Cell Death-Ligand 1
PFS	Progression Free Survival
PI	Principal Investigator
PK	Pharmacokinetic
PR	Partial Response
PSA	Prostate Specific Antigen

Abbreviation	Definition
PT	Preferred Term
Q3W	Every 3 weeks
RBCC	Red Blood Cell Count
RECIST 1.1	Response Evaluation Criteria in Solid Tumors version 1.1
RNA	Ribonucleic Acid
RO	Receptor Occupancy
RP2D	Recommended Phase 2 Dose
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SARS-Cov-2	Severe Acute Respiratory Syndrome Coronavirus 2
SD	Stable Disease
SDV	Source Document Verification
SIMOA	Single Molecule Array
SOC	System Organ Class
SOP	Standard Operating Procedure
SRC	Safety Review Committee
StD	Standard Deviation
SUSAR	Suspected Unexpected Serious Adverse Reactions
t½	Half-life
T4	Thyroxine
t_{max}	Time to maximum observed serum concentration
TC	Tumor cells
TCGA	The Cancer Genome Atlas
TCR	T Cell Receptor
T_{Eff}	T-effector cells
TGF-β	Transforming Growth Factor Beta
TILs	Tumor-Infiltrating Lymphocytes
TK	Toxicokinetics
TKI	Tyrosine Kinase Inhibitor
TMB	Tumor Mutational Burden
TME	Tumor Microenvironment
TNBC	Triple Negative Breast Cancer
TNFα	Tumor Necrosis Factor alpha
TPS	Tumor Proportion Score

Abbreviation	Definition
T_{Regs}	Regulatory T cells
UCC	Urothelial Cell Carcinoma
ULN	Upper Limit of Normal
USA	United States of America
UTI	Urinary Tract Infection

1 BACKGROUND INFORMATION

1.1 Introduction

In recent years there has been a significant paradigm shift in cancer therapies with the approval of antibodies targeting immune checkpoints (eg, ipilimumab for cytotoxic T lymphocyte antigen-4 [CTLA-4], nivolumab and pembrolizumab for programmed cell death protein-1 [PD-1] and atezolizumab, durvalumab and avelumab for programmed cell death-ligand 1 [PD-L1]) (1). These immune checkpoint inhibitors (ICI) are associated with a strong and long-lasting response in patients suffering from several malignancies, including but not limited to metastatic melanoma, non-small cell lung cancer (NSCLC), head and neck squamous cell carcinoma (HNSCC), Hodgkin lymphoma, renal and bladder cancer (1). A high proportion of patients, however, show intrinsic or acquired resistance to ICI monotherapies (2). These patients represent a population with high unmet medical needs that might benefit from alternative approaches, such as combination therapies, whereby different immune modulators, by affecting the signaling of distinct pathways, may provide enhanced activity in combination.

There is accumulating evidence that the immunosuppressive tumor microenvironment (TME) is one of the major challenges in cancer immunotherapy as it is one of the major causes of ICI failure. It is therefore important to understand and tackle the tissue-protective cellular elements of the TME to improve the response rate to ICI. Analysis of human cancers and mouse models has demonstrated that non-responsiveness to ICI can often be caused by suppressive mechanisms in the TME. Amongst these, regulatory T cells (T_{Regs}), which express high levels of inducible T cell costimulator (ICOS), play a vital immunosuppressive role (3).

ICOS, a third member of the cluster of differentiation (CD)28/CTLA-4 family, is expressed on activated T cells and is a marker for highly suppressive antigen-specific T_{Regs} (4, 5). ICOS signaling controls forkhead box P3 $(FOXP3)^+$ T_{Regs} expansion, survival, and interleukin-10 (IL-10) production. High levels of $ICOS^+$ T_{Regs} have been described in several indications, including HNSCC, NSCLC, esophageal, hepatocellular carcinoma (HCC) and cervical cancer (The Cancer Genome Atlas [TCGA] data analysis and [6]), and represent an unfavorable prognostic indicator in advanced cancer (3, 6, 7). Finally, the preferential high expression of ICOS on intratumoral T_{Regs} makes this protein a strong candidate for a depleting antibody strategy.

By immunizing Kymouse™ in which endogenous *Icos* gene has been knocked out, the Sponsor identified a novel fully human immunoglobulin (Ig)G1 monoclonal antibody, KY1044, which binds to ICOS and depletes $ICOS^{high}$ expressing cells by virtue of fragment crystallizable gamma (Fcγ) receptor interactions, while stimulating $ICOS^{low}$ expressing T-effector cells (T_{Eff}). The depletion of $ICOS^+$ T_{Regs} with KY1044, or the combined effect of KY1044 and PD-L1 blockade in the clinic may have significant antitumor efficacy and the potential to rescue patients that are proven to be refractory or resistant to PD-(L)1 inhibitors as single agents.

1.2 An Introduction to ICOS and its Biology

ICOS is a member of the CD28/CTLA-4 family, and is expressed upon activation on T cells (5). At steady state, ICOS is also expressed on memory T cells ($CD45RO^+$or $CD44^{high}$) as well as on the majority of $FOXP3^+$ regulatory $CD4^+$ T cells. Importantly, available data demonstrate that T_{Regs} express significantly higher levels of ICOS than T_{Eff} (Figure 1-1) (8). ICOS has only one known ligand, called ICOSLG/B7-H2 (5), which is constitutively expressed on antigen

presenting cells (APCs) such as B cells and dendritic cells, but has also been shown to be up-regulated in response to tumor necrosis factor alpha (TNFα) and lipopolysaccharide (LPS) (9, 10). Activation of ICOS prevents cell death, modifies T cells' cytoskeleton and upregulates cellular metabolism (5). In response to ICOS signaling, IL-10 production is specifically observed in $ICOS^{high}$ T_{Regs} (11). ICOS-mediated costimulation of T cells also leads to the production of effector cytokines such as IL-4, interferon gamma (IFNγ), and (TNFα) from $ICOS^{+}$ CD8 and CD4 T cells (12). Since its discovery two decades ago, ICOS has been shown to play a key role in immune cell signaling, and the overall immune response towards pathogens and immunogenic tumors (13, 14), and is necessary for the establishment and maintenance of antigen specific T_{Eff} and T_{Regs} (11, 15, 16).

ICOS knockout mice are viable and fertile (4, 17, 18). Extended phenotyping analyses confirmed that the mice demonstrate immune-related defects including reduced humoral immunity, as shown by impaired Ig class-switching and a reduction in the size and number of germinal centers. Mice fully lacking ICOS signaling also demonstrate reduced T cell activation, proliferation and survival. Finally, ablation of ICOS in mice is also associated with a lower number of memory and T_{Regs} (11).

ICOS is expressed on different CD4 T cell subsets. Although blockage of CTLA-4 with ipilimumab has been shown to induce ICOS expression on Th1 CD4 T cells which is associated with a higher response rate in treated patients (15), it was previously reported that ICOS is expressed more on the surface of Th2 cells (which are IL-4 and IL-10 producing cells) rather than on Th1 cells (which produce IFNγ) (12). Similarly, murine $ICOS^{+}$ CD4 T_{Regs} are characterized by superior survival and highly suppressive properties compared with $ICOS^{-}$ T_{Regs} (8). Altogether, these data demonstrate that ICOS is preferentially expressed on the surface of pro-tumorigenic T cells.

1.2.1 Expression of ICOS in Cancer

In humans, ICI have shown to be particularly active in the so-called immunological/inflammatory and/or highly mutated tumors. These include melanoma, NSCLC, HNSCC, gastric cancer, Hodgkin lymphomas, microsatellite instability (MSI) positive tumors, renal and urothelial cell carcinoma (UCC) (19). Although ICI show good efficacy and have been approved in these indications, there are still high numbers of patients not responding to these therapeutic antibodies. One of the resistance mechanism associated with lack of response to ICI is the presence of immune suppressive mechanisms such as presence of T_{Regs} in the TME (19). In addition, recent publications have shown that poor prognosis in ovarian, gastric and liver cancers is associated with a high number of $ICOS^{+}$ T_{Regs} (3, 6, 7). In HCC, it has been demonstrated that around 45% of the T_{Regs} are $ICOS^{+}$ and are highly immunosuppressive as they are expressing both IL-10 and transforming growth factor beta (TGF-β) (6). Similarly, it was reported that $ICOS^{+}$ T_{Regs} isolated in melanoma samples are the most prominent suppressive cells in the TME (20).

In order to assess ICOS expression in other indications, TCGA datasets were interrogated for the relative levels of ICOS messenger ribonucleic acid (mRNA) expression in different cancers. From this exercise, indications that exhibit high levels of ICOS transcript were identified. These include tumors originating from the esophagus, head and neck, stomach, cervix, testis, skin and the lung. However, differences were also observed within the immune cell types (CD8 and T_{Regs}) expressing ICOS in these indications, which could be associated with a different level of sensitivity to anti-ICOS therapy.

Finally, a link between viral etiology or the presence of certain bacteria with T cell exhaustion and high T_{Regs} content has been previously highlighted (21). Since ICOS expression on T_{Regs} has been reported during chronic infection disease (22), it is hypothesized that an anti-ICOS antibody with cell killing (antibody-dependent cellular cytotoxicity [ADCC] and antibody-dependent cellular phagocytosis [ADCP]) properties may also be beneficial to treat squamous cell cancers associated with chronic viral infections (eg, human papillomavirus in esophageal and cervical cancer or Epstein-Barr virus-associated nasopharyngeal cancer) and gastric cancer with *Helicobacter pylori* infections (3, 21, 22).

1.3 Overview of Disease and Current Trends in Treatment

This study will be conducted in patients whose tumors are most likely to benefit from inhibition of ICOS as single agent or in combination with anti-PD-L1.

Patients recruited in the study will have either exhausted, or will be ineligible for current options of standard of care. In several of these indications, check point inhibitors have either been approved in the first-, second- and later line setting, or are currently under investigation with preliminary encouraging data. This study will address an urgent medical need also for patients who have progressed with either primary or secondary resistance to previous immunotherapy.

In this study, patients with advanced/metastatic malignancies will be enrolled in the Phase 1 dose escalation part, with preference for HNSCC, gastric/esophageal cancer, HCC, NSCLC, melanoma, cervical, renal, pancreatic and triple negative BC, as high expression of ICOS and FOXP3 have been described as prognostic factors in these cancer indications. Some of these tumors are amongst the most frequent tumor types worldwide (23).

Advances in recent years and the use of targeted therapies and ICI have resulted in improvements in patient outcomes compared to chemotherapy. Selection of molecularly defined subtypes of cancer patients and a better understanding of the TME, in particular basic mechanisms of tumor biology and immunology, has revolutionized results eg, in patients with melanoma treated with ipililumab or BRAF inhibitors. Subsequently treatment with anti-PD-(L)1 checkpoint inhibitors has produced extremely encouraging results in several cancer indications. These results led to the marketing approval of pembrolizumab, nivolumab, atezolizumab, durvalumab and avelumab across multiple tumor indications.

Anticancer immunotherapy has surpassed outcomes in subgroups of patients treated with molecular targeted agents in terms of durable response and overall survival (OS) and offers a change in future perspectives for these patients. Despite these encouraging results, the proportion of patients who do not respond to immunotherapy (innate resistance) or who progress (develop secondary resistance mechanisms) is still high and there is room for further improvement and unmet clinical need. Furthermore, analysis of biomarkers such as PD-L1 positivity by immunohistochemistry (IHC) has shown initial promising results for patients with high expression of PD-L1 (Tumor Proportion Score [TPS] >50%) and has led to the approval of pembrolizumab in first line metastatic NSCLC. However, the predictive value of PD-L1 expression in other malignancies remains inconsistent. Frequently PD-L1 undefined or patients with low expression of PD-L1 can respond well, depending on the indication (nivolumab in gastric cancer [CheckMate-032] [24]) and in second-line metastatic NSCLC (25). Similarly it was reported that the tumor mutation burden is also a useful predictive biomarker for treatment response to ICI. An increased number of non-synonymous point mutations is associated with improved objective response and a durable clinical benefit (26).

The overall response rates with current checkpoint inhibitors in the second line metastatic setting range from 12% to 25% for several tumor types like HNSCC (27, 28, 29), NSCLC (30) and gastric/esophageal cancer (31, 32, 33) and can achieve response rates of around 30% in melanoma (34).

These results clearly illustrate the following:

1. Immunotherapy works extremely well under the right circumstances and offers promising future treatment opportunities when such circumstances are even better defined, by identifying and treating resistance mechanisms.
2. Around 60% to 80% of patients still do not respond to immunotherapy unless markers such as MSI-high, mismatch repair deficiency, high mutational burden or PD-L1 positive status can be identified. Across the tumor types, however, the percentage of patients with high mutational burden does not exceed 18% (analysis of 12,019 cancers, representing 32 distinct tumor types; [35]) and the degree of expression of PD-L1 is very variable (meta-analysis of 61 studies; 10,310 patients all studies; 23 to 1420 patients per study [36]), which makes further investigation into additional immunosuppressive differentiation, potentially contributing to these different factors, even more important.

In summary, there is still an urgent unmet medical need for the majority of cancer patients, despite these great advantages to further improve outcomes of immunotherapy.

1.4 Investigational Medicinal Product(s)

The Investigational Medicinal Products (IMPs), KY1044 and atezolizumab (trade name TECENTRIQ®), are used in this study.

1.4.1 Identity of IMPs

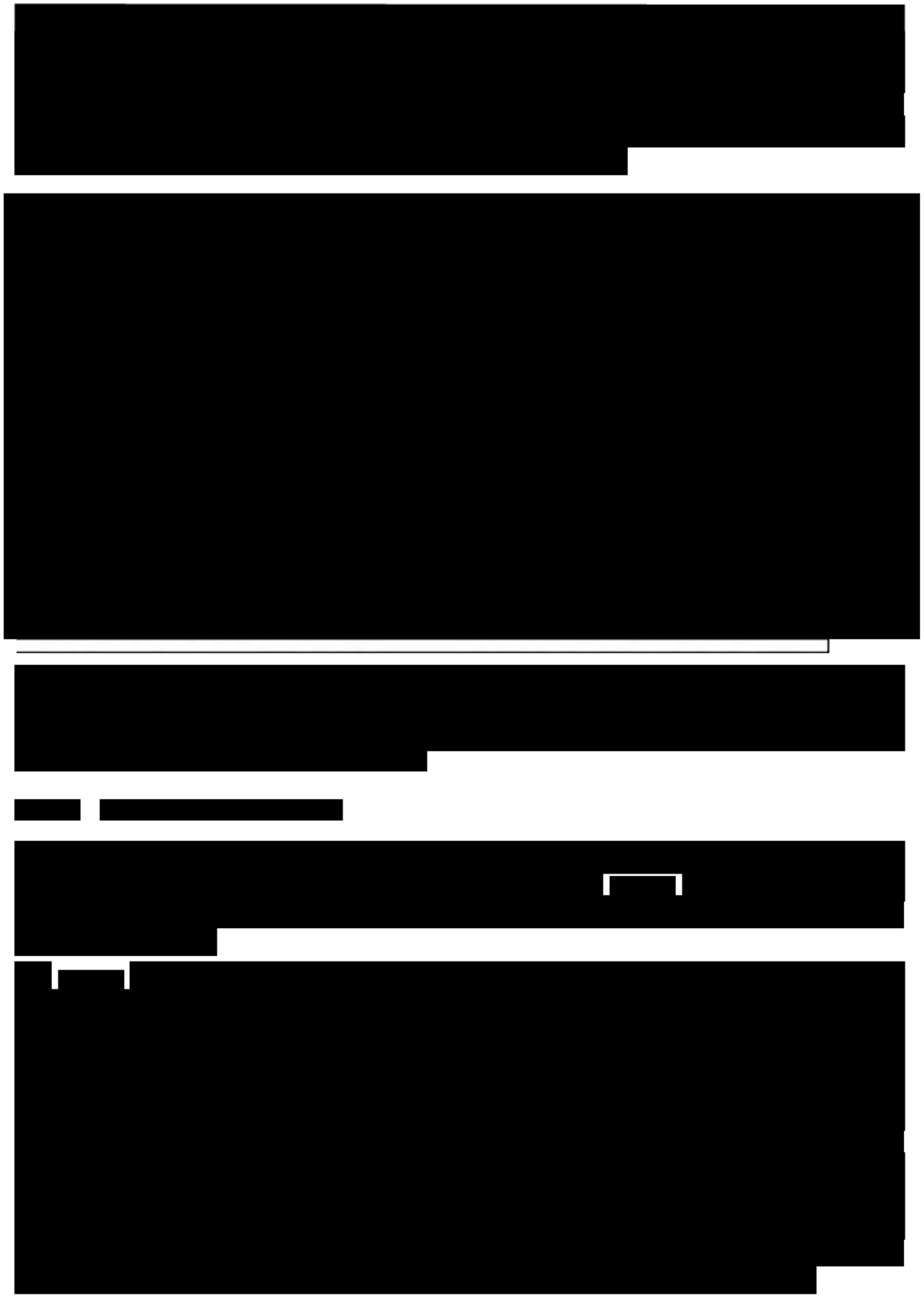
KY1044 is a fully human anti-ICOS subclass G1 kappa monoclonal antibody that selectively binds to ICOS. KY1044 is presented as a liquid solution for intravenous (IV) administration.

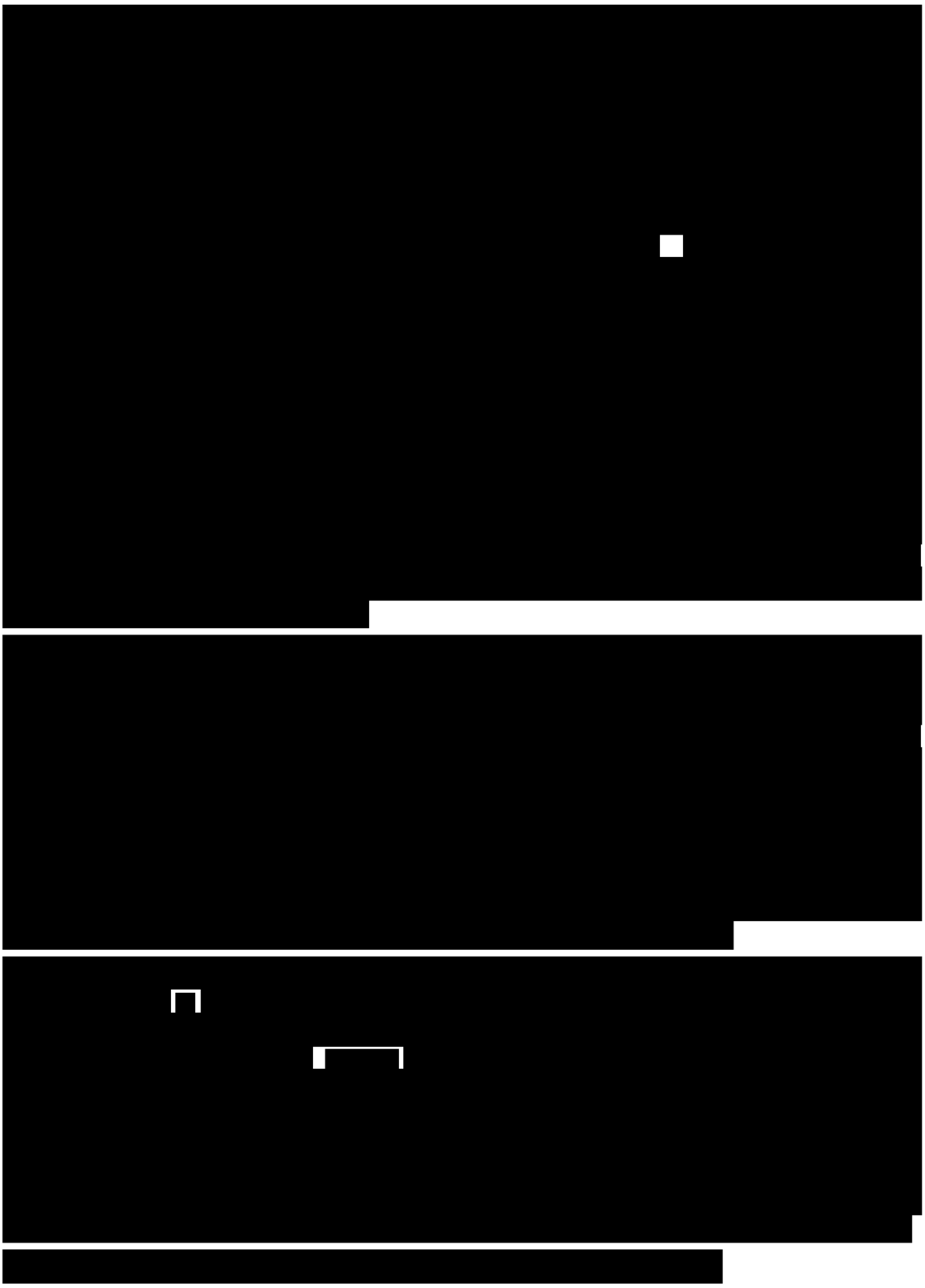
Atezolizumab (TECENTRIQ®) is an immunoglobulin G1 (IgG1) monoclonal antibody that targets PD-L1. Atezolizumab is presented as a liquid solution for IV administration.

Additional information for KY1044 and atezolizumab can be found in Section 5 and in the Investigator's Brochures (IBs) for KY1044 and atezolizumab respectively.

1.4.2 Overview of KY1044

KY1044 has been characterized *in vitro* and *in vivo* in addition to evaluation in non-clinical toxicology studies. [redacted]





1.4.2.4 Clinical Data

This is a first in man study and therefore clinical data are not available.

1.4.3 Overview of Atezolizumab

For non-clinical toxicology, clinical pharmacology, pharmacokinetics, please refer to the atezolizumab IB.

1.4.3.1 Clinical Data Summary of Atezolizumab Safety and Efficacy

As of the end of 2018, atezolizumab is approved for patients with locally advanced or metastatic UCC who are cisplatin ineligible or whose tumors have progressed following prior platinum-containing chemotherapy. It is also approved for patients with metastatic NSCLC after platinum containing chemotherapy. Approvals in these indications have been granted in a number of countries including the United States of America (USA), Taiwan and the EU. Data presented in this Section are those reported by Shah et al, 2018 (42) post approval of atezolizumab in the USA and EU.

Safety:

The recommended dose for atezolizumab is 1200 mg every 3 weeks given via intravenous infusion (42).

In a Phase 1 study of 277 patients with advanced cancer, atezolizumab was well tolerated as a single agent with an incidence rate of 12.6% for Grade 3 to 4 treatment related adverse events (AEs). Immune-related Grade 3 to 4 treatment-related AEs had a low incidence rate of 1%. Notably, there were 3 cases of Grade 3 to 4 aspartate aminotransferase (AST) increase and 3 cases of Grade 3 to 4 alanine aminotransferase (ALT) increase. No Grade 3 to 5 cases of pneumonitis were reported.

Safety in urothelial cell carcinoma:

A Phase 1 study of atezolizumab was performed with a cohort of 68 patients with previously treated urothelial bladder cancer. Atezolizumab was well tolerated with a median duration of treatment of 65 days. Treatment-related AEs were reported in 57% of patients, however, only 4% were Grade 3 in severity. These comprised one case each of asthenia, thrombocytopenia and hypophosphatemia. The most common immune-mediated AEs (decreased appetite and fatigue) were Grade 1 to 2 in severity.

A Phase 2 study (IMvigor 210) was subsequently performed with 2 cohorts; Cohort 1 included 119 treatment naïve patients with advanced urothelial cancer ineligible for cisplatin therapy, whilst Cohort 2 included 310 patients previously treated with platinum-based chemotherapy. Both cohorts received atezolizumab 1200 mg every 3 weeks until progression. In Cohort 1, the most common treatment-related AEs included fatigue, diarrhea and pruritus. Grade 3 to 4 treatment-related AEs were reported in 16% of patients and included fatigue (3%), ALT increase (3%) and AST increase (3%). There was a single Grade 5 treatment-related event which was a case of sepsis. In Cohort 2, 69% of patients reported treatment-related AEs. There were no treatment-related deaths and only 16% of AEs were Grade 3 to 4. The most common Grade 3 to 4 treatment-related AE was fatigue (2%). Immune-mediated AEs were present in 7% of patients and included two cases each of pneumonitis, ALT increase, AST increase, rash and dyspnea.

Safety in NSCLC:

Several Phase 2/3 studies have investigated the use atezolizumab in patients with NSCLC, including BIRCH (NCT02031458), FIR (NCT01846416), POPLAR (NCT01903993) and OAK (NCT2008227). Patients were given atezolizumab 1200 mg every 3 weeks by intravenous infusion.

The Phase 2 POPLAR study compared atezolizumab to docetaxel (75 mg/m^2 every 3 weeks) in patients previously treated for NSCLC. Atezolizumab had a favorable toxicity profile compared to docetaxel with fewer Grade 3 to 4 AEs (40% vs 53%), fewer treatment related Grade 3 to 4 AEs (11% vs 39%), fewer treatment-related AEs causing dose modification or interruption (11% vs 24%) and fewer discontinuations (1% vs 18%). There was a single Grade 5 treatment-related AE of cardiac failure in the atezolizumab arm whilst the docetaxel arm had three Grade 5 treatment-related AEs. Immune-related AEs were also reported in the atezolizumab arm and included AST increase (4% of patients), ALT increase (4%), pneumonitis (3%) and colitis (1%).

In the Phase 3 OAK study, atezolizumab and docetaxel (75 mg/m^2 every 3 weeks) were compared and atezolizumab demonstrated a superior safety profile. The most common treatment-related AEs in the atezolizumab arm were fatigue (14%), nausea (9%), decreased appetite (9%) and asthenia (8%). Immune-related AEs including pneumonitis, hepatitis and colitis had a low incidence rate (≤1%). There were fewer Grade 3 to 4 treatment related AEs with atezolizumab compared to docetaxel (15% vs 43%) and fewer AEs leading to discontinuation (8% vs 19%).

For immune-related AEs please refer to Section 1.6.

Further information on the current atezolizumab safety data can be found in the latest atezolizumab Investigator Brochure.

Efficacy data

Phase 1 monotherapy

A response rate of 18% and median progression free survival (mPFS) of 18 weeks was reported in 175 evaluable patients with activity seen in multiple tumor types.

Atezolizumab monotherapy efficacy data from the OAK and POPLAR studies in advanced, metastatic second line NSCLC versus docetaxel (850 and 287 patients respectively) and the IMvigor 210 study in locally advanced, metastatic UCC, either in patients who were cisplatin ineligible (Cohort 1, 119 patients) or in cisplatin-resistant patients (Cohort 2, 310 patients) are summarized below (for further details please refer to the atezolizumab label [43]) and Weinstock et al., 2017 (44).

Efficacy in urothelial cell carcinoma:

PD-L1 status:

Tumor specimens were evaluated prospectively using the VENTANA PD-L1 (SP142) Assay and subgroups were defined by PD-L1 expression on tumor cells (TC) and immune cells (IC). In immune cells, Grade IC0 corresponded to <1% PD-L1 expression, Grades IC1, IC2 and IC3 corresponded to 1% to 4%, 5% to 9% and ≥10%, respectively. In TCs, TC0 corresponded to <1% PD-L1 expression, grades TC1, TC2 and TC3 corresponded to 1% to 4%, 5% to 49% and ≥50%, respectively.

Study IMvigor210 (Cohort 1): The ORR was 23% (n=119) in all patients.

Study IMvigor210 (Cohort 2): The ORR was 15% in all patients (n=310), 26% in the IC2/3 group and 18% in the IC1/2/3 group.

Efficacy in NSCLC:

PD-L1 status: In both studies, eligible patients were stratified by PD-L1 expression status in tumor-infiltrating IC, by the number of prior chemotherapy regimens, and by histology. Overall, 16% of patients in both studies were classified as having high PD-L1 expression, defined as having PD-L1 expression on ≥50% of TC or ≥10% of IC.

Study OAK: OS was 13.8 months for atezolizumab versus 9.6 months for docetaxel. ORR was 14% for atezolizumab and 13% for docetaxel, however, in the atezolizumab group the DOR was 16.3 months versus 6.2 months in the docetaxel group. At IC-TC 3, OS was 20.5 months for atezolizumab versus 8.9 months for docetaxel; ORR was 31% for atezolizumab and 11% for docetaxel.

Study POPLAR: Atezolizumab showed an improvement in median OS of 12.6 months, versus 9.7 months for docetaxel. ORR was 15% for both drugs, atezolizumab and docetaxel, however, in the atezolizumab group the DOR was 14.3 months versus 7.2 months in the docetaxel group. At IC-TC 3, OS was 15.5 months for atezolizumab versus 11.1 months for docetaxel; ORR was 38% for atezolizumab and 13% for docetaxel.

1.4.4 Overview of the Combination of KY1044 with Anti-PD-(L)1 Inhibitors

1.4.4.1 *Non-clinical Data*

Pre-clinical tumor efficacy studies have been conducted in the CT26.WT syngeneic model with KY1044 in combination with anti-PD-L1 mIgG2a or anti-PD-1 antibodies. These experiments demonstrated that in this syngeneic model, KY1044 was associated with a better anti-tumor response when combined with anti-PD-L1 than with anti-PD-1 (See Section 1.4.2.2) and refer to Figure 1-2 and to the KY1044 IB (37).

1.4.4.2 Clinical Data

This is a first in man study therefore clinical data of the combination of KY1044 with atezolizumab are not available.

1.5 Rationale

1.5.1 Study Rationale and Purpose

KY1044 is a new investigational medicinal product intended for the treatment of patients with advanced/metastatic malignancies to overcome specific tumor escape mechanisms and activate anti-tumor effector cells. Pre-clinical studies of KY1044 as single agent and in combination with anti-PD-L1 have demonstrated efficacy with the synergistic activity of the combination capable of improving survival and preventing recurrence of the same tumor. Pre-clinical studies have not demonstrated any toxicities in rodents and/or non-human primates. Taken together, these data suggest that killing of the $ICOS^{high}$ T_{Regs} combined with a stimulation of T_{Eff} using KY1044 may lead to significant anti-tumor efficacy in patients with advanced/metastatic malignancies.

PD-(L)1 blockade has proven clinical efficacy in various disease settings; a great proportion of patients, however, do not respond or progress on anti-PD-(L)1 therapies as single agent. One

of the indicated reasons for lack of response or progression is the non-permissive immunosuppressive TME, often rich in T_{Regs}. These patients are thus ideally placed to test KY1044 as single agent or in combination with atezolizumab.

1.5.2 Rationale for Study Design

This is a first in human (FIH), open-label, Phase 1/2 study of parallel cohorts with KY1044 as single agent and in combination with atezolizumab. The purpose of the study is to evaluate the safety and tolerability, determine the maximal tolerated dose (MTD) or recommended Phase 2 dose (RP2D) and to assess preliminary efficacy of KY1044 as single agent or in combination with atezolizumab in a range of indications.

The study consists of the following parts:

Phase 1:

- A Phase 1 dose escalation part with KY1044 as single agent in patients with advanced/metastatic malignancies (all comers) and selected indications.
- A Phase 1 dose escalation part with KY1044 in combination with atezolizumab in all comers and selected advanced/metastatic malignancies. This part of the study will start after at least two cohorts of KY1044 as single agent have been considered to be safe and tolerable.

These parts of the study will allow determination of the MTD/RP2D of KY1044 (as single agent and in combination with atezolizumab) from the collective experience in the clinic considering the safety data, PK data, pharmacodynamic data and any early anti-tumor activity observed.

Enrichment part (optional):

To further explore safety, PK, pharmacodynamic markers and preliminary anti-tumor activity at different dose levels, additional patients may be recruited in cohorts of KY1044 as single agent or in combination with atezolizumab already considered to be safe. The overall number of patients included across all cohorts in the Phase 1 dose escalation and enrichment parts will be approximately 150.

Phase 2:

In the absence of identifying an MTD or single efficacious dose in Phase 1, an initial Phase 2 dose assessment part will be opened to compare the efficacy and biomarker readouts of two biologically relevant dose levels of KY1044 as a single agent or in combination with atezolizumab, in one or more specific indication(s) to support further definition of the RP2D for future indications. Once the MTD/RP2D has been established, a Phase 2 expansion component will open to evaluate clinical efficacy of KY1044 as single agent and in combination with atezolizumab in selected indications which should benefit from the KY1044 MoA.

Because ICOS plays a more subtle role in modulating T cell function than either PD-L1 or PD-1, it is not expected that KY1044 would have major anti-tumor activity as single agent in the clinic. Therefore, patients will be treated with KY1044 as single agent in Phase 2 only if evidence of anti-tumor activity is detected in the dose escalation/enrichment Phase 1 parts.

[redacted]

[redacted]

1.6 Summary of Known and Potential Risks and Benefits

1.6.1 Unmet Need in the Selected Indications

Patients recruited into the study will be ineligible for or will have exhausted current standard of care options in each indication and therefore will be patients for whom a clinical trial is appropriate.

The study will be conducted in patients with advanced/metastatic malignancies which, according to published data, are rich in T_{Regs} and therefore most likely would benefit from the dual MoA of KY1044. This dual MoA is also anticipated to improve the T_{Eff} to T_{Reg} ratio and overcome resistance mechanism against anti-PD-(L)1 inhibitors, which are mediated via T_{Regs}, and therefore patients who have progressed or who did not respond to previous checkpoint inhibitor treatment are also included in this study.

1.6.2 Possible Immune-related Toxicities Identified with Other ICIs

The manipulation of the immune response via checkpoint inhibition is associated with a unique spectrum of side effects termed immune-related adverse events (irAEs) or, occasionally, adverse events of special interest (AESI). IrAEs include dermatologic, gastrointestinal (GI), hepatic, endocrine, and other less common inflammatory events. IrAEs are believed to arise from general immunologic enhancement, and temporary immunosuppression with corticosteroids, TNFα antagonists, hormone replacement or other agents can be an effective treatment in most cases. These irAEs might also be expected after treatment with KY1044.

In general, treatment of moderate or severe irAEs requires interruption of the checkpoint inhibitor and the use of corticosteroid immunosuppression. Treatment is based upon the severity of the observed toxicity:

- For patients with Grade 2 (moderate) immune-related toxicities, treatment with the checkpoint inhibitor should be withheld and should not be resumed until symptoms or toxicity is Grade 1 or less. Corticosteroids (prednisone 0.5 mg/kg/day or equivalent) should be started immediately if applicable.
- For patients experiencing Grade 3 or 4 (severe or life-threatening) immune-related toxicities, treatment with the checkpoint inhibitor should be permanently discontinued. High doses of corticosteroids (prednisone 1 to 2 mg/kg/day or equivalent) should be given. When symptoms subside to Grade 1 or less, steroids can be gradually tapered over at least 1 month.

Serologic, immunologic and histologic (biopsy) data should be used to support an irAE diagnosis. Appropriate efforts should be made to rule out neoplastic, infectious, metabolic, toxin, or other etiologic causes of the irAE.

1.6.3 Potential Risks of KY1044 Therapy as Single Agent and in Combination with Atezolizumab

Due to the MoA of KY1044, there is a potential risk of shifting the balance of immune tolerance towards a more immune activated state, by depleting $ICOS^{high}$ T_{Regs} cells and stimulating T_{Eff}, thereby promoting irAEs.

The MoA of KY1044 requires TCR dependent engagement to act as an agonistic/co-stimulatory antibody. This excludes the risk of a cytokine release syndrome as

observed by superagonistic antibodies that do not require TCR engagement (see Section 1.4.2.3).

KY1044 will preferentially deplete ICOS^{high} expressing cells by ADCC (especially in the TME), and should have minimal depleting effects on ICOS$^{medium/low}$ T_{Eff} in the tumor and lymphoid tissues. The level of ICOS expression on T_{Regs} varies depending on the tissue analyzed. Pre-clinical experiments in tumor-bearing mice have shown that intratumoral T_{Regs} expressed nearly 10-fold more ICOS (as quantified by mean fluorescent intensity) than peripheral lymphoid organs. Altogether this differential expression would make the intratumoral T_{Regs} more sensitive to depletion than T_{Regs} in peripheral organs.

Single and repeated administration of KY1044 to cynomolgus monkeys led to reductions in total CD4$^+$ memory T cells in peripheral blood. There was no clear evidence of reversibility after administration of single doses at 0.1, 1 and 10 mg/kg over the 28 day post-dose observation period and absolute counts at 28 days post-dose were +18%, -20%, -56% and -63% of mean pre-treatment values at dose levels of 0, 0.1, 1 and 10 mg/kg, respectively. Reductions in total CD4$^+$ memory T cells of up to 80% were observed at dose levels of 30 and 100 mg/kg after repeated weekly administration of KY1044 for 4 weeks. As outlined in Section 1.5.3 in more detail, this limited depletion of circulating memory cells *per se* is not considered to present a significant risk of loss of immunologic memory to previous pathogenic antigen exposure or vaccinations due to the different effects of KY1044 observed in peripheral blood and lymphoid tissue and the lack of effects on naïve CD4 cells. Intact memory T cell response with effective tumor cell rejection was also observed in mice, after treatment with KY1044 (see Section 1.4.2.2).

KY1044-related changes in rats and monkeys consisted of reductions in lymphoid follicles/germinal centers in spleen and lymph nodes and these are consistent with the expected pharmacology (see above). After repeat dosing, the germinal centers/follicles in lymphoid tissue were reduced (ranging from minimal to marked in severity) but were not fully ablated, even at doses as high as 150 mg/kg. In addition, the number of B cells in monkeys was not diminished and there was no indication of higher susceptibility to infections in rats or monkeys, therefore these changes are not considered to pose an increased risk for infections.

Taken together there is a potential for aggravating immune related AEs however, considering the heterogeneity of T_{Regs} and the fact that KY1044 will preferentially deplete ICOS^{high} expressing cells, the risk seems to be justified considering the disease state of the patients enrolled in this study and the potential benefit of enhancing an anti-tumor immune response.

For more detail on non-clinical safety, please refer to Section 1.4.2.

1.6.4 Key Risks of Atezolizumab

Key risks are presented below. For more details, please refer to the atezolizumab IB and Section 1.4.3.

Overall the safety profile of atezolizumab seems to be very similar to that reported with other Anti-PD-(L)1 inhibitors recently analyzed in a large meta-analysis across 48 trials, including 6938 patients (46),

When combining ICI, for example ipilimumab plus nivolumab in melanoma, an increase of CTCAE v5 ≥Gr3 irAE by up to 20% (when compared to ipilimumab monotherapy) and up to 40% (when compared to nivolumab monotherapy), has been observed together with significant

gains in efficacy (improvement of ORR and mPFS of 11.5 months versus 2.9 months for ipilimumab monotherapy or 6.9 months for nivolumab monotherapy).

As outlined above, there is also a potential risk for aggravating immune related AEs, when combining KY1044 with atezolizumab. The incidence of irAEs for atezolizumab as monotherapy is summarized below:

Incidence of irAEs across all clinical trials:

Across all clinical trials (n=2616 patients) the incidences of immune-related events were as follows: Infections (42%), colitis/diarrhea (20%), immune related hepatitis (9.0%) hypothyroidism (4.6%), pneumonitis (2.6%), hyperthyroidism (1.6%), infusion reactions (1.3%), adrenal insufficiency (0.4%), type I diabetes mellitus (<0.1%) and hypophysitis (<0.1%), (atezolizumab label [43]).

Other clinically significant immune-related adverse reactions were reported in ≤1.0% of patients:

Cardiac: myocarditis.

Dermatologic: bullous dermatitis, pemphigoid, erythema multiforme, Stevens Johnson Syndrome (SJS)/toxic epidermal necrolysis (TEN).

Gastrointestinal: pancreatitis, including increases in serum amylase or lipase levels.

General: systemic inflammatory response syndrome, histiocytic necrotizing lymphadenitis.

Hematological: autoimmune hemolytic anemia, immune thrombocytopenic purpura.

Musculoskeletal: myositis, rhabdomyolysis. Neurological: Guillain-Barre syndrome, myasthenia syndrome/myasthenia gravis, demyelination, immune-related meningoencephalitis, aseptic meningitis, encephalitis, facial and abducens nerve paresis, polymyalgia rheumatica, autoimmune neuropathy, and Vogt-Koyanagi-Harada syndrome.

Ophthalmological: uveitis, iritis.

Renal: nephrotic syndrome, nephritis.

Vascular: vasculitis.

Overall the incidence of AEs leading to discontinuations was small and was reported for pneumonitis and hepatitis in 0.4% of patients, and for diarrhea and colitis in 0.2% of patients.

Summary Benefit: Risk Statement

Although potential benefits of KY1044 as single agent or in combination with atezolizumab in advanced/metastatic malignancies are unknown at this time, the study design aims to minimize potential risks for patients and will try to maximize clinical benefit. In all late stage tumor indications, and in the preferred tumor indications, there is a high unmet medical need for novel therapeutic agents and improvement of efficacy over currently approved treatments.

There are precedents for an antibody against ICOS with dual MoA (for example, JTX-2011). Although patient numbers are limited, the reported Phase 1/2 data investigating JTX-2011 as single agent and in combination with nivolumab seem to have been well tolerated (47, 48).

Based on the pre-clinical data and the MoA, KY1044 as single agent and in combination with atezolizumab offers the option of a potentially well tolerated immune checkpoint combination without further aggravation of toxicities, by selectively targeting $ICOS^{high}$ T_{Regs}, and

stimulating T_{Eff} and overall improving the CD8: T_{Regs} ratio leading to an enhanced anti-tumor response.

The starting dose for the Phase 1 dose escalation with KY1044 as single agent were selected on the basis of PK/PD modelling of pre-clinical data, target engagement in tumor tissue, efficacy in pre-clinical pharmacology studies and characterization of the safety profile of KY1044 in cynomolgus monkeys and rats.

KY1044 is not considered to be a high-risk biologic based on the MoA and antibody characteristics, the nature of the target, and the relevance of the animal species. No KY1044-related adverse effects have been identified to date in GLP and non-GLP dose range finding studies in cynomolgus monkeys up to 100 mg/kg and rats up to dose levels of 150 mg/kg.

Atezolizumab is approved for treatment of locally advanced or metastatic UCC and metastatic NSCLC after platinum containing chemotherapy and is currently being tested as monotherapy and in combination in clinical trials in several other indications, as discussed in the atezolizumab IB.

No additional risks compared to other checkpoint inhibitor trials have been identified that would preclude investigation in combination with KY1044.

The available data suggest that the benefit/risk of evaluating KY1044 as single agent and in combination with atezolizumab in this Phase 1/2 study appears acceptable based on the lack of effective alternative treatments, the limited life expectancy due to advanced disease, and the strength of the scientific hypothesis under evaluation. Furthermore, the study design (see Section 3.1) aims to minimize potential risks, and safety monitoring for each of the indication enrolled is in place for those risks deemed to be most likely or serious (see Section 5.4 and Section 5.6).

1.6.5 Benefit/Risk of KY1044 as Single Agent and in Combination with Atezolizumab Regarding Potential Infections with Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-Cov-2)

There is no change in the overall benefit/risk of treating cancer patients with KY1044 as single agent or in combination with atezolizumab in regard to the coronavirus disease 2019 (COVID-19) pandemic. In case of the implementation of restrictions due to COVID-19, the advice provided in Addendum 1 should be followed.

2 OBJECTIVES AND ENDPOINTS

2.1 Objectives

2.1.1 Primary Objective

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.

2.1.2 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 PK profile of KY1044 as single agent and in combination with atezolizumab
- To assess PK of atezolizumab in combination with KY1044
- To assess emergence of anti-KY1044 and anti-atezolizumab antibodies following one or more IV infusions of KY1044 single agent and/or in combination with atezolizumab
- 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

2.1.3 Exploratory Objectives

- 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)

2.2 Endpoints

2.2.1 Primary Endpoints

Phase 1

- Safety: Incidence and severity of AEs and SAEs, including changes in laboratory parameters, vital signs and electrocardiograms (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 Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST 1.1)

2.2.2 Secondary Endpoints

Efficacy measures:

- Best Overall Response (BOR), PFS and 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:

- Serum concentrations and PK parameters (eg, Cmax, t1/2) of KY1044 and of atezolizumab if in combination

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)

2.2.3 Exploratory Endpoints

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 (eg, IFNγ TNFα, granulocyte-macrophage colony-stimulating factor (GM-CSF)) contingent on availability of assay (ie, SIMOA)
- Phenotype and markers of IC activation in peripheral blood (eg, CD3, CD8, CD4, T_{Regs}, CD4 memory cells, CD25, FOXP3, CD45RA, ICOS, CD14, CD45, CD56, CD19 and ICOSLG) (fluorescence-activated cell sorting (FACS) or ChipCytometry)
- PBMCs gene signature (ribonucleic acid, RNA) (transcriptomics/Nanostring)
- ICOS Receptor Occupancy (RO) in PBMCs (KY1044 as single agent in Phase 1 only)

3 STUDY DESIGN

3.1 Overall Study Design and Plan

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 have been treated with KY1044 as single agent and the treatment is considered to be safe and tolerable.

An initial Phase 2 dose assessment part will open in one or more specific indication(s) to compare the efficacy and biomarker readouts of two biologically relevant dose levels of KY1044 (as single agent or in combination with atezolizumab) that have been determined to be safe in Phase 1. These data in combination with safety, efficacy and biomarker data from Phase 1 will support definition of the RP2D.

Once the MTD and/or RP2D for KY1044 as single agent or in combination with atezolizumab has been defined, the Phase 2 component may be extended to assess preliminary anti-tumor efficacy in additional selected indications. TNBC and HNSCC are selected as indications of interest for Phase 2. KY1044 and atezolizumab will be administered IV Q3W until a patient experiences unacceptable toxicity, progressive disease as per RECIST 1.1/iRECIST and/or withdraws consent. Patients should not discontinue treatment based on progressive disease per RECIST 1.1 unless clinical deterioration or increase in tumor markers is observed. iRECIST should always be considered. The maximum treatment period for each patient may be up to 48 months. Provisions may be made to continue treatment after this timepoint for patients who show clinical benefit.

The overall study design is presented in Figure 3-1.

3.1.1 Definitions of Study Cohorts and Groups:

Phase 1 cohorts:

All cohorts in Phase 1 will be defined by dose level.

Phase 2 groups:

Groups will be defined based on previous anti-PD-(L)1 treatment per tumor indication.

3.1.2 Tumor Indications in Phase 1 and Phase 2

Phase 1:

In Phase 1, patients with advanced/metastatic malignancies (all comers) and with preferred indications will be enrolled. Preferred indications are: HNSCC, gastric/esophageal cancer, HCC, NSCLC, melanoma, cervical cancer, renal cell cancer, pancreatic cancer and triple negative BC (TNBC).

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, TNBC.

3.1.3 Phase 1

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 be $ICOS^+$, will be treated with KY1044 as single agent Q3W until the MTD is reached or a lower 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 [49]), which is an adaptive dose-finding method that allows dose escalation and de-escalation according to the precalculated decision table in Section 9. 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 (for further details see Section 4.1.1).

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 (49), which is an adaptive dose-finding method that allows dose escalation and de-escalation according to the precalculated decision table. The maximum sample size for dose escalation will be 36 patients using cohorts of a minimum of three patients. (for further details see Section 4.1.1).

Optional Phase 1 enrichment part

An optional enrichment part may include the testing of additional patients at one or more dose levels to better understand the safety, tolerability, 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 parts 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.

3.1.4 Phase 2

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 (ie, 15 anti-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 single agent

A Phase 2 part may be opened should signs of anti-tumor activity (defined as CR, PR or durable SD with tumor shrinkage that does not qualify for PR) be seen in at least one patient in the Phase 1 dose escalation/enrichment 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, 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 patient will also 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, certain indications (TNBC and HNSCC) may be further expanded to up to approximately 40 patients.

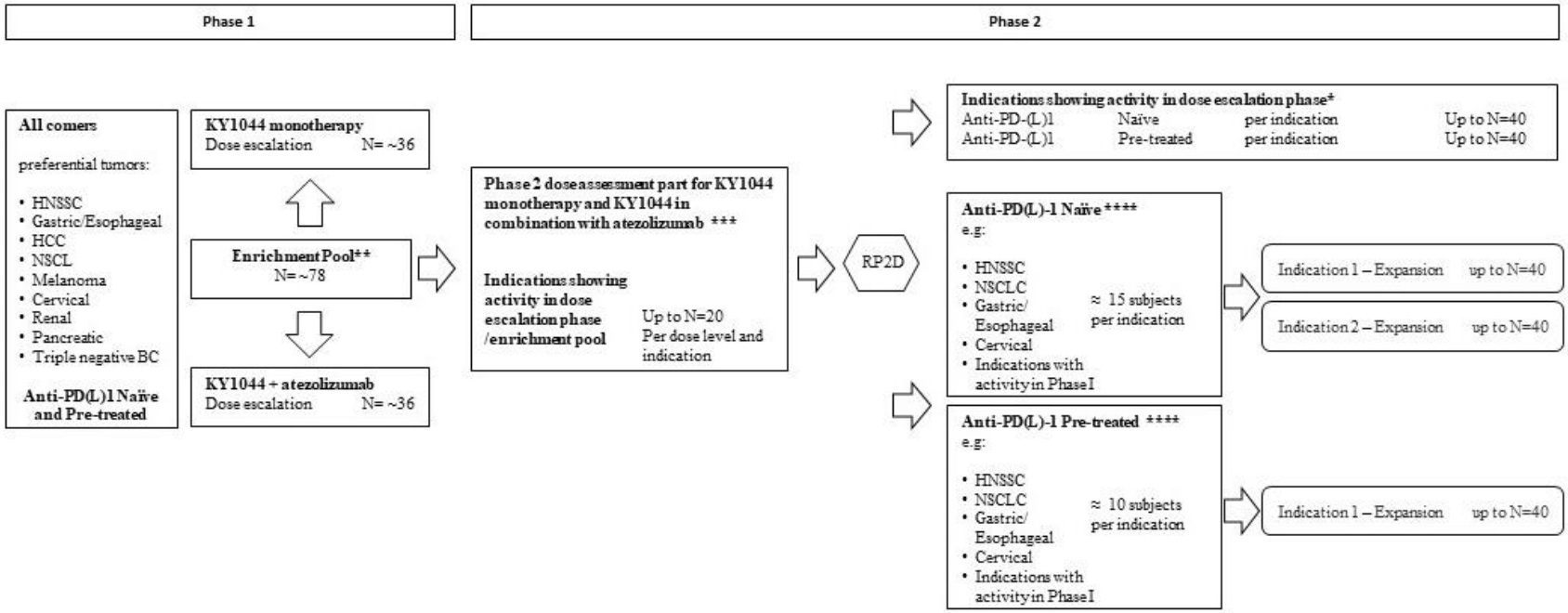
In the anti-PD-(L)1 pre-treated group, initially a minimum of 10 patients will be enrolled in each of the defined indications (HNSCC) which may be further expanded to up to 40 patients, depending on emerging efficacy data.

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 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.

Figure 3-1: Study Design



BC=breast cancer; CR=complete response; HCC=hepatocellular carcinoma; HNSCC=head and neck squamous cell carcinoma; min=minimum; NSCLC=non-small cell lung cancer; PD-L1=programmed cell death ligand 1; PR=partial response; RP2D=recommended Phase 2 dose; SD=stable disease.

* This part will only be opened in relevant indications if signs of anti-tumor activity (defined as at least one confirmed CR, PR or durable SD with tumor shrinkage that does not qualify for PR) are observed in the Phase 1 dose escalation/enrichment part with KY1044 as single agent.

** Enrichment part: Should more data about safety, biomarkers or PK be required more patients may be tested at different doses levels with KY1044 as single agent or in combination with atezolizumab.

*** In the initial Phase 2 dose assessment part, two dose levels (for KY1044 as single agent or in combination) will be explored in one or more indication(s) which has shown efficacy during Phase 1, to identify the RP2D.

**** For selected tumor types, the number of patients enrolled per group could be reduced, depending on enrolment feasibility in the ongoing study.

3.2 Study Flow

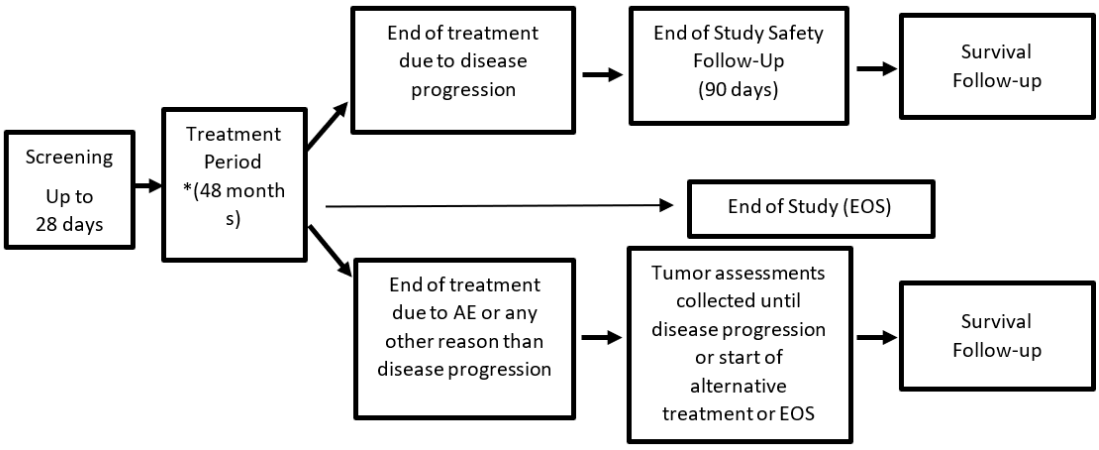
Patients will undergo assessments during a (maximum) 28-day screening period, pre-dose and periodically during treatment, as outlined in Section 6. For both regimens of KY1044 administration as single agent and in combination with atezolizumab, treatment will continue until a patient experiences unacceptable toxicity, progressive disease as per iRECIST and/or withdrawal of consent.

Safety follow-up will be performed 90 days after the end of treatment.

Patients who do **not** have progressive disease (as per RECIST 1.1/iRECIST) at the time of discontinuing treatment will receive tumor assessments for evaluation of PFS until disease progression, or starting alternative treatment or the overall end of study (EOS) if earlier (see Section 8.2.1).

All patients who do not withdraw consent for the study will be followed up for survival unless they are lost to follow-up, or overall EOS has been declared (see Section 3.6).

Figure 3-2: Study Flow per Patient



* 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.

3.3 Study Safety Review Committee (SRC)

A safety review committee (SRC), will be responsible for review of all safety data arising from the study on an ongoing basis and for dose escalation decisions after each cohort in the Phase 1 parts, as described in Section 5.4.

During Phase 1, regular meetings will be held to review and monitor safety and tolerability of KY1044. Dose escalation will be considered at a meeting after the minimum DLT period of 21 days for each cohort. Safety, tolerability and PK data will be reviewed to confirm the safety of the current dose level and agree the next step for dose escalation until identification of the MTD and/or RP2D, completion of all defined dose levels, or a decision that further increase of dose is not warranted. Safety data reviewed will be cumulative, including later occurring Aes (after Cycle 1), which will be considered at subsequent SRC meetings and dose decisions may

be amended depending on emerging data. The dose escalation decisions will be formally minuted and the minutes distributed to all members.

The SRC may decide to stop one or more cohorts, or the entire study, if it judges that patients are placed at undue risk because of clinically significant findings. Enrolment to the study will be paused in the event of any Grade 4 or 5 (death) toxicities which are not clearly explained by the underlying disease or extraneous causes. In case of a decision to stop further enrolment or stop patient's treatment the sites and the Clinical Research Associates will be notified immediately via email about the decision, its reason and expectations regarding further actions. Additionally, appropriate measures will be taken in the Interactive X=Voice/Web Response System (IXRS; blocking dispensing of IMP, blocking screening and enrolment as appropriate). Additional actions may include requesting sites to contact patients and requesting ad hoc visits to provide relevant information and evaluate safety as needed. The event will be notified to relevant Ethics Committees, Independent Review Boards and Regulatory Authorities as required by local regulations, including local law and institutional requirements. Only following a comprehensive investigation on the cause of these events, which rules out the role of the investigational drug, and after fulfillment of relevant regional or national regulatory requirements, can enrolment be restarted in agreement with the SRC.

The SRC will comprise as a minimum the Principal Investigator's (Pis) (or medically qualified designee) and the Sponsor's physicians. Further internal or external experts may be consulted by the SRC as necessary. A complete list of members of the SRC will be included into the cohort management plan.

The SRC will remain in place for Phase 2, and meeting frequencies will be decided dependent on emerging data.

There will be no formal independent data monitoring board for this study.

3.4 Study Duration

The study duration for an individual patient will include the screening period of up to 28 days, a study period of up to 48 months of treatment (approximately 70 cycles), and 90 days of safety follow-up after the last dose of study treatment. Provision may be made for patients who are still on treatment and receiving documented clinical benefit at 48 months. In this instance, Investigators should consult with the Sponsor prior to continuing treatment beyond 48 months. All patients will be followed up for survival up to 2 years (or as long as the treatment continues if it lasts more than 2 years) after the start of treatment unless they withdraw consent, are lost to follow-up or the overall end of the study is declared by the Sponsor.

3.5 Timing of Interim Analysis and Design Adaptations

Preliminary analysis:

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.

Final data analysis:

A final data analysis will be performed at the end of the study.

3.6 Definition of End of Study (EOS)

The completion of the study is defined as the last visit for the last patient on treatment (for patients, who stopped treatment earlier follow-up will be ended at this point). Additional provisions for treatment continuation may be made for patients who are ongoing on treatment and having clinical benefit at 48 months.

3.7 Early Study Termination

The study can be terminated at anytime for any reason by the Sponsor (including failure to enroll, futility, SRC decision etc.). Should this be necessary, ongoing patients should be seen as soon as possible for the End of Treatment (EOT) visit and the assessments for EOT and safety follow-up visit, should be performed as described in Section 8.

In terminating the study, the Sponsor will ensure that adequate consideration is given to the protection of the patients' interests. The Sponsor will ensure that the Investigators/institutions/ Institutional Review Boards (IRBs) and/or independent ethics committees (IECs) and the regulatory authority(ies) are promptly informed of the termination or suspension of the study and of the reason(s) for the termination or suspension.

Early termination for individual patients is addressed in Section 8.

3.8 Blinding

Not applicable. This is an open-label study.

4 STUDY POPULATION

Adult patients with advanced/metastatic malignancies and selected tumor indications, who are either anti-PD-(L)1 therapy naïve or pre-treated will be recruited into the study. Details of indications selected for each part of the study are specified in the inclusion criteria (Section 4.2).

4.1 Number of Patients

Each of the Phase 1 dose escalations (single agent and combination therapy) will include a maximum of 36 patients, unless no dose levels are determined to be safe or the SRC decides to stop the dose escalation part. If fewer than 36 patients are required to dose escalate, the remainder may be included in the enrichment part. The total number of patients included across all cohorts in the Phase 1 dose escalation and enrichment parts will be approximately 150.

The actual number of patients recruited in the Phase 2 component will depend on the number of tumor indications investigated and on the number of expansions; however the total number of patients in Phase 2 is not anticipated to exceed 262 patients.

4.1.1 Number of Patients for Dose Escalation and Cohort Composition

The Phase 1 dose escalation parts of the study will be based on cohorts of 3 patients. More patients may be enrolled into each cohort to assure at least 3 evaluable patients for dose escalation decisions. To assess the safety profile of KY1044 it will be required that each cohort satisfies the following requirements:

- At least two patients are anti-PD-(L)1 naïve.

- Only one patient has a non-preferred tumor type (See Section 3.1.2).
- All inclusion/exclusion criteria are met.

4.2 Inclusion Criteria

Patients eligible for inclusion in this study must meet all of the following criteria:

1. Written informed consent must be obtained prior to any procedures
2. Age ≥18 years (≥20 years in Taiwan)
3. Histologically documented advanced/metastatic malignancies
4. Phase 1 and Phase 2 patients with advanced/metastatic malignancies who have measurable disease (non-measurable disease is allowed only in Phase 1) as determined by RECIST 1.1 (refer to Appendix 1) will be eligible if, according to the NCCN guidelines, there are no available therapies known to confer a clinical benefit for their disease, or they have exhausted all such available options. Additionally, the following specific tumor indications will be enrolled:
   a. **Phase 1 (including enrichment part):**

      Patients with advanced/metastatic malignancies, and preferred indications as identified in Section 3.1 (NSCLC, HNSCC, HCC, melanoma, cervical, gastric/esophageal, renal, pancreatic, and triple negative BC)
   b. **Phase 2 KY1044 single agent:**

      Patients with advanced/metastatic malignancies in indications in which signs of anti-tumor activity (CR, PR or durable SD with tumor shrinkage that does not qualify for PR) were seen during the dose escalation/enrichment of KY1044 as single agent.
   c. **Phase 2 KY1044 in combination with atezolizumab:**

      Patients with advanced/metastatic malignancies in the selected indications below, and/or indications which have shown promising activity in Phase 1:
      - NSCLC (anti-PD-(L)1 therapy naïve and pre-treated between 1 and 2 prior lines of systemic therapy for advanced disease)
      - Gastric/Esophageal (anti-PD-(L)1 therapy naïve and pre-treated)
      - Recurrent and/or metastatic HNSCC (anti PD (L)1 therapy naïve and pre treated between 1 and 2 prior lines of systemic therapy for advanced disease)
      - Cervical (anti-PD-(L)1 therapy naïve and pre-treated)
      - Indications, in which signs of anti-tumor activity has been observed in Phase 1 with KY1044 in combination with atezolizumab
5. Prior therapy with anti-PD-(L)1 inhibitors is allowed provided any toxicity attributed to prior anti-PD-(L)1-directed therapy did not lead to discontinuation of therapy
6. Eastern Cooperative Oncology Group (ECOG) Performance Status 0-1
7. Life expectancy longer than 12 weeks.
8. Must have a site of disease amenable to biopsy, and be a candidate for tumor biopsy according to the treating institution's guidelines. Patient must be willing to undergo a new tumor biopsy at screening, and during therapy on the study
9. Females of childbearing potential must be using two highly effective contraceptive measures for the duration of study participation and for at least 5 months after discontinuing study treatment, or longer if the half-life of KY1044 is observed to exceed that of

atezolizumab (see Section 5.8). Females must not be breast feeding and must have a negative pregnancy test prior to start of dosing or must have evidence of non-childbearing potential by fulfilling one of the following criteria at screening:

- Post-menopausal defined as aged ≥50 years and amenorrhoeic for at least 12 months following cessation of all exogenous hormonal treatments
- Women less than 50 years old would be considered postmenopausal if they have been amenorrhoeic for at least 12 months following the cessation of exogenous hormonal treatments, and have serum follicle-stimulating hormone and luteinizing hormone levels in the postmenopausal range for the institution
- Documentation of irreversible surgical sterilization by hysterectomy, bilateral oophorectomy or bilateral salpingectomy but not tubal ligation

10. For the duration of study participation and for at least 5 months after discontinuing study treatment, or longer if the half-life of KY1044 is observed to exceed that of atezolizumab, sexually active males must use barrier contraception (ie, condoms). See Section 5.8.

4.3 Exclusion Criteria

Patients eligible for this study must not meet any of the following criteria:

1. Presence of symptomatic CNS metastases, or CNS metastases that require local CNS-directed therapy (such as radiotherapy or surgery), or increasing doses of corticosteroids within the prior 2 weeks of first dose of study treatment. Patients with treated brain metastasis, unless neurologically stable (for 4 weeks post-treatment and prior to study enrolment) and off of steroids for at least 2 weeks before the first dose of study treatment
2. History of severe hypersensitivity reactions to other mAbs and/or their excipients
3. Known presence of neutralizing anti-atezolizumab antibodies (for patients previously treated with atezolizumab)
4. Having out of range laboratory values defined as:
   - Creatinine clearance or glomerular filtration rate ≤30 mL/min estimated by the Cockroft-Gault (C-G) or other medically acceptable formulas such as MDRD (Modification of Diet in Renal Disease) or CKD-EPI (the Chronic Kidney Disease Epidemiology Collaboration)
   - Total bilirubin >1.5 x Upper Limit of Normal (ULN), except for patients with Gilbert's syndrome who are excluded if total bilirubin >3.0 x ULN or direct bilirubin >1.5 x ULN
   - ALT >3 x ULN, except for patients that have tumor involvement of the liver, who are excluded if ALT >5 x ULN
   - AST >3 x ULN, except for patients that have tumor involvement of the liver, who are excluded if AST >5 x ULN
   - Absolute neutrophil count (ANC) <1.0 x 10^9/L
   - Platelet count <75 x 10^9/L
   - Hemoglobin <9 g/dL
5. Impaired cardiac function or clinically significant cardiac disease, including any of the following:

- Clinically significant and/or uncontrolled heart disease such as congestive heart failure requiring treatment (New York Heart Association (NYHA) Grade ≥2), uncontrolled hypertension or clinically significant arrhythmia
- QTcF >470 msec on screening ECG using Fridericia's formula (QTcF) or congenital long QT syndrome
- Acute myocardial infarction or unstable angina pectoris <3 months prior to first dose of study treatment

6. Known human immunodeficiency virus (HIV), active hepatitis B virus (HBV) or active hepatitis C virus (HCV) infection. Active HBV infection is defined as HBV viral load ≥2000 IU/mL (104 copies/mL). Active HCV infection is defined as anti-HCV positive or detectable HCV RNA. HBV or HCV positive patients with HCC who started anti-viral therapy before initiation of IMP and have HBV viral load <2000 IU/mL (104 copies/mL) and no detectable HCV RNA titers are eligible. The anti-viral therapy should continue throughout the treatment period.

   Patients with any severe infection within 4 weeks prior to initiation of study treatment including, but not limited to, hospitalization for complications of infection.
7. Malignant disease, other than that being treated in this study. Exceptions to this exclusion criterion include the following: malignancies that were treated curatively and have not recurred within 2 years prior to the first dose of study treatment; completely resected basal cell and squamous cell skin cancers; and completely resected carcinoma in situ of any type
8. Any medical condition that would, in the Investigator's judgment, prevent the patient's participation in the clinical study due to safety concerns, compliance with clinical study procedures or interpretation of study results
9. Active autoimmune disease or a documented history of autoimmune disease, including ulcerative colitis and Crohn's disease or any condition that requires systemic steroids, except vitiligo or resolved asthma/atopy that is treated with broncho-dilators (eg, albuterol)
10. Patients previously exposed to anti-PD-(L)1 treatment who are not adequately treated for skin rash or had no replacement therapy for endocrinopathies should be excluded
11. Patients with a history of drug-induced pneumonitis or current pneumonitis
12. Systemic steroid therapy or any immunosuppressive therapy (≥10 mg/day prednisone or equivalent). Topical, inhaled, nasal, and ophthalmic steroids are not prohibited
13. Herbal preparations/medications (including, but not limited to: St. John's Wort, kava, ephedra (ma huang), gingko biloba, dehydroepiandrosterone, yohimbe, saw palmetto, and ginseng) are prohibited from the time that patients enter the screening period (at least 7 days prior to first dose of study treatment) until the last dose of study treatment (3 weeks for St John's Wort)
14. Warfarin and other types of long acting anticoagulants (such as phenprocumon and or anti-Xa inhibitors with a half-life of >12 hours) is prohibited within 4 weeks of the first dose of study treatment and patients requiring anticoagulant treatment should switch to low molecular weight heparin or anti-Xa inhibitors with a half-life of ≤12 hours
15. Use of live or live attenuated vaccines against infectious diseases (examples include, but are not limited to, intranasal influenza, measles, mumps, rubella, oral polio, Bacillus Calmette-Guérin vaccine, rotavirus, varicella, yellow fever, TY21a typhoid vaccines etc) within 4 weeks of the first dose of study treatment and it should not be planned to administer such a vaccine during the course of the study. SARS-CoV-2 vaccines authorized for use by the competent local regulatory health authorities for active

immunization to prevent COVID-19 are allowed (unless the vaccine is live or live attenuated) and must be given in accordance with the prevailing immunization guidelines. SARS-CoV-2 vaccination may be given at least 7 days prior to the planned first dose of study treatment. Refer to Table 5-6 for more instruction with regard to SARS-CoV-2 vaccination.

16. Systemic anti-cancer therapy (TKI and/or chemotherapy) within 2 weeks of the first dose of study treatment. For cytotoxic agents that have major delayed toxicity, eg, mitomycin C and nitrosoureas, 4 weeks is indicated as washout period
17. Major surgery within 2 weeks of the first dose of study treatment (mediastinoscopy, insertion of a central venous access device, and insertion of a feeding tube are not considered major surgery)
18. Anti-CTLA4, anti-PD-(L)1 treatment within 4 weeks of the first dose of study treatment
19. Pre-treatment with anti-CTLA4 antibodies in combination with any other antibody or drug specifically targeting T-cell co-stimulation or checkpoint pathway
20. Participation in an interventional, investigational study within 4 weeks of the first dose of study treatment
21. Presence of CTCAE v5 ≥Grade 2 toxicity (except alopecia, peripheral neuropathy and ototoxicity, which are excluded if CTCAE v5 ≥Grade 3) due to prior cancer therapy
22. Use of hematopoietic colony-stimulating growth factors (eg, granulocyte-colony stimulating factor (G-CSF), GM-CSF, M-CSF) ≤2 weeks prior to start of study treatment. An erythroid stimulating agent is allowed if it was initiated at least 2 weeks prior to the first dose of study treatment and the patient is on a stable dose
23. Radiotherapy within 2 weeks of the first dose of study treatment, except for palliative radiotherapy to a limited field, such as for the treatment of bone pain or a focally painful tumor mass. To allow evaluation for response to treatment, patients enrolled in the Phase 2 part must have remaining measurable disease that has not been irradiated.
24. Pregnant or lactating women, where pregnancy is defined as the state of a female after conception and until the termination of gestation, confirmed by a positive human chorionic gonadotropin (hCG) laboratory test. In rare cases of an endocrine-secreting tumor, hCG levels may be above normal limits, but without existing pregnancy. In these cases, there should be a repeat serum beta-hCG test (with a non-rising result) and a vaginal/pelvic ultrasound to rule out pregnancy. Upon confirmation of results and discussion with the Medical Monitor, these patients may enter the study.

5 TREATMENT OF PATIENTS

5.1 Presentation of Study Treatments

5.1.1 KY1044

KY1044 is presented as a clear to opalescent sterile solution that is colorless to slightly yellow, brown or brown-yellow, and is filled to a nominal 1 mL volume in a single-dose 2 mL clear glass vial. KY1044 is formulated at a nominal concentration of 50 mg/mL in 25 mM L-histidine/histidine hydrochloride, 240 mM sucrose and 0.02% (weight/volume) polysorbate 80 at pH 5.5. KY1044 will be diluted in 0.9% NaCl solution prior to administration via IV infusion.

5.1.2 Atezolizumab (TECENTRIQ®)

Atezolizumab is presented as a colorless to slightly yellow sterile solution, filled to a nominal 20 mL volume in a single-dose vial. Atezolizumab is formulated at a nominal concentration of 60 mg/mL in glacial acetic acid (16.5 mg), L-histidine (62 mg), sucrose (821.6 mg) and polysorbate 20 (8 mg) at a pH of 5.8. Atezolizumab will be added to an IV infusion bag containing 0.9% NaCl solution prior to administration.

5.2 Study Treatment Administration

The study treatment is defined as KY1044 as single agent or in combination with atezolizumab. All dosages prescribed and dispensed to patients and all dose changes during the study must be recorded in the patient's hospital files and on the electronic case report form (eCRF).

5.2.1 Dosing Regimen

Table 5-1: Dose and Treatment Schedule

Study treatments	Pharmaceutical form	Route of administration	Dose			Frequency and/or Regimen
			Phase 1	Phase 2 dose assessment	Phase 2	
KY1044	Solution	IV infusion	Escalating doses starting at 0.8 mg	One of two biologically relevant doses	RP2D	Q3W (±3 days)
Atezolizumab	Solution	IV infusion	1200 mg	1200 mg	1200 mg	Q3W (±3 days)

Q3W=every three weeks

Patients are to receive KY1044 doses (either as single agent or in combination with atezolizumab) within a 3 days visit window. However, the next dose (as single agent or in combination) may be delayed by up to 7 days to recover from previous Aes.

If doses are not received within this time frame, the dose should be missed and patients should receive the next planned dose according to the schedule on Day 1 of the next cycle. If the patient experiences a related toxicity, the management guidelines provided in Section 5.6 should be followed.

5.2.2 Infusion of IMPs

KY1044 will be administered via IV infusion over 30 to 60 minutes. If well tolerated at the first infusion, subsequent infusions may be given over 30 minutes.

Atezolizumab will be administered via IV infusion over 60 minutes. If well tolerated at the first infusion, subsequent infusions may be given over 30 minutes.

When given in combination, both IMPs are to be administered within 24 hours, however separate infusion sets must be used for each investigational product. KY1044 is to be administered first and promptly followed by a saline solution flush to empty the line as

described in the pharmacy manual. Slow saline infusion will continue for approximately 1 hour before starting the atezolizumab infusion in the same infusion site. There should be a period of at least 1 hour after the infusion(s) are complete whereby the patient requires close observation.

After receiving the first infusion in Phase 1, patients will be either hospitalized or remain in the clinic for at least 6 to 8 hours until the last assessments. They will be provided with instructions for after hour care per institutional standard and will return to the clinic on C1D2. At all other infusion visits the observation period after the infusion should be at least 3 hours before patients are discharged. In Phase 2, the observation period after infusion of IMP should initially be at least 3 hours before patients are discharged. This time window maybe further reduced during later cycles and when more safety data for each patient are available.

Neither KY1044 or atezolizumab should be co-administered with other drugs through the same IV line. The date, start time, completion time and time and length of any interruptions must be recorded in the eCRF.

Further instructions for the preparation and administration of KY1044 and atezolizumab are described in the Pharmacy Manuals.

5.2.3 Precautions for IMP Administration (KY1044 and Atezolizumab)

A physician must be present at the site or immediately available to respond to emergencies during all administrations of KY1044 alone or with atezolizumab. Fully functional resuscitation facilities should be available. KY1044 or atezolizumab must not be administered via IV push or bolus.

In each cohort of the dose escalation of KY1044 as a single agent, dosing will be staggered such that administration of the first patient in each cohort is separated by at least 48 hours from dosing the next patient. Subsequent patients will be treated at least 24 hours apart during the Phase 1 dose escalation part of the study.

In the combination cohorts, dosing will be staggered, such that administration of the first patient in the first cohort is separated by at least 72 hours from dosing the next patient, with subsequent patients being treated at least 24 hours apart in this cohort. In subsequent cohorts the first patient in each cohort will always be dosed 48 hours apart from the next patient. Subsequent patients will be treated at least 24 hours apart during the dose escalation part of the study.

5.2.4 Monitoring of IMP Administration (KY1044 and Atezolizumab)

Patients will be monitored during and after the infusion with assessment of vital signs at the times specified in Section 6.5.7.

In the event of an infusion-related reaction ≤Grade 2, the infusion rate of KY1044 or atezolizumab must be decreased by 50% or interrupted until resolution of the event (up to 4 hours) and re-initiated at 50% of the initial rate until completion of the infusion. If the infusion reaction is caused by KY1044, the atezolizumab infusion may be delayed until the next day and/or until recovery from the event. For these patients, subsequent infusions may be administered at 50% of the initial rate and premedication should be considered. In the event of more severe infusion reactions (CTCAE v5 >Grade 2), IMP should be permanently discontinued.

5.2.5 Ancillary Treatments

Patients should not receive premedication to prevent infusion reaction before the first infusion of KY1044, in order to determine if premedication is necessary. If a patient experiences an infusion reaction, he/she may receive premedication on subsequent dosing days. The premedication should be chosen per institutional standard of care, at the discretion of the treating physician.

Acute allergic reactions should be treated as needed per institutional standard of care. In the event of anaphylactic/anaphylactoid reactions, this includes any therapy necessary to restore normal cardiopulmonary status. If a patient experiences a Grade 3 anaphylactic/anaphylactoid reaction, the patient will be discontinued from the study.

Guidelines on management of KY1044 and atezolizumab infusion reactions are provided in Table 5-5.

The CTCAE v5 category of "Infusion related reaction" should be used to describe KY1044 and atezolizumab infusion reactions, unless the Investigator considers another category, such as "Allergic reaction," "Anaphylaxis," or "Cytokine release syndrome" more appropriate in a specific situation.

5.3 Treatment Duration

All patients treated with either KY1044 as single agent or in combination with atezolizumab will begin study treatment on Cycle 1 Day 1. Each cycle will consist of 21 days (±3 days). The next scheduled dose (as single agent or in combination) may be delayed by up to 7 days to recover from previous Aes. If the next dose (as single agent or in combination) cannot be administered within the above mentioned 7-day delay, then the dose should be skipped. Dosing will resume at the scheduled dose or the next lower dose. Dose modifications should follow Section 5.6.

If more than one consecutive dose of KY1044 as single agent or in combination with atezolizumab has to be skipped due to study treatment-related toxicities, then the default position is that IMPs should be permanently discontinued. However, if a patient who misses more than one consecutive dose due to a study treatment-related toxicity experiences clinical benefit, and in the opinion of the Investigator it is in the patient's best interest to remain on study, then the patient may continue treatment after discussion with the Medical Monitor.

A patient may continue treatment with KY1044 as single agent or in combination with atezolizumab within this clinical study, as long as they are continuing to derive benefit from treatment, until the patient experiences unacceptable toxicity or confirmed disease progression per iRECIST. Patients will not be withdrawn from the study due to progressive disease per RECIST 1.1, unless clinically indicated.

Criteria for treatment cessation or patient withdrawal from the study are outlined in Section 8, and management of toxicities is outlined in Section 5.6.

Patients with SD, PR, unconfirmed CR, and unconfirmed progressive disease **will continue treatment** in additional cycles.

Patients who meet the following criteria **will NOT continue treatment** in additional cycles:

- Patients who experience unacceptable toxicity.
- Patients with confirmed progressive disease. These patients will enter the Safety follow-up period unless the Investigator considers it to be in the patient's best interest to remain on the study, and after discussion with the Medical Monitor.

- Patients with an unconfirmed progressive disease who show signs of clinical deterioration or toxicity. These patients will enter the Safety follow-up period, and will continue to be followed-up until confirmed progressive disease or initiation of a new treatment.

Accumulating evidence indicates that objective responses to immunotherapy follows delayed kinetics of weeks or months and can be preceded by initial apparent radiological progression or appearance of new lesions (NLs) or some enlarging lesions, while other target lesions are regressing ("mixed response") (50). It is therefore reasonable to allow for these possibilities and continue to treat the patient until progression is confirmed and found to be advancing at the next imaging assessment as per iRECIST. These considerations should be balanced by clinical judgment as to whether the patient is clinically deteriorating and unlikely to receive any benefit from continued treatment.

Such deterioration will be assessed to have occurred after a clinical event that, in the Investigator's opinion, is attributable to disease progression, is unlikely to reverse with continued study treatment and therefore indicates that the patient is not benefiting from study treatment and cannot be managed by the addition of supportive care.

The decision to continue or stop treatment should be discussed with the Medical Monitor and will be documented in the study files.

The maximum duration of the treatment period for each patient within this study may be up to 48 months. Provisions may be made for patients who are still on treatment and receiving benefit at this timepoint.

5.4 Dose Escalation Guidelines

5.4.1 Starting Dose Rationale

Doses for the Phase 1 dose escalation part with KY1044 as single agent were selected based on PK/PD modelling of pre-clinical data, target engagement in tumor tissue, efficacy in pre-clinical pharmacology studies and characterization of the safety profile of KY1044 in cynomolgus monkeys and rats. The starting dose of KY1044 for the first cohort as single agent will be a single infusion of 0.8 mg KY1044. The proposed dose range for the Phase 1 dose escalation with KY1044 as single agent is 0.8 to 240 mg (and potentially above) with dose level increases between 300% to 333% for the next higher dose. Intermediate dose levels may also be explored, depending on emerging safety and PK/PD data. This dose range was selected to ensure a safe starting dose, to facilitate assessment of safety, tolerability and anti-tumor activity over a pharmacologically relevant dose range and to provide adequate exposure to support future clinical investigation of KY1044. Provisionally, the starting dose for KY1044 in combination with atezolizumab is expected also to be 0.8 mg, unless emerging safety data and the SRC recommend to start at a lower dose level. For more detail please refer to Section 5.4.2.

5.4.2 Provisional Dose Levels

Table 5-2 and Table 5-3 describe the starting dose for the Phase 1 parts, and the dose levels that may be evaluated during this trial.

Table 5-2: Provisional Dose Levels (Phase 1 KY1044 Single Agent)

Dose level	KY1044 proposed dose[a]	Increment from previous dose	Concentration after dilution	Type of infusion material
-1[b]	0.24 mg	-70%	0.048 mg/mL	10 mL syringe (PP)
1 (starting dose)	0.8 mg	Starting dose	0.08 mg/mL	10 mL syringe (PP)
2	2.4 mg	300%	0.12 mg/mL	20 mL syringe (PP)
3	8 mg	333%	0.4 mg/mL	20 mL syringe (PP)
4	24 mg	300%	0.24 mg/mL[d]	100 mL bag (PE or PVC)
5	80 mg	333%	0.8 mg/mL[d]	100 mL bag (PE or PVC)
6	240 mg [c]	300%	2.4 mg/mL[d]	100 mL bag (PE or PVC)

MTD=maximal tolerated dose; PD=pharmacodynamics; PE=polyethylene; PK=pharmacokinetic; PP=polypropylene; PVC=polyvinyl chloride.

[a] It is possible for additional and/or intermediate dose levels to be added during the study. Cohorts may be added at any dose level below the MTD to better understand safety, PK or PD. Multiple dose levels below the MTD may be evaluated simultaneously in order to obtain PK and PD data across a range of doses.

[b] Dose level -1 represents treatment doses for patients requiring a dose reduction from the starting dose level. No dose reduction below dose level -1 is permitted for this study

[c] Dose levels above 240 mg may be explored depending on emerging data

[d] Concentrations are approximate as there may be slight variation in the fill volume of commercially available saline IV bags. The whole contents of the bag will be delivered to ensure that the entire dose is delivered to the patient.

Table 5-3: Provisional Dose Levels (Phase 1 KY1044 in Combination with Atezolizumab)

Dose level	KY1044 proposed dose[a]	Atezolizumab proposed dose
-1[b]	0.24 mg	1200 mg
1 (starting dose)	0.8 mg	1200 mg
2	2.4 mg	1200 mg
3	8 mg	1200 mg
4	24 mg	1200 mg
5	80 mg	1200 mg
6	240 mg [c]	1200 mg

MTD=maximal tolerated dose; PD=pharmacodynamic; PK=pharmacokinetic.

[a] It is possible for additional and/or intermediate dose levels to be added during the study. Cohorts may be added at any dose level below the MTD in order to better understand safety, PK or PD. Multiple dose levels below the MTD may be evaluated simultaneously in order to obtain PK and PD data across a range of doses.

[b] Dose level -1 represents treatment doses for patients requiring a dose reduction from the starting dose level. No dose reduction below dose level -1 is permitted for this study.

[c] Dose levels above 240 mg maybe explored depending on emerging data

5.4.3 Cohort Modification

For the purposes of dose escalation decisions (Phase 1 of KY1044 as single agent or in combination with atezolizumab), each cohort will consist of three newly enrolled patients who will be treated at the specified dose level and will meet the criteria in Section 4.1.1. Should only two of these patients in the first cohort recruited to the study be considered evaluable (ie, meet the criteria described below for a patient to be considered evaluable [Section 5.4.5.1]) and neither patient has experienced a treatment-related toxicity CTCAE v5 >Grade 1, then a dose escalation decision may be made following a dose escalation meeting. If, one or both patients experience a treatment-related toxicity CTCAE v5 >Grade 1, or if the SRC decide additional information is required before making a dose escalation decision, then additional patients will be enrolled to this cohort to reach the minimum of three evaluable patients. Subsequent cohorts will have at least three evaluable patients.

5.4.4 Dose Escalation Procedures

The first cohort enrolled in the study will be treated with single agent KY1044 at the starting dose as specified in Table 5-2. Once this cohort has completed the DLT follow-up period (21 days) and the dose escalation decision has been determined by the SRC to escalate, the second cohort for the single agent will open for dosing. After the first two cohorts have been declared safe and tolerable, combination dosing will begin at the planned starting dose in parallel to proceeding with dose escalation of the single agent.

The combination dose escalation will proceed provided that the starting dose of the combination does not exceed the MTD of the single agent. Provisionally, the first cohort enrolled in the study will be treated with the starting dose for KY1044 at a flat dose of 0.8 mg in combination with atezolizumab (a lower dose of KY1044 may be considered for starting the combination if emerging data support this, but will not be higher than 0.8 mg for KY1044 and 1200 mg for atezolizumab).

The assessment of DLT data will be made after the third patient in a given cohort has completed the minimum DLT follow-up period (21 days) or is otherwise evaluable (see Section 5.4.5.1). The SRC will meet for the dose escalation meeting, once required data have been entered into the eCRF, cleaned and laboratory analyses have been performed.

After the dose escalation meeting, the new dose will be officially confirmed and the new cohort will be opened for dosing patients. Drug administration at the next dose level may not proceed until the Investigator receives written confirmation, indicating that the results of the previous dose level were evaluated and that it is permissible to proceed to a higher dose level. The number of cohorts explored will be dependent on the tolerability of the compound.

Dose escalation will continue until identification of the MTD and/or the RP2D, completion of all defined dose levels, or a decision that further increase of dose is not warranted.

5.4.5 Dose Escalation Decisions

5.4.5.1 Evaluable Patients

For dose escalation decisions, patients in either single agent or combination cohorts can be considered evaluable after having met the following criteria:

- Have completed a minimum of one cycle of treatment with the minimum safety evaluation (Cycle 1, 21 days) or have had a DLT within the first cycle of treatment (first 21 days)
- Have adequate drug exposure (ie, full infusion of planned doses of KY1044 and atezolizumab if appropriate)

Dose escalation decisions will occur when the cohort of at least three patients has met these criteria. If only two patients in a cohort are evaluable and neither patient has experienced a treatment-related toxicity CTCAE v5>Grade 1, dose escalation decisions may be considered (see Section 5.4.3).

5.4.5.2 Data for Dose Escalation Decisions

Decisions will be based on a synthesis of all relevant data available from all dose levels evaluated in the ongoing study, including safety information (all CTC grade Aes, ECGs and laboratory values, DLTs, all CTCAE v5>Grade 1 toxicity data) and available PK data from evaluable patients.

The SRC must reach a consensus on whether to declare the MTD, escalate the dose any further, or whether to de-escalate and/or recruit additional numbers of patients at the current dose level. The mTPI-2 decision table will be used by the SRC in addition to other data mentioned in this section to aid in the recommended escalation and de-escalation decisions (see Section 9).

Patient safety will be monitored on an ongoing basis by the SRC and the dose levels and continuation of dosing at a certain dose level will potentially be amended, depending on emerging data from earlier cohorts.

5.4.6 Maximum Tolerated Dose

5.4.6.1 MTD Definition

The MTD will be defined as follows in each of the Phase 1 parts:

- KY1044 single agent: the MTD is defined as the highest drug dosage not expected to cause DLT in 30% or more of the treated patients in the DLT follow-up period, corresponding to the first 21 days of KY1044 treatment during the escalation part of the study.
- KY1044 combination with atezolizumab: the MTD is defined as the highest drug dosage not expected to cause DLT in 30% or more of the treated patients in the DLT follow-up period, corresponding to the first 21 days of combined treatment during the escalation part of the study.
- The SRC will use all data previously mentioned as well as the mTPI-2 decision table in determining the MTD. The MTD is determined based on the isotonic regression specified in Guo et al. 2017 (49). The determined MTD is the dose for which the isotonic estimate of the toxicity rate is the closest to the target toxicity rate of 30% and

less than 35%. The parameters of mTPI-2 design and operating characteristics are described in Section 9.

5.4.7 Recommended Dose for Further Development

The RP2D will be declared when the MTD and/or the optimal biological dose(s) is established in the Phase 1 dose escalation and/or enrichment component and/or the initial Phase 2 dose assessment part of the study. This will be a composite of safety, drug exposure, target occupancy, PK/PD association and signs of anti-tumor activity.

5.4.8 Intra-patient Dose Escalation

Depending on emerging data and in the case that KY1044 as single agent or the combination with atezolizumab is well tolerated, intra-patient dose escalation of KY1044 dose may be permitted to RP2D once defined to avoid suboptimal dosing for patients treated in cohorts at lowest dose levels.

5.5 Dose Limiting Toxicities

A DLT is defined as a clinically relevant AE or abnormal laboratory value of CTCAE ≥Grade 3 assessed as unrelated to disease, disease progression, inter-current illness or concomitant medications, which occurs within the first cycle (21 days) of treatment with KY1044 as single agent or in combination with atezolizumab during the dose escalation part of the study, with the exceptions described in Table 5-4.

National Cancer Institute CTCAE Version 5.0 will be used for all grading. For dose-escalation decisions, DLTs will be considered by the SRC. Aes meeting the criteria of DLT (please refer to Table 5-4) will be also collected in Cycle 2 and later cycles and will be considered by the SRC for ongoing safety decision.

The Investigator must notify the Sponsor immediately of any unexpected CTCAE v5 ≥Grade 3 Aes or laboratory abnormalities. Prior to enrolling patients into a higher dose level, all CTCAE v5 ≥Grade 2 will be reviewed for all patients at the current dose level and will also be considered for further dose escalation.

Table 5-4: Criteria for Defining Dose Limiting Toxicities

For dose escalation and cohort expansion, DLT will be adjudicated as follows: **Any Grade 4 Aes will be adjudicated DLTs with the exception of:**
Neutropenia lasting <72 hours that is not associated with fever or other clinical symptoms.
Lymphopenia
Electrolyte abnormalities that are not associated with clinical sequelae and are corrected with appropriate management or supplementation within 72 hours of the onset.
Any Grade 3 Aes will be adjudicated as DLTs except for:
Nausea and vomiting persisting for <2 days after optimal anti-emetic therapy.
Thrombocytopenia without significant bleeding (including platelet transfusions).
Diarrhea persisting for <2 days after optimal anti-diarrhea treatment.
Hypertension persisting <7 days after treatment.

	Infection or fever in the absence of neutropenia persisting <5 days.
	Rash or photosensitivity persisting <7 days after treatment.
	Fatigue lasting <7 days.
	LFT elevations (AST/ALT) persisting <7 days after treatment with corticosteroids.
	Immune-related adverse events persisting <7 days after treatment with corticosteroids.
The following Grade 2 Aes will be adjudicated as DLTs:	
	Total bilirubin CTCAE v5 ≥Grade 2 with ALT/AST CTCAE v5 ≥Grade 2.
	Pneumonitis persisting >7 days despite treatment with corticosteroids.
	Eye pain or reduction of visual acuity that does not respond to topical therapy and does not improve to Grade 1 severity within 2 weeks of the initiation of topical therapy OR requires systemic treatment.
	Other clinically significant toxicities (cardiotoxicity, neurotoxicity) including a single event or multiple occurrences of the same event that lead to a dosing delay of >7 days in Cycle 1.

AE=adverse event; ALT=alanine aminotransferase; AST=aspartate aminotransferase; CTCAE v5=Common Terminology Criteria for Adverse Events Version 5; DLT=dose limiting toxicity; LFT=liver function test.

5.6 Dose Modifications and Management of Toxicities

5.6.1 Dose Modifications and Dose Delays

For patients who do not tolerate the protocol -specified dosing schedule, dose adjustments are permitted to allow the patient to continue the study treatment. The following guidelines must be followed:

- If a patient experiences an AE meeting the criteria for a DLT as outlined in Section 5.5 (including events occurring after Cycle 1), treatment should be withheld. Dose modifications for toxicities related to the study medication are summarized in Table 5-5. Following resolution of the toxicity to Grade 1 or to the patient's baseline value (as outlined in the safety management guidelines in Table 5-5), the patient may resume study treatment at the same or the next lower dose level (Table 5-2, Table 5-3) assessed to be safe (on the same dosing schedule [administration every 21 days]), if there is no evidence of disease progression as per iRECIST.
- For patients in the dose escalation part of the study receiving KY1044 in combination with atezolizumab, the KY1044 dose level will be lowered to the next lower dose level. **Dose reductions of atezolizumab are not allowed.**
- The decision to resume treatment with KY1044 as single agent or in combination with atezolizumab following the occurrence of a DLT is at the discretion of the Investigator. If the Investigator considers it to be in the patient's best interest to resume therapy before the toxicity has resolved to Grade 1, or to resume without dose reduction, this may be permitted on a case by case basis, following discussion with the Medical Monitor.
- Dose reductions for KY1044 to below 0.24 mg (less than starting dose -1) are not permitted.
- If a patient who misses more than one consecutive dose due to study treatment -related toxicity experiences clinical benefit, and in the opinion of the Investigator it is in the patient's best interest to remain on study, then the patient may continue treatment after discussion with the Medical Monitor.

- Patients who discontinue study treatment for a study related AE or a study -related abnormal laboratory value must complete their EOT visit and safety followup procedures as described in Section 5.6.2 below and be followed up for PFS and survival (please refer to Section 8.2.2).
- Active SARS-Cov-2 infections in patients enrolled into the study should be treated as Aes. This also applies to any other concurrent illnesses, which might occur during the study. Treatment interruption of KY1044 as single agent and in combination with atezolizumab should be considered on an individual patient basis after discussion with the Medical Monitor.
- All interruptions or change to study drug administration must be recorded in the patient's hospital files and eCRF.

5.6.2 Follow-up for Toxicities

- The emergence of irAEs may be anticipated based on overall experience in clinical studies with similar immunomodulators.
- An irAE is a clinically important AE of unknown etiology associated with the study drug exposure. IrAEs are typically low grade and self-limited, often occurring after multiple doses, and most frequently involving the GI tract (diarrhea/colitis), skin (rashes), liver (hepatitis), and endocrine systems (a variety of endocrinopathies) and lung (pneumonitis). Serologic, histologic (tumor sample) and immunological assessments should be performed as deemed appropriate by the Investigator, to verify the immune related nature of the AE, and exclude the neoplastic, infectious or metabolic origin of the AE. Management Algorithms (Table 5-5) have been developed to assist Investigators in assessing and managing the following groups of Aes: Infusion reactions, Hematological, Cardiological, GI, Renal, Pulmonary, Hepatic, Endocrinopathy, Dermatological, Neurological, Ophthalmological, and Rheumatological Aes.
- Patients whose treatment is interrupted or permanently discontinued due to an irAE, AE or clinically significant laboratory value, must be followed-up at least once a week (or more frequently if required by institutional practices, or if clinically indicated) for 4 weeks, and subsequently at approximately 4-week intervals, until resolution or stabilization of the event, whichever comes first. Appropriate clinical experts should be consulted as deemed necessary.
- In case of a suspected irAE, the relevant immunological assessments (eg, rheumatoid factor, anti-deoxyribonucleic acid (DNA) Ab, etc.) should be performed and guidelines as outlined in Table 5-5 (and laboratory assessments Section 6.5.6) should be followed.

All patients must be followed up for irAEs, Aes and SAEs for 90 days following the last dose of KY1044 as single agent or in combination with atezolizumab.

Table 5-5 outlines the follow-up evaluation recommended for selected toxicities. For any irAEs/Aes Grade 1 and/or Grade 2, treatment with KY1044 and atezolizumab (if applicable) should be maintained at the determined dose and schedule, unless otherwise specified in Table 5-5.

Table 5-5: Management of Toxicities Defined as Study Treatment-related Only

Infusion Reaction and Cytokine Release Syndrome (CRS)			
Grade	**CTCAE description**	**Management**	**Specialist referral**
1	Mild transient reaction; infusion interruption not indicated; intervention not indicated	• Drug infusion rate may be decreased, or infusion temporarily interrupted, until resolution of the event • Consider reducing the rate of infusion upon re-initiation or subsequent infusions • NSAIDs (eg, acetaminophen), antihistamines, opioids, and corticosteroids may be used per Investigator/ institutional guidelines • Consider premedication for subsequent infusions per Investigator/ institutional guidelines • If CRS is suspected (very high fever and precipitous drops in blood pressure, myalgia, change in mental status) treat with corticosteroids according to local standards (and/or with tocilizumab)[1] • Take blood for cytokine measurements immediately after the occurrence of the AE and during treatment	
2	Therapy or infusion interruption indicated but responds promptly to symptomatic treatment (eg, antihistamines, NSAIDS, narcotics, IV fluids); prophylactic medications indicated for ≤24 hours		
3	Prolonged (eg, not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for clinical sequelae	• **Permanently discontinue ICI** • For severe/life-threatening reactions, manage the patient as clinically appropriate (eg, antihistamines, oxygen, fluids, opioids, corticosteroids, bronchodilators, etc.) per Investigator/institutional guidelines • Provide supplemental oxygen, fluids, and other resuscitative measures and/or measures for symptomatic relief (see under Grade 2, above) as needed. Monitor vital signs (eg, BP, HR, respiration, and temperature) every 15 ±5 minutes until resolution	✓ Refer to allergist to prevent future reactions
4	Life-threatening consequences; urgent intervention indicated		

HAEMATOLOGICAL			
Grade	**CTCAE description**	**Management**	**Specialist referral**
Anemia			
1	Hgb **<LLN-10.0 g/dL;** (<LLN-6.2 mmol/L; <LLN-100 g/L)	• Monitor closely while continuing ICI	✓
2	Hgb **<10.0–8.0 g/dL;** (<6.2–4.9 mmol/L; <100-80 g/L)	• Monitor closely while continuing ICI • Evaluate for possible causes and refer to hematology if no obvious cause if identified	✓
3	Hgb **<8.0 g/dL;** (<4.9 mmol/L; <80 g/L;) transfusion indicated	• Hold ICI • Consider Coombs testing and evaluation for hemolytic anemia • Consider re-treating with ICI if hemolytic anemia responds promptly (within a few days) to corticosteroids	✓
4	Life-threatening consequences; urgent intervention indicated	• Permanently discontinue ICI	✓
Notes: 1. No firm recommendations for corticosteroid management are provided here as treatment should be individualized. 2. If unexplained anemia does not respond to steroids, consider bone marrow biopsy			
Neutropenia (ANC)			
3	ANC <1000-500/mm^3	• Dose delay for study treatment-related Grade 3 until resolved to ≤Grade 1	✓
4	ANC <500/mm^3	• Discontinue for study treatment-related Grade 4 >7 days duration	✓
Febrile neutropenia			
3 **4**	ANC <1.0x10^9/L, fever ≥38.5°C	• Dose delay for study treatment-related Grade 3 until resolved to ≤Grade 1 • Discontinue for study treatment-related Grade 4	✓
Thrombocytopenia			
3	PLT <50,000-25,000/mm^3	• Dose delay for study treatment-related Grade 3 until resolved to ≤Grade 1 • Discontinue for study treatment-related Grade 3 >7 days or associated with bleeding	✓

4	PLT <25,000/mm^3	• Discontinue for study treatment-related Grade 4	✓
Notes: *Progressive or Grade 3 unexplained thrombocytopenia:* consider work up for autoimmune disease and rule out DIC or other cause of thrombocytopenia that may be related to underlying disease *Precipitous development of thrombocytopenia:* consider steroid intervention pending clinical condition (brain metastases, colitis, etc.) and evaluate for immune-mediated thrombocytopenia Permanently discontinue ICI for clinically significant, steroid refractory ICI-associated thrombocytopenia			
Lymphopenia			
3	<0.5-0.2x10^9/L	• Maintain dose level for study treatment-related ≤Grade 3	
4	<0.2x10^9/L	• Dose delay for study treatment-related Grade 4 until resolved to ≤Grade 3 • Study treatment-related Grade 4 lymphopenia or leukopenia does not require discontinuation	
RENAL			
Grade	**CTCAE description**	**Management**	**Specialist referral**
Nephritis (Creatinine increase)			
1	Creatinine >1.5–2xabove baseline; >0.3 mg/dL	• Continue ICI but initiate work-up to evaluate possible causes and monitor closely	
2	Creatinine >2-3xabove baseline	• Dose delay for study treatment-related ≥Grade 2 until resolved to ≤Grade 1 • Start corticosteroids (Note 3) • Discontinue ICI for persistent or recurrent elevation	
3	Creatinine >3xbaseline or >4 mg/dL Hospitalization indicated	• Hold ICI • Consider resuming treatment if Grade 3 resolves (Note 2) and cause of event is confirmed. Timing of event and response to treatment should be considered in making a decision • Start corticosteroids (Note 3) • Discontinue ICI for persistent or recurrent elevation	
4	Creatinine >6.0xULN Life threatening consequences dialysis indicated	• Discontinue for study treatment-related Grade 4 • Start corticosteroids (Note 3)	✓

Notes:
1. Grades are those listed under 'acute kidney injury' in CTCAE[2].
2. Consider using increase from baseline rather than absolute value for creatinine monitoring, especially in patients with primary renal carcinoma or other baseline renal conditions.
3. For persistent creatinine elevation ≥Grade 2 with no other identifiable cause, start corticosteroids. Dose and schedule should be individualized and based on grade. Taper corticosteroids when creatinine improves to Grade 1.

HEPATIC

Hepatitis

Grade	CTCAE description	Management	Specialist referral
1	AST, ALT >ULN-3xULN; total bilirubin >ULN-1.5xULN	• Continue ICI • CMP or hepatic function panel once weekly • If liver enzyme and function tests are stable, reduce frequency of blood tests	
2	AST, ALT >3-≤5xULN; total bilirubin >1.5-≤3xULN	• Hold ICI • Rule out viral hepatitis, autoimmune disease, biliary obstruction, new metastasis or thrombosis • Start prednisone 0.5-1 mg/kg/day (or equivalent dose of methylprednisolone) with 4-week taper • Monitor CMP twice a week • Liver biopsy is optional • Resume ICI when corticosteroid taper to 10 mg/day (toxicity Grade ≤1)	
3 and 4	AST, ALT >5xULN; total bilirubin >3xULN	• Permanently discontinue ICI • Monitor CMP every 1–2 days • Start prednisone 1–2 mg/kg/day ○ If refractory after 3 days, consider mycophenolate • If liver enzymes improve, taper corticosteroid over 4 weeks • Consider liver biopsy	

Note: If Grade 3 or 4 hyper-bilirubinemia is due to the indirect (non-conjugated) component only, and hemolysis as the etiology has been ruled out as per institutional guidelines (eg, review of peripheral blood smear and haptoglobin determination), then reduce one dose level and continue treatment at the discretion of the Investigator.

Asymptomatic amylase and/or lipase elevation			
3	>2.0-5.0xULN	Any study treatment-related Grade ≥3 isolated amylase or lipase abnormality that is not associated with symptoms or clinical manifestations of pancreatitis does not require dose delay or discontinuation. The Kymab Medical representative should be consulted for such amylase or lipase abnormalities.	
4	>5.0xULN		
Note: A CT scan or other imaging study to assess the pancreas, liver, and gallbladder must be performed within 1 week of the first occurrence of any ≥Grade 3 of amylase and/or lipase. If asymptomatic Grade 2 elevations of lipase and/or amylase occur again at the reduced dose, patients will be discontinued permanently from study treatment.			
CARDIAC			
Grade	**CTCAE description**	**Management**	**Specialist referral**
1	Abnormal cardiac biomarker testing, including abnormal ECG	• Recommend baseline ECG and cardiac biomarker assessment (BNP, troponin) to establish if there is a notable change during therapy • Mild abnormalities should be observed closely during therapy	✓ if abnormal
2	Abnormal screening tests with mild symptoms	• Control cardiac diseases (eg, heart failure, atrial fibrillation) optimally • Control cardiac disease risk factors proactively (including hypertension, hyperlipidemia, discontinue smoking, and monitor diabetes)	✓
3	Moderately abnormal testing or symptoms with mild activity	• BNP >500 pg/mL, troponin >99% institutional normal, new ECG findings (QTc prolongation, new conduction disease, or ST-T wave changes) • Consider withholding ICI ○ If a period of stabilization is achieved and definite cardiac toxicity was not identified, it may be reasonable to consider re-challenging the patient with ICI, with heightened monitoring. • If confirmed cardiac injury or decompensation, hold ICI therapy until stabilized. • Optimally treat identified cardiac conditions • Consider corticosteroids if myocarditis suspected (Note 2)	✓
4	Moderate to severe decompensation, intravenous medication or intervention required, life threatening conditions	• Permanently discontinue ICI • If myocarditis is identified, consider high-dose corticosteroids (1 mg/kg methylprednisolone (IV) for at least several days) until improved to Grade ≤1, after that consider at least 4–5 weeks of tapering doses (Note 2). • Add additional immunosuppressive agents in severe refractory cases.	✓

		• Give additional supportive treatments, including appropriate treatment of heart failure. Additional treatment of detected cardiac conditions should be provided.*	

Notes:

1. Grades outlined here are not drawn from CTCAE (see Putzanov et al "cardiovascular adverse events"[3,4])
2. Patients with confirmed myocarditis (or in cases of reasonable suspicion) should receive emergent high-dose corticosteroids. Until data are available (eg, cut-off levels of troponin) to determine when to start corticosteroids in patients with possible (as opposed to confirmed) myocarditis, this decision should be made on a case by case basis. The importance of active, ongoing consultation with a cardiologist to discuss the benefit/risk of continuing ICI therapy, starting corticosteroids, or instituting other cardiac treatments, cannot be overstated.

* Other therapies for management of myocarditis or pericarditis (viral based therapy, immunoglobulins, or plasmapheresis) are speculative at this point in time.

ENDOCRINE

Hypophysitis			
Grade	**CTCAE description***	**Management**	**Specialist referral?**

1	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated	• Hold ICI if ≥Grade 2 irAE until work up is completed and appropriate hormone replacement is started
		• If central adrenal insufficiency: start physiologic steroid replacement: Hydrocortisone ~10 mg/m^2 (HC 15 mg am, 5 mg at 3 pm)
		  ○ Periodic assessment (eg, every 3 months in the first year, every 6 months thereafter): clinical monitoring and repeat hormone levels (am cortisol and ACTH and/or low dose cosyntropin stimulation test) to assess recovery
		• If central hypothyroidism: start thyroid hormone (levothyroxine 1 mcg/kg)
		  ○ Repeat thyroid function testing 6-8 weeks after initiation of thyroid hormone and then periodically (eg, every 3 months in the first year and every 6 months thereafter) to assess recovery
		• If central hypogonadism, repeat hormone levels in 2–3 months and consider testosterone in men or HRT in women if appropriate for cancer type
		For severe/life-threatening symptoms such as adrenal crisis, severe headache, visual field deficiency:
		• Hospitalize as appropriate.
		• High dose corticosteroid (prednisone 1 mg/kg/day) (or equivalent dose of methylprednisolone) in the acute phase, followed by taper over 1 month.
		• Adrenal crisis should be managed per standard guidelines.
			✓

2	Moderate; minimal, local or non-invasive intervention indicated; limiting age appropriate instrumental ADL		
3	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of existing hospitalization indicated; disabling; limiting self-care ADL		
4	Life-threatening consequences; urgent intervention indicated		

		• If central hypothyroidism, replace thyroid hormone (see above) after corticosteroids have been initiated	
Note: In the uncommon scenario of MRI findings without pituitary deficiency, consider high dose corticosteroids for prevention of hormonal dysfunction. * Hypophysitis is not defined in CTCAE Version 4.0. This classification is drawn from the CTCAE category 'Endocrine disorders - Other'.			
Hypothyroidism			
Grade	**CTCAE description**	**Management**	**Specialist referral?**
1	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	• Hold ICI for ≥Grade 3 irAEs • ICI can be continued after resolution of symptoms to Grade 2 or better. • Start standard thyroid replacement therapy: initial dose can be the full dose (1.6 mcg/kg) in young, healthy patients, but a reduced dose of 25-50 mcg should be initiated in elderly patients with known cardiovascular disease. • Repeat TSH and free T4 testing after 6-8 weeks and adjust thyroid hormone dose accordingly. If TSH is above reference range, increase thyroid hormone dose by 12.5 mcg to 25 mcg • After identification of the appropriate maintenance dose, further evaluation is required every year, or sooner if patient's status changes • After identification of the appropriate maintenance dose, further evaluation is required every year, or sooner if patient's status changes	✓
2	Symptomatic; thyroid replacement indicated; limiting instrumental ADL		
3	Severe symptoms; limiting self-care ADL; hospitalization indicated		
4	Life-threatening consequences; urgent intervention indicated		
Hyperthyroidism			
Grade	**CTCAE description**	**Management**	**Specialist referral?**
1	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	• Hold ICI for ≥Grade 3 irAEs • Standard therapy for hyperthyroidism should be followed • *Thyroiditis* is self-limiting and has 2 phases: ○ In the hyperthyroid phase, patients may benefit from beta blockers if symptomatic (eg, atenolol 25-50 mg daily, titrate for HR <90 bpm if BP allows). Monitor closely with regular symptom evaluation and free T4 testing every 2 weeks.	✓
2	Symptomatic; thyroid suppression therapy indicated; limiting instrumental ADL		
3	Severe symptoms; limiting self-care ADL; hospitalization indicated		

4	Life-threatening consequences; urgent intervention indicated	○ Introduce thyroid hormones (see hypothyroidism management) if the patient becomes hypothyroid (low free T4/T3, even if TSH is not elevated). • Graves' disease should be treated per standard guidelines.	
Note: High dose corticosteroids (1 mg/kg/day) are not routinely required.			
Type 1 diabetes (CTCAE defines hyperglycemia not diabetes)			
Grade	**CTCAE description**	**Management**	**Specialist referral?**
1	Fasting glucose >ULN-160 mg/dL (>ULN-8.9 mmol/L)	• Type 1 DM with diabetic ketoacidosis: Hold ICI; hospitalize and initiate treatment per standard guidelines. • Type 1 DM without diabetic ketoacidosis: Hold ICI for hyperglycemia ≥Grade 3. Treat with insulin and continue ICI when patient recovers to Grade 1. • Treat with insulin per standard guidelines and restart ICI when patient recovers to Grade 1. • Provide patient education on diet and lifestyle modification, and blood glucose testing	✓
2	Fasting glucose >160-250 mg/dL (>8.9-13.9 mmol/L)		
3	Fasting glucose >250-500 mg/dL (>13.9-27.8 mmol/L); hospitalization indicated		
4	Fasting glucose >500 mg/dL (>27.8 mmol/L); life-threatening consequences		
DERMATOLOGIC			
Maculopapular rash/dermatitis			
Grade	**CTCAE description**	**Management**	**Specialist referral?**
1	Macules/papules covering <10% BSA with or without symptoms (eg, pruritus, burning, tightness)	• Continue ICI • Oral antihistamines ○ Cetirizine/loratidine 10 mg daily (non-sedating); hydroxyzine 10-25 mg QID, or at bedtime • Topical corticosteroids ○ Class I topical corticosteroid (eg, clobetasol propionate, halobetasol propionate, betamethasone dipropionate cream or ointment) for body; Class V/VI corticosteroid (eg, aclometasone, desonide, hydrocortisone 2.5% cream) for face	

2	Macules/papules covering 10-30% BSA with or without symptoms (eg, pruritus, burning, tightness); limiting instrumental ADL	• Continue ICI
		• Non-urgent dermatology referral
		• Oral antihistamines
		  o Cetirizine/loratidine 10 mg daily (non-sedating); hydroxyzine 10-25 mg QID, or at bedtime
		• Topical corticosteroids
		  o See Grade 1
		  o Cetirizine/loratidine 10 mg daily (non-sedating); hydroxyzine 10-25 mg QID, or at bedtime
			✓

3	Macules/papules covering >30% BSA with or without associated symptoms; limiting self-care ADL	• Hold ICI • Same day dermatology consult • Rule out systemic hypersensitivity: CBC with differential, CMP • Oral antihistamines o Cetirizine/loratidine 10 mg daily (non-sedating); hydroxyzine 10-25 mg QID, or at bedtime • Systemic corticosteroids • Prednisone 0.5-1 mg/kg/day (or equivalent dose of methylprednisolone) until rash resolves to ≤Grade 1	✓
Pruritus*			
Grade	**Description**	**Management**	**Specialist referral?**
1	Mild or localized; topical intervention indicated	• Emollients with cream or ointment based, fragrance-free products o Class I topical corticosteroid (eg, clobetasol propionate, halobetasol propionate, betamethasone dipropionate) for body; Class V/VI corticosteroid (eg, aclometasone, desonide, hydrocortisone 2.5%) for face, AND oral antihistamines (eg, cetirizine/loratidine 10 mg daily, hydroxyzine 10-25 mg QID, or at bedtime	
2	Intense or widespread; intermittent; skin changes from scratching (eg, edema, papulation, excoriation, lichenification, oozing/crusts);	• Dermatology referral o Class I topical steroid (eg, clobetasol propionate, halobetasol propionate, betamethasone dipropionate) for body; class V/VI steroid (aclometasone, desonide, hydrocortisone 2.5%) for face, AND oral antihistamines (eg, cetirizine/loratidine 10 mg daily, hydroxyzine 10-25 mg QID, or at bedtime	✓

	oral intervention indicated; limiting instrumental ADL	• Oral corticosteroids ○ Prednisone 0.5-1 mg/kg/day (or equivalent of methylprednisolone) tapered over 2 weeks	
3	Intense or widespread; constant; limiting self-care ADL or sleep; oral corticosteroid or immunosuppressive therapy indicated	• Dermatology referral • GABA agonist (eg, pregabalin, gabapentin 100-300 mg TID) • Oral corticosteroid ○ Prednisone 0.5-1 mg/kg/day (or equivalent of methylprednisolone) tapered over 2 weeks	✓
Notes: 1. Grade 4 maculopapular rash/dermatitis is not included in CTCAE *Recommendations provided are based on case reports, series and expert consensus. Use of suggested therapies must be discussed with medical oncology based on individual patient considerations. The impact of these therapies on the anti-tumor immune response and efficacy of cancer treatment is unknown and requires further research.			
GASTROINTESTINAL			
Colitis			
Grade	**CTCAE description**	**Management**	**Specialist referral?**
1	Asymptomatic; clinical or diagnostic observations only; intervention not indicated [Grade 1 diarrhea frequency ≤4/day]	• Close follow-up within 24-48 h for changes or progression • Continue ICI • If symptoms persist, start routine stool and blood tests • Bland diet advisable during period of acute diarrhea • Anti-diarrheal medication is optional but not highly recommended when infectious work-up is negative.	
2	Abdominal pain; mucus or blood in stool [Grade 2 diarrhea frequency 4-6/day]	• Hold ICI • Outpatient stool and blood work; CRP, ESR, fecal calprotectin, lactoferrin, imaging and endoscopy are optional • If diarrhea only, observe for 2-3 days. If no improvement start prednisone 1 mg/kg/day (or equivalent dose of methylprednisolone); anti- diarrheal medication is not recommended • If diarrhea and colitis symptoms (abdominal pain ± blood in BM), start prednisone 1 mg/kg/day (or equivalent dose of methylprednisolone) immediately	✓ See note 5

		○ If no improvement in 48 h, increase corticosteroid dose to prednisone 2 mg/kg/day (or equivalent dose of methylprednisolone) ○ If patient improves – Taper corticosteroid over 4–6 weeks may be needed – Resume ICI when corticosteroid is tapered to ≤10 mg/ day and patient remains symptom-free (Grade ≤1) – Continue ICI monotherapy – If using combination anti-CTLA-4/ICI immunotherapy, continue ICI agent only – ICI dose reduction is not recommended • If colitis returns on resuming ICI: ○ Grade ≤2: temporarily hold ICI ○ Grade ≥3: permanently discontinue ICI	
3 and 4	Grade 3: Severe abdominal pain; change in bowel habits; medical intervention indicated; peritoneal signs [Grade 3 diarrhea frequency ≥7×/day] Grade 4: Life-threatening consequences; urgent intervention indicated	• Grade 3: withhold ICI; consider resuming ICI when corticosteroid is tapered to ≤10 mg/day and patient remains symptom-free (Grade ≤1). Consider hospitalization • Grade 4: permanently discontinue ICI and hospitalize • Blood and stool infection work-up, inflammatory markers, imaging, endoscopy and GI consult • Start intravenous prednisone 1-2 mg/kg/day (or equivalent dose of methylprednisolone) immediately ○ If patient improves, follow instructions for 'If patient improves' for Grade 2 • If refractory or no improvement on IV corticosteroid, start prednisone 2 mg/kg/day (or equivalent dose of methylprednisolone) for 3 days • Consider other anti-inflammatory agents eg, infliximab 5 mg/kg, which can be given again after two weeks if a second dose is needed. Vedolizumab may also be used (see Note 4).	

Notes.
1. CBC with differential, CMP, ESR and CRP are recommended before starting immunotherapy, to provide baseline values for comparison over time. Despite the association between elevated ESR and CRP and colitis, some insurance companies may not cover these tests.
2. There is no proven role for prophylactic corticosteroids (budesonide) to prevent GI irAEs.[5,6]
3. Response to infliximab generally occurs within 1–3 days although some patients benefit from a second dose after 2 weeks. Prolonged oral prednisone taper may be required after infliximab administration. Whether infliximab reduces the anti-tumor efficacy of ipilimumab remains unknown.[7]
4. Case reports of successful treatment of steroid-dependent immune-related colitis using vedolizumab indicate this may benefit certain patients.

5. A GI consult is warranted in any patient who meets criteria for Grade 2 diarrhea/colitis with negative infectious stool work up.			
Fatigue/Asthenia			
Grade	**CTCAE description**	**Management**	**Specialist referral?**
3	Fatigue not relieved by rest, limiting self-care ADL	• Dose delay for study treatment-related Grade 3 until resolved to ≤Grade 1 • Discontinue for study treatment-related Grade 3 lasting >7 days or Grade 4	
NEUROLOGIC			
Encephalopathy/Leukoencephalopathy/Reversible posterior leukoencephalopathy syndrome (PRES)			
Grade	**CTCAE description**	**Management**	**Specialist referral?**
1	Mild symptoms	• Hold ICI and initiate diagnostic work-up • Consider permanent discontinuation of ICI if AE worsens or does not improve	
2	Moderate symptoms; limiting instrumental ADL	• Hold ICI • Start 0.5-1.0 mg/kg/day methylprednisolone equivalents PO or IV once infection has been excluded • Consider permanent discontinuation of ICI if AE worsens or does not improve.	✓
3	Severe symptoms; limiting self-care ADL	• Permanently discontinue ICI • Start 1-2 mg/kg/day methylprednisolone equivalents IV and prophylactic antibiotics • Consider plasmapheresis if no improvement or symptoms worsen after 3 days	✓
4	Life-threatening consequences; urgent intervention indicated	• Permanently discontinue ICI • Start 1-2 mg/kg/day methylprednisolone equivalents IV and prophylactic antibiotics • Consider plasmapheresis if no improvement or symptoms worsen after 3 days • Contact intensive care unit	✓ and contact intensive care unit
Notes: CTCAE provides grading criteria for encephalopathy, leukoencephalopathy, and PRES. For all these irAEs, ICI therapy may be continued for Grade 1 irAEs. However, ≥Grade 2 events require an ICI hold, and referral to neurology. For events of ≥Grade 3 severity, ICI should be permanently discontinued, IV corticosteroids administered, and plasmapheresis considered if there is no improvement, or symptoms worsen, after 3 days.			

OPHTHALMOLOGIC			
Uveitis			
Grade	**CTCAE description**	**Management**	**Specialist referral?**
1	Asymptomatic; clinical or diagnostic observations only	• Continue ICI • Ophthalmology referral within 1 week • Start lubrication drops (artificial tears)	✓
2	Anterior uveitis; medical intervention indicated	• Hold ICI • Ophthalmology referral within 2 days, prior to initiating uveitis treatment • Coordinate treatment with ophthalmologist (eg, topical corticosteroids, cycloplegic agents, systemic corticosteroids)	✓
3	Posterior or pan-uveitis (Note)	• Permanently discontinue ICI • In carefully selected cases it may be appropriate to restart treatment, cautiously, depending on severity, systemic response to immunotherapy and ocular response to topical, local or systemic prednisone (prescribed in coordination with ophthalmologist) • URGENT ophthalmology referral (preferably uveitis specialist) prior to initiating treatment. Co-ordinate treatment with specialists • Consider systemic corticosteroids in addition to intravitreal/periocular corticosteroids/topical corticosteroid treatment as recommended by ophthalmologist	✓ URGENT
4	Blindness (20/200 or worse) in the affected eye	• Permanently discontinue ICI • URGENT ophthalmology referral (preferably uveitis specialist) prior to initiating any treatment. Co-ordinate treatment with specialists • Consider systemic corticosteroids in addition to intravitreal/periocular corticosteroids/topical corticosteroid treatment as recommended by ophthalmologist	✓ URGENT
Note: Unlike anterior uveitis, posterior uveitis can be asymptomatic but nonetheless proceed to visual loss.			

Episcleritis (CTCAE scleral disorder)			
Grade	**CTCAE description**	**Management**	**Specialist referral?**
1	Asymptomatic; clinical or diagnostic observations only	• Continue ICI • Ophthalmology referral within 1 week • Start lubrication drops (artificial tears)	✓
2	Symptomatic, limiting instrumental ADL; moderate decrease in visual acuity (20/40 or better)	• Hold ICI • Ophthalmology referral within 2 days, prior to initiating uveitis treatment • Coordinate treatment with ophthalmologist (topical steroids, cycloplegic agents, systemic steroids) (See Note)	✓
3	Symptomatic, limiting self-care ADL; marked decrease in visual acuity (best corrected visual acuity worse than 20/40 or more than 3 lines of decreased vision from known baseline, up to 20/200);	• Permanently discontinue ICI • In carefully selected cases it may be appropriate to restart treatment, cautiously, depending on severity, systemic response to immunotherapy and ocular response to topical, local or systemic prednisone (prescribed in coordination with ophthalmologist) • URGENT ophthalmology referral (preferably uveitis specialist) prior to initiating treatment (See Note). Co-ordinate treatment with specialists. • Consider systemic steroids in addition to intravitreal /periocular steroids /topical steroid treatment as recommended by ophthalmologist	✓ URGENT
4	Blindness (20/200 or worse) in the affected eye	• Permanently discontinue ICI • URGENT ophthalmology referral (preferably uveitis specialist) prior to initiating any treatment (See Note). Co-ordinate treatment with specialists. • Consider systemic steroids in addition to intravitreal /periocular steroids /topical steroid treatment as recommended by ophthalmologist	✓ URGENT
Note: IMPORTANT: Starting treatment with steroids prior to conducting an eye exam may worsen ocular conditions that are due to infection (eg, herpetic keratitis/uveitis) or may mask accurate diagnosis and severity grading when the patient is examined by an ophthalmologist.			

Blepharitis			
Grade	**CTCAE diagnosis**	**Management**	**Specialist referral?**
Not defined in CTCAE		• Puffy eyelids may indicate early preseptal cellulitis, which requires systemic antibiotic treatment. Warning signs (eyelid swelling with pain and erythema, proptosis, pain with eye movements, movement restriction/diplopia, vision changes) should prompt urgent ophthalmology referral • In the absence of warning signs, start warm compresses and lubrication drops and refer to ophthalmology, especially if symptoms do not improve	✓ URGENT if warning signs
PULMONARY			
Pneumonitis			
Grade	**CTCAE description**	**Management**	**Specialist referral?**

1	Asymptomatic; clinical or diagnostic observations only	• Consider holding ICI
		• Consider pulmonary and infectious disease consultations
		• Reimage at least prior to every cycle of ICI treatment (at least every 3 weeks)
		  o If repeat imaging shows resolution of radiographic findings, no further CT imaging is necessary; resume therapy with close follow-up
		  o If evidence of progression, treat at higher grade
		  o If no change, consider continued therapy with close follow-up for new symptoms
		• If symptoms develop, treat at higher grade
		• Self-monitor symptoms and oxygen saturation (using personal pulse oximeter) every 2-3 days; weekly clinic visits
		• If chest imaging abnormalities resolve, consider resuming treatment with close follow-up
			✓

2	Symptomatic; limiting instrumental ADL; medical intervention indicated	• Hold ICI • Consider hospitalization • Pulmonary consultation for bronchoscopy with bronchoalveolar lavage. Consider biopsies for atypical lesions • Initiate methylprednisolone 1 mg/kg/day (IV or oral equivalent)	✓ (pulmonary and infectious disease)

		○ Day 2-3 of corticosteroids/supportive care: If symptoms improve to ≤Grade 2, start slow steroid taper over >1 month. If symptoms do not improve, or worsen, treat as Grade 3-4 • Consider drug re-challenge if symptoms and imaging abnormalities resolve	
3	Severe symptoms; limiting self-care ADL; oxygen indicated	• Permanently discontinue ICI • Hospitalize; consider ICU care	✓
4	Life-threatening respiratory compromise; urgent intervention indicated (eg, intubation)	• Pulmonary consultation for bronchoscopy with bronchoalveolar lavage. Consider biopsies for atypical lesions • Initiate methylprednisolone IV, 2 mg/kg/day • Day 2-3 of corticosteroids/supportive care: ○ If no clinical improvement, add infliximab or cyclophosphamide, mycophenolate mofetil or IVIG ○ If clinical improvement: reduce corticosteroids to 1 mg/kg/day and slowly taper over >2 months. • Drug re-challenge: ○ Grade 3: Consider drug re-challenge on a case-by-case basis after discussions weighing benefit/risk with the patient and only if symptoms and imaging abnormalities resolve ○ Grade 4: Permanently discontinue ICI	✓ (pulmonary and infectious disease)
Notes: 1. Consider prophylactic antibiotics for PCP for patients receiving at least 20 mg methylprednisolone or equivalent for ≥4 weeks 2. Consider calcium and vitamin D supplementation with prolonged steroid use 3. All patients with Grade 2-4 pneumonitis receiving steroids should also be on proton pump inhibitor therapy for GI prophylaxis 4. T-spot testing should be undertaken to exclude tuberculosis in any patient being considered for anti-TNF therapy, prior to starting anti-TNF treatment.			
Sarcoidosis			
Grade	**CTCAE description**	**Management**	**Specialist referral?**
1	Not defined in CTCAE	• Consider holding ICI • Close follow-up	✓
≥2		• Consider corticosteroids • Hold ICI	✓

		• Consider corticosteroid therapy for patients with sarcoidosis Grade 2 or higher and any of the following: o progressive radiographic change o persistent and/or troublesome pulmonary symptoms o lung function deterioration: TLC decline of ≥10%, FVC decline of ≥15%; DLCO decline of ≥20% o concomitant involvement of critical extrapulmonary organ systems o sarcoid-related hypercalcemia • Corticosteroid dose: prednisone 1 mg/kg (or IV equivalent of methylprednisolone) for Grade 2 sarcoidosis or severe cases requiring hospitalization. Taper steroids over 2-4 months, depending on response	
Note: To date, there are no studies focusing on management of sarcoidosis as a side effect of checkpoint inhibitor therapy. Current recommendations are based on clinical experience and case report publications.			
RHEUMATOLOGIC/MUSCULOSKELETAL[8]			
Inflammatory arthritis			
Grade	**CTCAE description (Note 1)**	**Management**	**Specialist referral?**
1	Mild pain with inflammatory symptoms (Note 2), erythema, or joint swelling (Note 3)	• Continue ICI • Analgesics: NSAIDs: naproxen 500 mg BID or meloxicam 7.5-15 mg daily orally for 4-6 weeks • If NSAIDs ineffective, consider prednisone 10-20 mg daily for 2-4 weeks • Consider intra-articular corticosteroid injection only if ≤2 joints affected and low dose prednisone (10 mg/day) and NSAIDs not effective • If no improvement in 2-4 weeks, escalate to Grade 2 management • Conduct serial rheumatologic examinations (2 weeks, 4 weeks, then 4-6 weekly) and functional assessment at follow-up	
2	Moderate pain associated with signs of inflammation, erythema, or joint swelling; limiting instrumental ADL	• Consider holding ICI • Rheumatology referral to confirm inflammatory arthritis, assess need for intra-articular injection and examine for signs of early bone damage	✓

		• Prednisone 20 mg daily for 2-4 weeks, increase to 1 mg/kg/ day, or equivalent. If no response in 2-4 weeks. Escalate to Grade 3 management • If symptoms improve, taper corticosteroid over 4-8 weeks or until Grade 1	
3	Severe pain associated with signs of inflammation, erythema, or joint swelling; irreversible joint damage (eg, erosion); disabling; limiting self-care ADL	• Hold ICI • Rheumatology referral • Prednisone 1 mg/kg/day or equivalent for 2-4 weeks, or until symptoms improve to Grade 1 • Consider additional immunosuppression (Note 4) (eg, methotrexate [Note 5], sulfasalazine, leflunomide). Consider anti-cytokine therapy (eg, TNF-inhibition) [Note 6] • If symptoms improve, taper corticosteroid over 4-8 weeks/until Grade 1; if symptoms do not improve in 4-6 weeks: permanently discontinue ICI	✓

Notes:
1. CTCAE includes separate listings for arthritis, joint effusion and arthralgia although there is overlap in presenting symptoms such as pain and effects on ADL
2. Joint stiffness after sleep or inactivity, improvement of symptoms with movement or heat.
3. Joint swelling refers to the clinical finding on examination, and may encompass soft tissue swelling, joint effusion or synovitis.
4. Before initiation of these drugs, screening for hepatitis B and C should be performed.
5. Methotrexate should be administered at a starting dose of 15 mg weekly, with daily folic acid supplementation. Titrate up to a maximum of 25 mg weekly, or switch to injectable methotrexate if patient cannot tolerate orally.
6. Before anti-cytokine therapy, evaluation for latent/active TB should be performed.

Peripheral motor and sensory neuropathy

Grade	CTCAE description	Management	Specialist referral?
1	Asymptomatic; clinical or diagnostic observations only	• Continue ICI • Consider permanent discontinuation of ICI if AE worsens or does not improve	
2	Moderate symptoms; limiting instrumental ADL	• Hold ICI • Refer to neurology • Consider permanent discontinuation of ICI if AE worsens or does not improve	✓
3	Severe symptoms; limiting self-care ADL	• Permanently discontinue ICI	✓

4	Life-threatening consequences; urgent intervention indicated	• Start 1-2 mg/kg/day methylprednisolone equivalents IV, and prophylactic antibiotics	
Note: CTCAE provides grading criteria for peripheral motor neuropathy and sensory motor neuropathy. For all these irAEs, ICI therapy may be continued for Grade 1 irAEs. However, ≥Grade 2 events require an ICI hold and referral to neurology. For events of ≥Grade 3 severity, ICI therapy should be permanently discontinued and IV corticosteroids administered.			

ACTH=adrenocorticotropic hormone; ADL=activities of daily living; AE=adverse event; ALT=alanine aminotransferase; ANC=absolute neutrophil count; AST=aspartate transaminase: BID=twice daily; BM-bowel movements; BNP=B-type natriuretic peptide; CBC=complete blood count; CMP=comprehensive metabolic panel; CRP=C-reactive protein; CRS=cytokine release syndrome; CT=computed tomography; CTCAE=Common Terminology Criteria for Adverse Events; DIC=disseminated intravascular coagulation; DLCO=diffusing capacity of the lungs for carbon monoxide; DM=diabetes mellitus; ECG=electrocardiogram; ESR=erythrocyte sedimentation rate; FVC=forced vital capacity; GABA=gamma-aminobutyric acid; GI=gastrointestinal; HC=hydrocortisone; ICI=immune checkpoint inhibitors; ICU=intensive care unit; IV=intravenous; IVIG=intravenous immunoglobulin; LLN=lower limit of normal; MRI=magnetic resonance imaging; NSAIDs=non-steroidal anti-inflammatory drugs; PCP=pneumocystis pneumonia; PLT=platelet; PO=per oral; PRES=posterior leukoencephalopathy syndrome; QID=4 times a day; SITC=Society of Immunotherapy of Cancer; TB=Tuberculosis; TLC=total lung capacity; TNF=tumor necrosis factor; TSH=thyroid stimulating hormone; ULN=upper limit of normal.

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2. SERVICES., U.S.D.O.H.A.H., Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0. 27 November 2017. https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_8.5x11.pdf
3. Bird BR, Swain SM. Cardiac toxicity in breast cancer survivors: review of potential cardiac problems. Clin Cancer Res. 2008;14(1):14-24.
4. Lurz P, et al. Diagnostic performance of CMR imaging compared with EMB in patients with suspected myocarditis. JACC Cardiovasc Imaging. 2012;5(5):513-24.
5. Berman D, et al. Blockade of cytotoxic T-lymphocyte antigen-4 by ipilimumab results in dysregulation of gastrointestinal immunity in patients with advanced melanoma. Cancer Immun. 2010;10:11.
6. Weber J, et al. A randomized, double-blind, placebo-controlled, Phase II study comparing the tolerability and efficacy of ipilimumab administered with or without prophylactic budesonide in patients with unresectable Stage III or IV melanoma. Clin Cancer Res. 2009;15(17):5591-8.
7. Pages C, et al. Ipilimumab-induced acute severe colitis treated by infliximab. Melanoma Res. 2013;23(3):227-30.
8. Naidoo J, et al. Inflammatory arthritis: a newly recognized adverse event of immune checkpoint blockade. Oncologist. 2017;22(6):627-30.

5.6.3 Atezolizumab Specific Recommendations:

For detailed specific safety information about atezolizumab, please refer to the atezolizumab Investigators Brochure, including any associated addenda.

As outlined in Section 5.6.1, there will be no dose reductions of atezolizumab however atezolizumab may be delayed for toxicity as described in Table 5-5.

Given the mechanism of action of atezolizumab, immune-mediated reactions are considered a potential risk when given in combination with other immunomodulating agents. Immune-mediated reactions may involve any organ system and may lead to hemophagocytic lymphohistiocytosis and macrophage activation syndrome, which are rare conditions characterized by an excessive immune response.

Immune-mediated reactions should be included in the differential diagnosis for patients who, in the absence of an alternate etiology, develop a sepsis-like syndrome after administration of atezolizumab, and the initial evaluation should include the following:

- Complete blood count with peripheral smear
- Partial thromboplastin, partial thromboplastin time, fibrinogen, and D-dimer
- Ferritin
- Triglycerides
- AST, ALT and total bilirubin
- LDH
- Complete neurologic and abdominal examination (assess for hepatosplenomegaly)

If immune-mediated reactions are still suspected after the initial evaluation, contact the Medical Monitor for additional recommendations.

If any irAEs occur and treatment with steroids is required until resolution or improvement of the condition to CTCAE **v5** Grade 1 or baseline and patients will be tapered off steroids, atezolizumab may be withheld for additional time from the last dose until steroids are discontinued or reduced to prednisone dose (or dose equivalent) ≤10 mg/day.

5.7 Concomitant Medication and Dietary Supplements

Concomitant therapies and supplements that are permitted, prohibited or restricted during the study are summarized in Table 5-6. All concomitant medications, vaccines (including SARS-CoV-2 vaccines) and supplements used during the study must be documented in the Prior/Concomitant Medication eCRF.

For SARS-CoV-2 vaccinations, report the following in the appropriate pages of the eCRF:

- Information on each administration of SARS-CoV-2 vaccine. Each injection of SARS-CoV-2 vaccine must be reported as separate entries, including the vaccine name, dose and date of injection (Prior/Concomitant Medication eCRF).
- Any observed AE following administration of the SARS-CoV-2 vaccine during the study treatment period (Adverse Events eCRF).
- COVID-19 antibody titers, if measured after vaccination and available (Unscheduled Local Lab Results eCRF).

Table 5-6: Permitted/Prohibited Concomitant Medications

Medication/class of drug	Usage guidelines/restrictions
Erythroid stimulating agents (eg, erythropoietin)	Patients already receiving erythropoietin at the time of screening for the study may continue it providing they have been receiving it for at least 2 weeks before study treatment is started and the patient is on a stable dose. Prophylactic erythropoietin should not be started during Cycle 1 of the study but may be started during Cycle 2 and after.
Immunosuppressive medications (including, but not limited to systemic corticosteroids at doses beyond 10 mg/day of prednisone or equivalent, methotrexate, azathioprine and TNFα blockers)	Generally prohibited from the time that patients enter the screening period until the last dose of study treatment. However, use of immunosuppressive medications for the management of investigational product-related AEs and in patients with contrast allergies is acceptable. In these cases, such medications may be used when needed and their use should be documented.
Any investigational therapy other than the protocol specified therapies	Prohibited from within 4 weeks prior to the first dose of study treatment until the last dose of study treatment.
Any concurrent chemotherapy, radiotherapy (except palliative radiotherapy), immunotherapy, biologic or hormonal therapy for cancer treatment	Prohibited from within 2 weeks prior first dose of study treatment until the last dose of study treatment. For cytotoxic agents, that have major delayed toxicity, eg, mitomycin C and nitrosoureas, 4 weeks is indicated as washout period
Herbal preparations/medications (including, but not limited to: St. John's Wort, kava, ephedra (ma huang), gingko biloba, dehydroepiandrosterone, yohimbe, saw palmetto, and ginseng)	Prohibited from the time that patients enter the screening period until the last dose of study treatment. Patients should stop using these herbal medications 7 days prior to first dose of study treatment (3 weeks for St John's Wort)
Warfarin and other long acting anticoagulants with a half-life of >12 hours	Prohibited from the time that patients enter the screening period until the last dose of study treatment.
Vaccines against infectious diseases	Use of any live or live attenuated vaccine against infectious diseases (examples include, but are not limited to, intranasal influenza, measles, mumps, rubella, oral polio, Bacillus Calmette-Guérin vaccine, rotavirus, varicella, yellow fever, TY21a typhoid vaccines etc) are prohibited within 4 weeks prior to the first dose of study treatment, during the study, and for 3 months after the last dose of study treatment. SARS-CoV-2 vaccines authorized for use by the competent local regulatory health authorities for active immunization to prevent COVID-19 are allowed (unless the vaccine is live or live attenuated) and must be given in accordance with the prevailing immunization guidelines. SARS-CoV-2 vaccination may be given at least 7 days prior to the planned first dose of study treatment. Otherwise, administer SARS-CoV-2 vaccine with at least a 7 day period before and after study treatment. Administer study treatment only if vaccine-related AEs have improved to Grade ≤1. Please report any SARS-CoV-2 vaccine-related AEs in the Adverse Events eCRF as "post-SARS-CoV-2 vaccine AEs" (eg, post-SARS-CoV-2 vaccine fever) and/or, SARS-CoV-2 vaccine site reaction(s) (eg, post-SARS-CoV-2 vaccine site pain or post-SARS-CoV-2 vaccine site erythema) (refer to Section 7 for further instructions on AE reporting).

Medication/class of drug	Usage guidelines/restrictions
Inhaled, intranasal, topical and ophthalmic and corticosteroids	Concurrent use is acceptable
Hormones for noncancer-related conditions (eg, insulin for diabetes and hormone replacement therapy)	Concurrent use is acceptable
Local treatment of isolated lesions for palliative intent (eg, by local surgery or radiotherapy)	Concurrent treatment is acceptable
Low molecular weight heparin	Concurrent treatment is acceptable
Blood transfusions	Allowed at any time during the study

AE=adverse event; COVID-19=coronavirus disease 2019; eCRF=electronic Case Report Form; TNFα=tumor necrosis factor alpha; SARS-CoV-2=Severe Acute Respiratory Syndrome Coronavirus 2.

5.8 Lifestyle Restrictions

The following restrictions (according to the CTFG (Clinical Trial Facilitation Group) Recommendations Related to Contraception and Pregnancy Testing in Clinical Trials in Women of Childbearing Potential apply while the patient is receiving study treatment and for the specified times before and after:

1. Females of childbearing potential must use two highly effective methods of contraception from the time of screening until 5 months after discontinuing study treatment, or longer, depending on the PK of KY1044 (contraception must be maintained for at least 5 half-lives).
   Acceptable methods of contraception include true sexual abstinence when this is in line with the preferred and usual lifestyle of the patient, tubal ligation, hormonal contraceptives that are not prone to drug-drug interactions (for example Levonorgestrel Intra Uterine System [Mirena], medroxyprogesterone injections [Depo Provera]), copper-banded intra-uterine devices and vasectomized partner. Periodic abstinence (eg, calendar, ovulation, symptothermal, post-ovulation methods), declaration of abstinence for the duration of a trial, and withdrawal are not acceptable methods of contraception. All methods of contraception must be used in combination with the use of a condom by their male sexual partner for intercourse.
2. Male patients must avoid unprotected sex with all sexual partners (by use of condoms) during the study, and for a washout period of at least 5 months after the last dose of IMP, depending on the PK of KY1044. A condom is also required to be used by vasectomized men in order to prevent delivery of the drug via seminal fluid. Where a sexual partner of a male participant is a woman of childbearing potential, patients must avoid procreation for at least 5 months after completion of treatment with IMP. Patients must refrain from donating sperm from the start of dosing until at least 5 months after discontinuing study treatment. If male patients wish to father children during the study period they should be advised to arrange for freezing of sperm samples prior to the start of study treatment.

5.9 Patient Numbering and Treatment Assignment

Patients will be assigned to two treatments groups in this study, KY1044 as single agent or in combination with atezolizumab in an open-label manner. Allocation of the IMP kits during the study period will be done via IXRS.

Phase 1: The assignment of a patient to a particular cohort during the Phase 1 dose escalation or enrichment components (KY1044 as single agent or in combination with atezolizumab) will be coordinated in IXRS in accordance with the Cohort Management Plan.

Patients will be identified with unique patient numbers assigned by IXRS at the time of screening and then at enrolment. Enrolment number will start with the digit "1" indicating that the patient is being treated in Phase 1 of the study, in addition to a digit indicating a cohort to which the patient was allocated and an arm of treatment (KY1044 single agent or in combination with atezolizumab). Enrolment number will identify the patient in all study databases including eCRF, central laboratory, central imaging and ECG and will be linked to the patient's name in an identification list retained in the Investigator's Site File.

Phase 2: The assignment of a patient to a particular group during the Phase 2 will be based on tumor indication and history of anti-PD-(L)1 treatment (Figure 3-1). In the initial Phase 2 dose assessment part, two biologically relevant dose levels of KY1044 (as single agent or in combination with atezolizumab) that have been determined to be safe in Phase 1 will be explored in one or more indication(s). In the Phase 2 expansion component, patients will receive the RP2D of KY1044 as single agent or in combination with atezolizumab that was established during the Phase 1 dose escalation and/or enrichment component and/or the initial Phase 2 dose assessment part of the study.

Patients will be identified with unique subject numbers assigned by IXRS at the time of screening and then at enrolment. Enrolment number will start with the digit "2" indicating that the patient is being treated in Phase 2 of the study, in addition to a digit indicating an arm of treatment (KY1044 single agent or in combination with atezolizumab). Enrolment number will identify the patient in all study databases including eCRF, central laboratory, central imaging and ECG and will be linked to the patient's name in an identification list retained in the Investigator's Site File.

5.10 Supply, Packaging, Labelling and Storage

IMPs are KY1044 and atezolizumab, both of which will be provided by the Sponsor to the investigational site as open-label liquid solutions in vials.

KY1044 drug substance has been manufactured in accordance with current Good Manufacturing Practice (GMP) at Lonza Biologics plc, Slough, UK, and subsequently KY1044 drug product has been manufactured by Nova Laboratories Ltd, Leicester, UK.

Atezolizumab drug product has been manufactured in accordance with current GMP and supplied by F Hoffman-La Roche.

Both IMPs (KY1044 and atezolizumab) will be labelled, packaged and distributed by PCI Clinical Services. Labelling will be done in accordance with GMP guidelines and regulatory requirements of each country participating in the study. Investigational sites will supply all ancillary supplies as detailed in the pharmacy manual, including all materials required for the preparation and administration of KY1044 and atezolizumab doses.

After release procedures have been completed in accordance with regulatory requirements and as needed thereafter, IMPs will be shipped with temperature monitoring devices to the responsible person at the investigational site pharmacy.

IMP delivered to sites, and prepared doses, must be maintained at 2 to 8°C and stored in a secure environment ie, with restricted access, and in accordance with any locally applicable regulations. Before administration, prepared doses of the IMP need to be brought to room temperature at least 1 hour before administration.

Details of procedures for the receipt, storage, and management of IMP supplies are provided in the Pharmacy Manual.

5.11 IMP Accountability Records

The Investigator is responsible for accountability of all used and unused supplies of KY1044 and atezolizumab at the site.

IMP accountability forms will be completed by the Investigator and filed in the Investigator Site File (ISF). The IMP accountability forms will be kept current and will contain the dates and quantities of drugs received at site, and details of disposition of all drug received and preparation of individual doses.

At the end of the study, a final IMP reconciliation statement must be completed by the Investigator and provided to the Sponsor.

All IMP accountability forms must be made available for inspection by the clinical monitor, the Sponsor or representatives of the Sponsor, and regulatory agency inspectors.

At the end of the study, or at intervals confirmed by the Sponsor, and after the accountability has been verified, all IMP supplies including unused, partially used, or empty containers, will be destroyed locally according to the site requirements and local regulations or returned as directed by the Sponsor. Proof of delivery, certificates of destruction and/or IMP return documentation will be filed in the eTMF.

5.12 Procedures for Monitoring Patient Compliance

The Investigator or designee is responsible for the administration of the IMPs. The monitor will assess compliance throughout the study by reviewing drug reconciliation/accountability records on a periodic basis as outlined in the monitoring plan and guidelines.

6 STUDY ASSESSMENTS

The schedule of procedures and assessments during the study is summarized and presented in Table 6-1 (Phase 1) and Table 6-2 (Phase 2).

Table 6-1: Phase 1 Assessments

Visit name	Screening	Cycle 1 (21 days; study Day 1-21; Week 1-3)						Cycle 2 (21 days; study Day 22-42; Week 4-6)				Cycle 3 (21 days; study Day 43-63; Week 7-9)					Cycle 4 (21 days) and all Cycles up to 48 months (4 years)		EOT[v] (up to 21 days after the last study dose)	Safety follow-up visit (90 days after the last study dose)
Day of cycle	-28 to -1	C1D1		C1D2	C1D8	C1D11	C1D15	C2D1		C2D8	C2D15	C3D1		C3D8	C3D11	C3D15	C4D1 and CXD1			
		pre-dose	post-dose					pre-dose	post-dose			pre-dose	post-dose				pre-dose	post-dose		
Obtain Informed Consent	X																			
Obtain pharmacogenomic informed consent	X																			
Hospital admission[a]		X																		
IXRS	X	X[b]						X[b]				X[b]					X[b]		X	
Demography	X																			
Inclusion/ exclusion criteria	X	X																		
Medical History[c]	X																			
Height	X																			
Weight	X	X						X				X					X		X	
Physical examination[d]	X	X						X				X					X		X	
Vital signs[e]	X	X	X	X				X	X			X					X		X	
ECOG performance	X	X						X				X					X		X	
Oxygen saturation test	X																			

Visit name	Screening	Cycle 1 (21 days; study Day 1-21; Week 1-3)						Cycle 2 (21 days; study Day 22-42; Week 4-6)				Cycle 3 (21 days; study Day 43-63; Week 7-9)					Cycle 4 (21 days) and all Cycles up to 48 months (4 years)		EOT[v] (up to 21 days after the last study dose)	Safety follow-up visit (90 days after the last study dose)
Day of cycle	-28 to -1	C1D1		C1D2	C1D8	C1D11	C1D15	C2D1		C2D8	C2D15	C3D1		C3D8	C3D11	C3D15	C4D1 and CXD1			
		pre-dose	post-dose					pre-dose	post-dose			pre-dose	post-dose				pre-dose	post-dose		
Cardiac markers[f]	X																			
12-Lead ECG[g]	X	X	X									X	X						X	
Review AE	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Review Concomitant Medications	X	X						X				X					X		X	X
Hematology	X	X[h]		X[h]	X[h]		X[h]	X[h]		X[h]	X[h]	X[h]		X[h]			X[h]		X	
Clinical Chemistry	X	X[h]			X[h]		X[h]	X[h]		X[h]	X[h]	X[h]		X[h]			X[h]		X	
Fasting lipid profile[i]	X																			
Coagulation (aPTT, INR)	X	X[h]						X[h]				X[h]					X[h]		X	
HbA1c[j]	X																		X	
Urinalysis	X	X						X				X					X		X	
Pregnancy test[k]	X	X						X				X					X		X	
Thyroid function[l]	X											X							X	
Viral testing, HIV, HBV, HCV[m]	X																			
Auto-Abs[n]	X							X									X		X	
Anti-KY1044 and Anti-atezolizumab (ADA)[o]		X						X				X					X			X

Visit name	Screening	Cycle 1 (21 days; study Day 1-21; Week 1-3)						Cycle 2 (21 days; study Day 22-42; Week 4-6)				Cycle 3 (21 days; study Day 43-63; Week 7-9)					Cycle 4 (21 days) and all Cycles up to 48 months (4 years)		EOT[v] (up to 21 days after the last study dose)	Safety follow-up visit (90 days after the last study dose)
Day of cycle	-28 to -1	C1D1		C1D2	C1D8	C1D11	C1D15	C2D1		C2D8	C2D15	C3D1		C3D8	C3D11	C3D15	C4D1 and CXD1			
		pre-dose	post-dose					pre-dose	post-dose			pre-dose	post-dose				pre-dose	post-dose		
PK (KY1044)[p]		X	X	X	X	X	X	X	X			X	X	X	X	X	X	X	X	X
PK (atezolizumab)[p]		X	X					X	X			X	X				X	X	X	X
RNA signature from PBMC (Nanostring)		X			X			X		X										
Fresh tumor biopsy[q]	X									X										
PBMC FACS or ChipCytometry analysis		X			X			X		X										
ICOS Receptor Occupancy (PBMC)[r]		X			X			X		X										
Plasma cytokine /chemokine panel		X		X	X			X	X[s]	X		X	X	X						
Serological tumor markers[t]	X	X						X				X					X		X	
Tumor Imaging RECIST 1.1[u]	X													X						
KY1044 administration[w]		X						X				X					X			
Atezolizumab administration (only for patients on combination therapy)		X						X				X					X			

A window of 3 days is permissible to complete Day 1 assessments, a window of 1 day is permissible to complete all other assessments

a After receiving the first infusion in Phase 1, patients will be either hospitalized or remain in the clinic for at least 6 to 8 hours until the last assessments. They will be provided with instructions for after hour care as per institutional standard and will return to the clinic on C1D2. Patients should remain in the clinic for at least 3 hours at all other visits where infusions are given.

b IXRS contact can be performed prior to the patient's CXD1 visit to receive treatment allocation.

c Medical History including date of diagnosis and dates and extent of cancer, prior antineoplastic therapies (chemotherapies, targeted agents, radiation, surgery) and current concomitant medication (including SARS-CoV-2 vaccines).

d Complete physical examination should be performed at screening and at the EOT. This should also include a full dermatological examination (complete skin and mucosal exam). Abbreviated physical examination will be performed every cycle (see Section 6.5.2).

e Vital signs: during Cycles 1 and 2, blood pressure (BP) and HR will be monitored in the clinic every 15 minutes during the infusions of study treatment and every 30 minutes inbetween the infusions (for combination therapy) and 60 min after the last infusion of study treatment and before the patients are discharged from the hospital on Cycle 1 Day 2. See Section 6.5.7.

f Cardiac markers at screening will include: Baseline Troponin I for all patients. Additionally, N-terminal pro B-type natriuretic peptide (NT-pro-BNP) will only be taken for patients with a history of cardiac disease (according to exclusion criteria). Repeated assessments of cardiac markers during the study will be performed only when clinically indicated .

g ECGs will be taken pre- and post-dose at Cycles 1, 3 and 6 as close as possible to the relevant PK timepoints (see Section 6.5.8). In the event of abnormal ECG findings and if clinically indicated, an unscheduled PK sample should be collected and Troponin I , together with assessments for CK, CK-MB, AST and lactate dehydrogenase (LDH). NT-pro-BNP should be measured together with the other cardiac markers as outlined above only in patients with previous cardiac complications at screening.

h All samples will be analyzed centrally. On the occasions marked [h] only, duplicate samples for immediate access to key safety laboratory parameters (hematology, clinical chemistry and coagulation) will be analyzed at local labs as well.

i At screening, clinical chemistry includes collection of a fasting lipid profile sample.

j HbA1c should be measured every 12 weeks throughout the study and will be assessed at EOT only if the previous assessment has not been performed within the last 3 months.

k Serum pregnancy test (β-HCG) will be performed at screening. Urine dipstick test will be performed at all other visits.

l Thyroid function includes free T4 and TSH and the analyses will be repeated every 3 cycles and at EOT.

m Virology testing will be performed at screening for HIV, HBV and HCV. In patients, who are known to be positive for HBV and HCV, tests will be repeated every cycle pre-dose and a confirmatory sample should be taken when clinically indicated. See Section 6.5.9 for more details.

n Auto-antibodies include: anti-DNA, anti-nuclear, anti-mitochondrial and anti-phospholipid antibodies and Rheumatoid factor (RF) and acetyl-choline receptor antibodies (AChR). When a blood sample is positive for ANA (ie, titer >40) it will be tested for antibodies against extractable nuclear antigens. Samples for auto-antibody analyses will be collected at screening, every second cycle pre-dose for the first six cycles (C2, C4, C6), then every 12 weeks up to 48 months of treatment, when clinically indicated and at EOT.

o ADA samples should be collected at every cycle at pre-dose on Day 1 and unscheduled at any time, when clinically indicated. For detailed ADA sample collection schedule see Section 6.4.2.

p PK samples will be taken pre- and post-dose during all cycles and unscheduled at any time, when clinically indicated. For detailed PK analysis timings please refer to Section 6.4.2.
Note: On days and timepoints when biomarker and pharmacokinetic blood samples are being collected, the PK sample must be drawn first. For further details please see schedule of PK assessments in Section 6.4.2 and biomarker assessments in Section 6.3.1.

q In patients with measurable disease, a fresh tumor biopsy should be taken once other screening investigations strongly suggest the patient is likely to be eligible, to avoid unnecessary risk of biopsy for a patient who is not going to be eligible. Where a prior (archival) biopsy is available that is less than 3 months old this may be substituted for a fresh tumor biopsy at screening. A fresh tumor biopsy is mandatory on treatment (C2D8). Where feasible, collection of a tumor biopsy at progression is encouraged.

r Samples for the analysis of ICOS Receptor Occupancy will be collected from patients on KY1044 single agent only.

s Plasma sample for cytokine analysis post dose timepoint is 6 to 8 hours post-infusion on C2D1 and C3D1. Unscheduled sample may be collected if required.

t Blood sample for measurement of serological tumor markers will be taken at screening, pre-dose of every cycle and EOT only for those patients that have tumors with correlative serological markers.

u Tumor Imaging RECIST 1.1 assessment is done every 8 weeks (±7 days) after the start of treatment for the first 16 weeks, after that every 12 weeks (±7 days) for 48 months of treatment duration or until objective disease progression; visit window for assessment is ±7 days. In case of progression of disease without clear clinical signs of progression, the patient should continue

treatment. In this case a confirmatory scan should be scheduled 4 to 8 weeks later as per iRECIST guidelines. The thorax CT/ magnetic resonance imaging (MRI) scan performed at screening as part of the RECIST assessment will document the lung parenchyma status.

v Please see Section 8.1 for details of follow up after end of treatment visit.

w KY1044 is always to be administered first followed by a saline solution flush to empty the line as described in the pharmacy manual. For the combination part, a slow saline infusion will continue (after this saline flush) for approximately 1 hour before starting the atezolizumab infusion at the same infusion site. There should be a period of at least 1 hour after the infusion(s) is complete whereby the patient requires close observation as outlined in Section 5.2.2.

Table 6-2: Phase 2 Assessments

Visit name	Screening	Cycle 1 (21 days; study Day 1-21; Week 1-3)				Cycle 2 (21 days; study Day 22-42; Week 4-6)				Cycle 3 (21 days; study Day 43-63; Week 7-9)			Cycle 4 (21 days) and all Cycles up to 48 months (4 years)		EOT[u] (up to 21 days after the last study dose)	Safety follow-up visit (90 days after the last study dose)
Day of cycle	-28 to -1	C1D1		C1D8	C1D15	C2D1		C2D8	C2D15	C3D1		C3D8	C4D1 and CXD1			
		pre-dose	post-dose			pre-dose	post-dose			pre-dose	post-dose		pre-dose	post-dose		
Obtain Informed Consent	X															
Obtain pharmacogenomic informed consent	X															
IXRS	X	X[a]				X[a]				X[a]			X[a]		X	
Demography	X															
Inclusion/ exclusion criteria	X	X														
Medical History[b]	X															
Height	X															
Weight	X	X				X				X			X		X	
Physical examination[c]	X	X				X				X			X		X	
Vital signs[d]	X	X	X			X	X			X			X		X	
ECOG performance	X	X				X				X			X		X	
Oxygen saturation test	X															
Cardiac markers[e]	X															
12-Lead ECG[f]	X	X	X							X	X				X	

Visit name	Screening	Cycle 1 (21 days; study Day 1-21; Week 1-3)				Cycle 2 (21 days; study Day 22-42; Week 4-6)				Cycle 3 (21 days; study Day 43-63; Week 7-9)			Cycle 4 (21 days) and all Cycles up to 48 months (4 years)		EOT[u] (up to 21 days after the last study dose)	Safety follow-up visit (90 days after the last study dose)
Day of cycle	-28 to -1	C1D1		C1D8	C1D15	C2D1		C2D8	C2D15	C3D1		C3D8	C4D1 and CXD1			
		pre-dose	post-dose			pre-dose	post-dose			pre-dose	post-dose		pre-dose	post-dose		
Review AE	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Review Concomitant Medications	X	X				X				X			X		X	X
Hematology	X	X[g]		X[g]	X[g]	X[g]		X[g]	X[g]	X[g]		X[g]	X[g]		X	
Clinical Chemistry	X	X[g]		X[g]	X[g]	X[g]		X[g]	X[g]	X[g]		X[g]	X[g]		X	
Fasting lipid profile[h]	X															
Coagulation (aPTT, INR)	X	X[g]				X[g]				X[g]			X[g]		X	
HbA1c[i]	X														X	
Urinalysis[j]	X	X				X				X			X		X	
Pregnancy test[k]	X	X				X				X			X		X	
Thyroid function[l]	X									X					X	
Viral testing, HIV, HBV, HCV[m]	X															
Auto-Abs[n]	X					X							X		X	
Anti-KY1044 and Anti-atezolizumab (ADA)[o]		X				X				X			X			X
PK (KY1044)[p]		X	X			X	X			X	X		X	X	X	X
PK (atezolizumab)[p]		X	X			X	X			X	X		X	X	X	X

Visit name	Screening	Cycle 1 (21 days; study Day 1-21; Week 1-3)				Cycle 2 (21 days; study Day 22-42; Week 4-6)				Cycle 3 (21 days; study Day 43-63; Week 7-9)			Cycle 4 (21 days) and all Cycles up to 48 months (4 years)		EOT[u] (up to 21 days after the last study dose)	Safety follow-up visit (90 days after the last study dose)
Day of cycle	-28 to -1	C1D1		C1D8	C1D15	C2D1		C2D8	C2D15	C3D1		C3D8	C4D1 and CXD1			
		pre-dose	post-dose			pre-dose	post-dose			pre-dose	post-dose		pre-dose	post-dose		
RNA signature from PBMC (Nanostring)		X		X		X		X								
Fresh tumor biopsy[q]	X							X								
PBMC FACS or ChipCytometry analysis		X		X		X		X								
Plasma cytokine /chemokine panel		X	X[r]	X		X	X[t]	X		X	X	X				
Serological tumor markers[s]	X	X				X				X			X		X	
Tumor Imaging RECIST 1.1[t]	X											X				
KY1044 administration[v]		X				X				X			X			
Atezolizumab administration (only for patients on combination therapy)		X				X				X			X			

A window of 3 days is permissible to complete Day 1 assessments, a window of 1 day is permissible to complete all other assessments

a IXRS contact can be performed prior to the patient Day 1 visit to receive treatment allocation.
b Medical History including date of diagnosis and extent of cancer, prior antineoplastic therapies (chemotherapies, targeted agents, radiation, surgery) and current concomitant medication (including SARS-CoV-2 vaccines).
c Complete physical examination should be performed at screening and at the EOT. This should also include a full dermatological examination (complete skin and mucosal exam). Abbreviated physical examination will be performed every cycle.

d Vital signs: during Cycles 1 and 2, BP and HR will be monitored in the clinic every 15 minutes during the infusions of study treatment and every 30 minutes inbetween the infusions (for combination therapy), 60 min after the last infusion of study treatment. See Section 6.5.7.

e Cardiac markers at screening will include: Baseline Troponin I for all patients. Additionally, N-terminal pro B-type natriuretic peptide (NT-pro-BNP) will only be taken for patients with a history of cardiac disease (according to exclusion criteria). Repeated assessments of cardiac markers during the study will be performed only when clinically indicated.

f ECGs will be taken pre- and post-dose at Cycles 1, 3 and 6 as close as possible to each of the PK timepoints (see Section 6.5.8). In the event of abnormal ECG findings and if clinically indicated, an unscheduled PK sample should be collected and Troponin I, together with assessments for CK, CK-MB, AST and LDH. NT-pro-BNP should be measured together with the other cardiac markers as outlined above only in patients with previous cardiac complications at screening.

g All samples will be analyzed centrally. On the occasions marked [g] only, duplicate samples for immediate access to key safety laboratory parameters (hematology, clinical chemistry and coagulation) will be analyzed at local labs as well.

h At screening, clinical chemistry includes collection of a fasting lipid profile samplI.

i HbA1c should be measured every 12 weeks throughout the study and will be assessed at EOT only if the previous assessment has not been performed within the last 3 months.

j Urinalysis will include pH, protein, glucose, ketones, blood and urine dipstick pregnancy test.

k Serum pregnancy test (β-HCG) will be performed on screening. Urine dipstick test will be performed at all other visits.

l Thyroid function includes free T4 and TSH and the analyses will be repeated every 3 cycles and at EOT.

m Virology testing will be performed at screening for HIV, HBV and HCV. In patients, who are known to be positive for HBV and HCV, tests will be repeated every cycle pre-dose and a confirmatory sample should be taken when clinically indicated. See Section 6.5.9 for more details.

n Auto-antibodies include: anti-DNA, anti-nuclear, anti-mitochondrial and anti-phospholipid antibodies and Rheumatoid factor (RF) and acetyl-choline receptor antibodies (AChR). When a blood sample is positive for ANA (ie, titer>40) it will be tested for antibodies against extractable nuclear antigens. Samples for auto-antibody analyses will be collected at screening, every second cycle pre-dose for the first six cycles (C2, C4, C6), at EOT and then every 12 weeks up to 48 months of treatment and when clinically indicated.

o ADA samples should be collected at every cycle on Day 1 and unscheduled at any time, when clinically indicated. For detailed ADA sample collection schedule see Section 6.4.2.

p PK samples will be taken pre- and post-dose during all cycles and unscheduled at any time, when clinically indicated. For detailed PK analysis timings please refer to Section 6.4.2.
Note: On days and timepoints when biomarker and pharmacokinetic blood samples are being collected, the PK sample must be drawn first. For further details please see schedule of PK assessments in Section 6.4.2.

q Fresh tumor biopsy should be taken once other screening investigations strongly suggest the patient is likely to be eligible to avoid unnecessary risk of biopsy for a patient who is not going to be eligible. Where a prior (archival) biopsy is available no older than 3 months, the archival tissue may be substituted for a fresh tumor biopsy at screening. A fresh tumor biopsy is mandatory on treatment (C2D8). Where feasible, collection of a tumor biopsy at progression is encouraged.

r Plasma sample for cytokine analysis post dose timepoint is 6 to 8 hours post-infusion on C1D1 and C2D1 and C3D1. Unscheduled sample may be collected if required.

s Blood sample for measurement of serological tumor markers will be taken at screening, pre-dose of every cycle and EOT only for those patients that have tumors with correlative serological markers.

t Tumor Imaging RECIST 1.1 assessment is done every 8 weeks (±7 days) after the start of treatment for the first 16 weeks, after that every 12 weeks (±7 days) for 48 months of treatment duration or until objective disease progression; visit window for assessment is ±7 days. In case of progression of disease without clear clinical signs of progression, the patient should continue treatment. In this case a confirmatory scan should be scheduled 4 to 8 weeks later as per iRECIST guidelines. The thorax CT/MRI scan performed at screening as part of the RECIST assessment will document the lung parenchyma status.

u Please see Section 8.1 for details of follow up after end of treatment visit.

v KY1044 is always to be administered first followed by a saline solution flush to empty the line as described in the pharmacy manual. For the combination part, a slow saline infusion will continue (after this saline flush) for approximately 1 hour before starting the atezolizumab infusion at the same infusion site. There should be a period of at least 1 hour after the infusion(s) are complete whereby the patient requires close observation as outlined in Section 5.2.2.

6.1 Screening Assessments

6.1.1 Written Informed Consent

Written informed consent for the study will be obtained from each patient before any protocol-specific procedures are carried out.

At the screening visit, the Investigator will explain the aims, methods, anticipated benefits and potential risks of participating in the study and should inform the patient that participation is voluntary and that they can withdraw from the study at any time. Each patient will be given a study-specific Patient Information Sheet to read as part of the informed consent process and will be given adequate time to ask questions. In accordance with ICH GCP and 21 Code of Federal Regulations (CFR) 50, informed consent shall be documented by the use of an Informed Consent Form (ICF) approved by the IEC/IRB. The ICF will be signed and personally dated by the patient, and by the site personnel responsible for obtaining consent.

In addition to the ICF for the study, the patient may be asked to participate in the pharmacogenomic sampling section of the study, for which there is a separate ICF and Patient Information Sheet. The importance of this assessment should be clearly outlined to all patients. The use of genomic test such as FoundationOne (Foundation Medicine Cambridge, MA, USA) may be conducted at a later stage to understand the molecular/mutanome profiling of the tumors in order to correlate response (or lack of response) with specific genomic profiles (eg, tumor mutation burden, EGFR status etc.). However, lack of informed consent to participate in the pharmacogenomic sampling section of the study does not preclude patients from participating in the clinical trial.

Informed consent procedure will be documented in the patient's medical records. The patient will be given a copy of the Patient Information Sheet and their signed and dated ICF, and the original ICF will be filed in the ISF.

6.1.2 Screening and Enrollment into the Study

All screening assessments must be performed within the 28-day screening period. All screened patients will be allocated a unique screening number (See Section 5.9).

Assessment of inclusion and exclusion criteria must be checked during the screening period and finally confirmed prior to patient admission on C1D1. Emergency cards will be handed out to patients prior to first administration of IMP (IMPs). After receiving the first infusion in Phase 1, patients will be either hospitalized or remain in the clinic for at least 6 to 8 hours until the last assessments. They will be provided with instructions for after hour care per institutional standard and will return to the clinic on C1D2. In Phase 2, patients will be admitted prior to the first dose and will remain in the clinic for 6 to 8 hours after the first dose administration for all assessments to be performed.

6.1.3 Screen Failures

A patient who signed an ICF but failed to be started on-treatment for any reason will be considered a screen failure. The reason for screening failure will be entered into the eCRF.

The demographic information, informed consent, and inclusion/exclusion pages must also be completed for screen failure patients. No other data will be entered into the clinical database

for patients who are screen failures, unless the patient experienced an SAE during screening or died or withdrew consent, when the appropriate eCRF pages should be completed.

6.1.4 Demographic Information

Demographic information will be collected at the screening visit as follows:

- Age
- Year of birth
- Sex
- Race
- Ethnicity

6.1.5 Medical History

The Investigator will be responsible for review of the medical history of patients to ensure that they meet the criteria for eligibility for the study. Data to be collected will include relevant medical, surgical and radiation history and current medical conditions, diagnosis, including date and extent of tumor, details of prior anti-neoplastic treatments, current concomitant medication, SARS-CoV-2 vaccines, current significant non-drug therapies and other important molecular tumor characteristics. Medical history will be taken at screening and concomitant medications and vaccines, including SARS-CoV-2 vaccines, will be assessed throughout the study according to the schedules in Table 6-1 and Table 6-2.

For SARS-CoV-2 vaccinations, report the following in the appropriate pages of the eCRF:

- Information on each administration of SARS-CoV-2 vaccine. Each injection of SARS-CoV-2 vaccine must be reported as separate entries, including the vaccine name, dose and date of injection (Prior/Concomitant Medication eCRF).
- Any observed AE following administration of the SARS-CoV-2 vaccine during the study treatment period (Adverse Events eCRF).
- COVID-19 antibody titers, if measured after vaccination and available (Unscheduled Local Lab Results eCRF).

6.2 Assessment of Efficacy

6.2.1 Tumor Assessments

Tumor response will be determined locally according to two sets of criteria:

- RECIST 1.1: Appendix 1 (51, 52)
- iRECIST: Appendix 2 (53)

The Investigator's assessment according to both RECIST 1.1 and iRECIST will be used for the analysis of response and for treatment decisions (study discontinuation due to progressive disease as per iRECIST). During the course of the study, the Sponsor may decide to have a central review of the radiological assessments performed. In such case, the Investigator's staff will be instructed on how to send data from these radiological assessments to a CRO for central review when needed.

RECIST 1.1 guidelines for measurable, non-measurable, target lesions (TLs) and non-target lesions (NTLs) and the objective tumor response criteria are presented in Appendix 1 of this protocol.

Screening tumor assessments will include CT of the thorax and abdomen (including liver and adrenal glands) and pelvis and should encompass all areas of known predilection for metastases in the disease under evaluation and will additionally investigate areas that may be involved based on signs and symptoms of individual patients. Brain magnetic resonance imaging (MRI) is mandatory for patients with known or suspected brain metastases.

If a patient is intolerant to iodine-based contrast agents, CTs may be performed without contrast. MRI may be used to evaluate sites of disease where a CT without IV contrast is not adequate or to evaluate sites of disease that are not adequately imaged by CT. Ultrasound should not be used to measure sites of disease.

Screening assessments should be performed no more than 28 days before the start of study treatment, and ideally should be performed as close as possible to the start of study treatment. Scans obtained as part of standard clinical practice, prior to informed consent, but within the 28-days prior to treatment are acceptable.

The methods of assessment used at screening should be used at each subsequent follow-up assessment every 8 weeks (±7 days) after the start of treatment for 16 weeks, after that every 12 weeks (±7 days) for 48 months of treatment of duration or until objective disease progression as defined by RECIST 1.1/iRECIST (see Table 6-3). Scans confirming progression should preferably not be conducted within 1 week of a progression biopsy to allow for reduction in inflammation.

Any other sites at which new disease is suspected should also be appropriately imaged. If an unscheduled CT/MRI scan is performed and the patient has not progressed, every attempt should be made to perform subsequent assessments at the scheduled visits whilst the patient remains on study treatment.

Table 6-3: Disease Assessment Collection Plan

Procedure	Screening	During treatment/Follow-up
CT **with (or without) contrast enhancement** or MRI (Thorax, Abdomen, Pelvis)	Mandated	**During treatment**: Every 8 weeks (+7 days) for the first 16 weeks and then every 12 weeks until progression of disease as per iRECIST or patient withdrawal.
Brain CT or MRI with contrast	Mandated (for patients with known or suspected brain metastases)	If disease was detected at screening, or if clinically indicated.

CT=computed tomography; iRECIST=immune-related response evaluation criteria in solid tumors; MRI=magnetic resonance imaging

6.2.1.1 RECIST 1.1

Categorization of objective tumor response at each visit will be based on the RECIST 1.1 guidelines for response: CR, PR, SD and progression of disease. For ORR, a visit response of CR or PR must be confirmed by a later scan conducted at least 4 weeks after the initial response is observed.

Target lesion progression will be calculated in comparison to when the tumor burden was at a minimum (ie, smallest sum of diameters previously recorded on study). In the absence of progression, tumor response (CR, PR, SD) will be calculated in comparison to the baseline tumor measurements obtained before starting treatment.

If the Investigator is in doubt as to whether progression has occurred, particularly with response to NTLs or the appearance of a NL, it is advisable to continue treatment and reassess the patient's status at the next scheduled assessment or sooner if clinically indicated.

To achieve 'unequivocal progression' on the basis of non-target disease, there must be an overall level of substantial worsening in non-target disease such that, even in presence of SD or PR in target disease, the overall tumor burden has increased sufficiently to merit discontinuation of therapy. A modest 'increase' in the size of one or more NTLs is usually not sufficient to qualify for unequivocal disease progression status.

If repeated scans confirm progression, then the date of the initial scan should be declared as the date of progression.

All RECIST 1.1 assessment images will be reviewed at site. Duplicates may be collected, stored and can be sent for independent central RECIST 1.1 review, if deemed appropriate.

It is important to follow the assessment schedule as closely as possible. Please refer to the Schedule of Assessments see Section 6.

6.2.1.2 iRECIST

RECIST 1.1 has been modified to take into consideration the unique response kinetics which have been observed with immunotherapy in some patients where responses to immune therapies may occur after progression has been assessed (53). Therefore patients should be treated and followed up post initial progression until subsequent disease progression (confirmed progression). Note: patients with rapid tumor progression or with symptomatic progression that requires urgent medical intervention will not be eligible to continue to receive treatment.

In this study a confirmation of progression scan is required at no less than 4 weeks and preferably at the next scheduled visit after first overall visit response of progression of disease. Confirmed progression is defined as:

- ≥20% increase in sum diameters of target lesions compared to the nadir at 2 consecutive visits
- And/or significant progression (worsening) of NTLs or NLs at the confirmatory progressive disease timepoint compared with the first timepoint where progression of NTLs or NLs identified
- And/or additional new unequivocal lesions at the confirmatory progressive disease timepoint compared with the first timepoint NLs identified

If progression is not confirmed then the overall visit response should be assessed as SD/PR or CR and the patient should continue scheduled RECIST 1.1 CT/MRI scans. If progression is confirmed the overall visit response should be assessed as progressive disease.

6.3 Assessment of Pharmacodynamics

6.3.1 Biomarkers

Biological samples (eg, archived and fresh tumor samples or blood samples) will be collected and may be analyzed for exploratory predictive or responsive biomarkers (see Section 6.3.2 and Section 6.3.3).

There is a high need to identify and validate biomarkers with the aim of selecting indications and patients who will best respond to KY1044 as single agent and/or to the combination with atezolizumab and also to correlate the PD effects of the treatments with clinical outcomes such as efficacy and toxicity. Such biomarkers will be explored at the soluble (plasma), cellular, and transcriptomic levels.

In addition, it is proposed to use PD readouts to contribute to the process of RP2D decision. These biomarkers/PD markers include immune cell profiling (to be analyzed by RNA and/or Protein) in the blood and in the TME (T_{Regs} quantification, ICOS expression, number of CD8, TILs contents) pre and post treatment. Diagnostic and prognostic gene signatures derived from pre-clinical *in vitro* and *in vivo* models will also be examined using relevant patient samples (PBMC and Tumor) where appropriate consent has been provided.

Finally, cytokines such as IFNγ, TNFα and GM-CSF will be assessed in the plasma of the patients.

Alternative biomarkers may be evaluated as determined by additional data associated with safety, disease progression or response to KY1044 as single agent or in combination with atezolizumab. The results obtained from this study may be pooled with biomarker data from other studies to test existing hypotheses or to generate hypotheses to be tested in future studies where KY1044 may be combined with other agents. A summary of the biomarker samples is provided in Table 6-4.

Table 6-4: Biomarker Sample Collection Plan (Tumor/Blood Samples) for Phase 1 and 2

Sample type	Visit/ Timepoint[a]	Approx. volume (blood samples)	Marker[b]	Purpose
Tumor samples[c]				
Newly obtained tumor sample	Screening and during treatment C2D8	N/A	IHC expression of markers such as: ICOS, CD8, FOXP3 (secondary endpoint) and other markers such as CD163, CD68, PD-L1 etc. (exploratory endpoint)	Assess expression status of potential predictors of efficacy. PD markers
			Transcriptomic analysis of immune-related genes (exploratory endpoint)	

Sample type	Visit/ Timepoint[a]	Approx. volume (blood samples)	Marker[b]	Purpose
			Analysis of pharmacogenomics markers	
Blood samples				
Blood sample (Plasma) for cytokine analysis[b]	C1D1 (pre-infusion) C1D2, C1D8, C2D1 (pre-infusion), C2D1 (6-8 hours post-infusion), C2D8 C3D1(pre-infusion), C3D1 (6-8 hours post-infusion),C3D8 and unscheduled[d]	1 x 5 mL of blood per timepoint	Cytokine analysis (eg, IFNγ, TNFα, GM-CSF) (exploratory endpoint)	PD effect
Blood sample (PBMC) for Immunoprofilling	C1D1 (pre-infusion), C1D8, C2D1 (pre-infusion), C2D8 and unscheduled	1 x 4 mL of blood per timepoint	Phenotypic characterization of circulating ICs by FACS/ChipCytometry (eg, CD8, CD4, T_{Regs} and B cells) (exploratory endpoint)	PD effect
Blood sample (PBMC) for pharmacogenomics testing	C1D1 (pre-infusion), C1D8, C2D1 (pre-infusion), C2D8 and unscheduled	1 x 8 mL of blood per timepoint	Transcriptomic analysis of PBMC using customized IO360 panel from Nanostring (exploratory endpoint)	PD effect Samples will be taken only if PGx ICF is signed
			Analysis of pharmacogenomics markers	
Blood Samples (PBMC) for receptor occupancy (KY1044 single agent in Phase 1 only)	C1D1 (pre-infusion), C1D8, C2D1 (pre-infusion), C2D8 and unscheduled	1 x 8 mL of blood per timepoint	KY1044 binding to CD4/CD8 cells by FACS (exploratory endpoint)	Target engagement Samples will be taken only from patients receiving monotherapy

FACS=fluorescence-activated cell sorting; FOXP3=forkhead box; GM-CSF=granulocyte-macrophage colony-stimulating factor; ICF=informed consent form; ICOS=inducible T cell costimulatory; IFNγ=interferon gamma; IHC=immunohistochemistry; PBMC=peripheral blood mononuclear cells; PD= pharmacodynamics; PD-L1=Programmed Cell Death-Ligand 1; PGx=pharmacogenomics; PK=pharmacokinetic; TNFα=tumor necrosis factor alpha.

a On days and timepoints when biomarker and pharmacokinetic blood samples are being collected, the PK sample must be drawn first. For further details please see schedule of PK assessments in Section 6.4.2.

b Patients need to stay in the clinic for as long as possible (6 to 8 hours) for collection of plasma cytokine samples (see schedule of assessments in Section 6) in Phase 1: C2D1 and C3D1 in Phase 2: C1D1, C2D1 and C3D1 at pre-infusion and 6 to 8 hours post-infusion.

c At screening where a prior (archival) biopsy is available that is less than 3 months old this may be substituted for a fresh tumor biopsy

d In Phase 2 - No C1D2, but instead C1D1 +6 to 8 hours post-infusion.

6.3.2 Tumor Samples

Fresh tumor biopsies for biomarker analysis will be collected during the screening period once other screening investigations strongly suggest the patient is likely to be eligible, to avoid unnecessary risk of biopsy for a patient who is not going to be eligible. Biopsies are mandatory except if associated with unacceptable clinical risk and after discussion with the Medical Monitor. Where a prior (archival) biopsy is available that is less than 3 months old this may be substituted for a fresh tumor biopsy at screening. A further biopsy will be obtained at C2D8.

Where feasible, collection of a tumor biopsy at progression is encouraged. This sample will be used to investigate changes in target expression and immune cell contexture and potential mechanisms of resistance (ie, change in immune cell contents, genetic alterations/new mutations, evidence of alternative pathway activation), RNA and protein.

6.3.2.1 Collection of Fresh Tumor Samples for Pharmacodynamic and Exploratory Biomarker Assessments

Tumor samples provided should be in a quantity sufficient to allow for analysis (see the Laboratory Manual). Tumor samples will preferably be in the form of a formalin-fixed paraffin embedded (FFPE) block. If this is not possible, 20 slides of freshly prepared unstained 5 μm sections from the tumor block should be provided.

If clinically practical, dependent to accessibility of the tumor lesion and disease indication, and within the same procedure, patients may undergo up to four core biopsies, (ideally minimum of at least two). The core biopsies will be placed in formalin and processed for FFPE.

Tumor biopsies will be stored at an appropriate vendor selected by the Sponsor. Core biopsies may be used for correlative studies such as IHC, transcriptomic analysis, proteomic analysis and tumor mutation analysis. Samples will be collected, labelled, stored and shipped as detailed in the Laboratory Manual.

6.3.2.2 Archival Tumor Samples

An unstained, archived tumor tissue sample (FFPE) in a quantity sufficient to allow for analysis (see the Laboratory Manual) will be requested, if available, from all enrolled patients. Any biopsy samples taken following previous lines of therapy will also be requested, if available. In each case the previous patient treatment must be clearly indicated for each sample provided. Tumor samples will preferably be in the form of a FFPE block. If this is not possible, 20 slides of freshly prepared unstained 5 μm sections from the archival tumor block should be provided.

6.3.2.3 Tumor Sample Analysis

The biomarkers to be investigated using the tumor samples may be assessed by IHC and transcriptomic analysis of RNA expression levels and may include but are not limited to ICOS, PD-L1, CD8, FOXP3. Tissue samples may also be analyzed for the presence of viral DNA/RNA or the presence of other pathogens associated with cancer (eg, helicobacter pilori) and for specific mutations where appropriate consent has been provided.

6.3.2.4 Assessment of Gene Signatures in Tumor Samples

Slides from FFPE biopsies will also be used to extract mRNA and monitor changes in gene signatures previously identified in pre-clinical work (ICOS co-regulated genes signature, KY1044 response signature). IFNγ signature and genes will be assessed using the Nanostring nCounter (PanInflammatory panel or the IO360 panel).

6.3.2.5 Tumor Samples for Pharmacogenomics

If a patient is eligible for enrollment into the study and has consented to provide DNA for genetic analysis, the baseline tumor sample may be used for pharmacogenomic analysis with The FoundationOne CDx™. This next generation sequencing based *in vitro* diagnostic device for detection of substitutions, insertion and deletion alterations (indels), and copy number alterations (CNAs) in 324 genes and select gene rearrangements, as well as genomic signatures including MSI and tumor mutational burden (TMB) is using DNA isolated from FFPE tumor tissue specimens. Handling and shipping of pharmacogenomic samples is described in the Laboratory Manual.

6.3.3 Blood Samples

Blood samples for biomarker analysis will be collected at C1D1 pre-dose and the times indicated in Table 6-1 (Biomarker sample collection plan (Section 6.3.1) and the table of blood volumes and timings in the laboratory manual). Samples will be used for the biomarker analysis listed below.

6.3.3.1 Collection of Samples for Circulating Soluble Factors

Plasma samples will be obtained for profiling of a variety of circulating soluble factors related to immune status including but not limited to cytokines such as IFNγ, TNFα and GM-CSF. EDTA plasma samples will be analyzed using ultra-sensitive protein detection SIMOA or other appropriate, qualified methods.

For post-dose sample collection the patients need to stay in the clinic for as long as possible (6 to 8 hours) for biomarker assessments.

- In Phase 1 on C2D1 and C3D1
- In Phase 2 on C1D1, C2D1 and C3D1

6.3.3.2 Collection of Samples for PBMC

Peripheral blood mononuclear cells will be isolated from whole blood and will be preserved (direct fixation on ChipCytometry slides or stored as frozen as described in the Laboratory Manual), and used for subsequent functional analysis such flow cytometry or ChipCytometry (immune cell profiling and receptor occupancy), transcriptomic analysis (Nanostring), to correlate the PD changes with the clinical responses.

6.3.3.3 Receptor Occupancy on PBMC

In patients receiving KY1044 as single agent in Phase 1, receptor occupancy will be determined by flow cytometry on CD4 and CD8 T cells using frozen PBMC.

6.3.3.4 Immune Cell Phenotyping in PBMC

Blood samples will be collected for analysis of immune cell subsets, such as T-cells subsets, B-cells, by flow cytometry or ChipCytometry (Zellkraftwerk, Leipzig, Germany). Markers may include but not be limited to CD3, CD4, CD8, CD25, FOXP3, CD45RA, ICOS, CD14, CD45, CD56, ICOSLG and CD19.

6.3.3.5 Assessment of Gene Signatures and Pharmacogenomics in PBMC

PBMCs will be isolated and used for extraction of mRNA for the Nanostring analysis as described for tumor samples in Section 6.3.2.4 and extraction of deoxyribonucleic acid (DNA) with the aim to determine which FCGRIIIA and FCGRIIB variant is expressed in the patient. Handling and shipping of PBMCs samples for mRNA and DNA is described in the Laboratory Manual.

6.3.4 Storage, Re-use and Destruction of Biological Samples

The number of samples taken, as well as the volume required for each analysis, are specified in the laboratory manual. Requirements may change during the study as emerging data on study treatments become available.

The Investigator will ensure that all biological samples are stored labelled and shipped in accordance with the Laboratory Manual. Records must be maintained of all samples collected and their disposition.

Samples will be stored for a maximum of 15 years from the date of the Last Patient's Last Visit, after which they will be destroyed. During this time samples may be used to evaluate emerging target related PD markers. The results of biomarker research may be reported either in the Clinical Study Report for this study, or as an addendum, or separately in a scientific report or publication. The results of this biomarker research may be pooled with biomarker data from other studies with IMP to generate hypotheses to be tested in future research.

6.4 Pharmacokinetic and Anti-drug Antibody Procedures

6.4.1 Pharmacokinetic Procedures

Blood samples will be withdrawn periodically for KY1044 and atezolizumab assay. Samples should not be taken from the arm that has recently (12 hours) been infused with the study treatment (KY1044 or atezolizumab) that is to be measured. Samples should not be taken from an arm that has any IV infusion running. If atezolizumab is to be administered into the arm opposite that used for infusing KY1044, KY1044 sample will be collected before the start of atezolizumab infusion.

6.4.2 Pharmacokinetic and Anti-drug Antibody Sampling Schedule

Serum concentrations of KY1044 and atezolizumab and detection of ADA will be assessed from blood samples taken during the study using validated bioanalytical methods. Assay methodologies and procedures will be described in analytical plans to be finalized before the start of sample analysis.

Multiple samples for concentration-time profiles for KY1044 will be taken in Cycles 1, 3 and 6 (see Table 6-5, Table 6-6, Table 6-7). For other cycles, samples will be taken for KY1044 serum concentrations and for atezolizumab serum concentrations at each cycle pre-infusion, end of infusion, End of Treatment and End of Study.

Anti-Drug Antibody samples will be drawn pre-infusion at all cycles and at the End of Study.

Samples will be collected at the timepoints specified in Table 6-5, Table 6-6, Table 6-7. Tolerances for deviation from the nominal time of sampling are provided in the tables below. These tolerances indicate the best time to allow interpretation of data. However, samples taken outside these tolerances will be evaluated so should be taken. The exact date and time of sampling will be recorded. Samples may also be drawn for serum concentration and/or ADA, with prior agreement with the Sponsor, at unscheduled times. Additionally, these blood samples may be used for *ad hoc* biomarker analysis (ie, safety and efficacy analyses).

Table 6-5: KY1044 PK Sampling Times

Cycle	Day relative to most recent infusion	Scheduled timepoint and tolerance
Phase 1		
1	1	Pre-infusion of Cycle 1
1	1	End of KY1044 infusion (up to 5 min delay allowed) [a] 1.5 h post-infusion start (±5 min) [a] 2.5 h post-infusion start (±5 min) [a] 8 h post-infusion start (±1 h) [a]
1	2	24 h post-infusion start (±2 h)
1	8	168 h post-infusion start (±8 h)
1	11	240 h post-infusion start (±24 h)
1	15	336 h post- infusion start (±24 h)
2	1	Pre-infusion of Cycle 2 (up to 24 h before 2nd infusion) End of KY1044 infusion (up to 5 min delay) [a]
3	1	Pre-infusion of Cycle 3 (up to 24 h before 3rd infusion) End of KY1044 infusion (up to 5 min delay) [a] 1.5 h post-KY1044 infusion start (±5 min) [a]
3	8	168 h post-KY1044 infusion start (±8 h)
3	11	240 h post-KY1044 infusion start (±24 h)
3	15	336 h post-KY1044 infusion start (±24 h)
4	1	Pre-infusion of Cycle 4 (up to 24 h before 4th infusion) End of KY1044 infusion (up to 5 min delay) [a]
5	1	Pre-infusion of Cycle 5 (up to 24 h before 5th infusion) End of KY1044 infusion (up to 5 min delay) [a]
6 and all other cycles	1	Pre-infusion of Cycle 6 (up to 24 h before 6th infusion) End of KY1044 infusion (up to 5 min delay) [a] 1.5 h post-KY1044 infusion start (±5 min) [a, b]
EOT	within 21 days of the last dose	EOT
End of safety follow-up	90 days after the last dose	End of safety follow-up

Cycle	Day relative to most recent infusion	Scheduled timepoint and tolerance
Phase 2		
1	1	Pre-infusion of Cycle 1 End of KY1044 infusion (up to 5 min delay) [a] 1.5 h post-KY1044 infusion start (±5 min) [a]
2	1	Pre-infusion of Cycle 2 (up to 24 h before 2nd infusion) End of KY1044 infusion (up to 5 min delay) [a]
3	1	Pre-infusion of Cycle 3 (up to 24 h before 3rd infusion) [a] End of KY1044 infusion (up to 5 min delay) 1.5 h post-KY1044 infusion start (±5 min) [a]
4	1	Pre-infusion of Cycle 4 (up to 24 h before 4th infusion) [a] End of KY1044 infusion (up to 5 min delay)
5	1	Pre-infusion of Cycle 5 (up to 24 h before 5th infusion) [a] End of KY1044 infusion (up to 5 min delay)
6 and all other cycles	1	Pre-infusion of Cycle 6 (up to 24 h before 6th infusion) End of KY1044 infusion (up to 5 min delay) [a] 1.5 h post-KY1044 infusion start (±5 min) [a, b]
EOT	within 21 days of the last dose	EOT
End of safety follow-up	90 days after the last dose	End of safety follow-up
Optional, Phase 1 or 2		
Unscheduled		Anytime

EOT=end of treatment; PK=pharmacokinetic
a Samples will be collected from the arm opposite of the KY1044 infusion site for the first 12 hours following infusion
b This sample will only be taken during Cycle 6

Table 6-6: Atezolizumab PK Sampling Times

Cycle	Day relative to most recent infusion	Scheduled timepoint and tolerance
Phase 1 and 2 patients receiving KY1044 in combination with atezolizumab		
1	1	Pre-KY1044 infusion of Cycle 1* End of atezolizumab infusion (up to 5 min delay) [a]
2	1	Pre-KY1044 infusion of Cycle 2 (up to 24 h before 2nd infusion) End of atezolizumab infusion (up to 5 min delay) [a]
3	1	Pre-KY1044 infusion of Cycle 3 (up to 24 h before 3rd infusion) End of atezolizumab infusion (up to 5 min delay) [a]
4	1	Pre-KY1044 infusion of Cycle 4 (up to 24 h before 4th infusion) End of atezolizumab infusion (up to 5 min delay) [a]
5	1	Pre-KY1044 infusion of Cycle 5 (up to 24 h before 5th infusion) End of atezolizumab infusion (up to 5 min delay) [a]

Cycle	Day relative to most recent infusion	Scheduled timepoint and tolerance
6 and all other cycles	1	Pre-KY1044 infusion of Cycle 6 (up to 24 h before 6th infusion) End of atezolizumab infusion (up to 5 min delay) [a]
EOT	within 21 days of the last dose	EOT
End of safety follow-up	90 days after the last dose	End of safety follow-up
Optional, Phase 1 or 2 patients		
Unscheduled		Anytime

EOT=end of treatment; PK=pharmacokinetic

a All baseline atezolizumab PK samples are to be taken ***before*** infusion with KY1044. Samples (ie, end of atezolizumab infusion) will be collected from the arm opposite of the atezolizumab infusion site for the first 12 hours following infusion.

Table 6-7: ADA Sampling Times (KY1044 and Atezolizumab)

Cycle	Day relative to most recent infusion	Scheduled timepoint and tolerance
Phase 1 and 2 patients		
1	1	Pre-KY1044 infusion of Cycle 1 for anti-KY1044 and for combination therapy patients, anti-atezolizumab
2	1	Pre-KY1044 infusion of Cycle 2 (up to 24 h before 2nd infusion) for anti-KY1044 and for combination therapy patients, anti-atezolizumab
3	1	Pre-KY1044 infusion of Cycle 3 (up to 24 h before 3rd infusion) for anti-KY1044 and for combination therapy patients, anti-atezolizumab
4	1	Pre-KY1044 infusion of Cycle 4 (up to 24 h before 4th infusion) for anti-KY1044 and for combination therapy patients, anti-atezolizumab
5	1	Pre-KY1044 infusion of Cycle 5 (up to 24 h before 5th infusion) for anti-KY1044 and for combination therapy patients, anti-atezolizumab
6 and all other cycles	1	Pre-KY1044 infusion of Cycle 6 (up to 24 h before 6th infusion) for anti-KY1044 and for combination therapy patients, anti-atezolizumab
End of safety follow-up	90 days after the last dose	End of safety follow-up for anti-KY1044 and for combination therapy patients, anti-atezolizumab
Optional, Phase 1 or 2 patients		
Unscheduled		Anytime for either/both anti-KY1044 and anti-atezolizumab

6.4.3 Pharmacokinetic and Anti-drug Antibody Sample Preparation and Shipment

The details of blood volume, type of tube, sample handling, storage and dispatch are described in the Laboratory Manual.

Up to 11 mL of whole blood will be collected at each sampling timepoint. Blood will be drawn into a Serum Separator Tube, spun down and aliquoted into a minimum of two labelled sample

tubes. Separate PK and ADA samples are needed for the KY1044 and atezolizumab assays. These samples must be stored on site at <-60°C and will periodically be shipped in a staged fashion. The Investigator will maintain a log of samples stored and dispatched.

KY1044 samples (for KY1044 serum concentration and for anti-KY1044 antibody) will be shipped to Intertek Pharmaceutical Services. Atezolizumab samples (for atezolizumab serum concentration and for anti-atezolizumab antibody) will be shipped and analyzed as outlined in the laboratory manual.

6.5 Assessment of Safety and Tolerability

The Investigator will review results of safety assessments on a regular basis and the Sponsor must be kept fully informed of any clinically significant findings either at screening or subsequently during study conduct.

6.5.1 Physical Examination

The Investigator will perform physical examinations, which will consist of assessment of: general appearance, ears, eyes, nose, throat, mouth, neck, thyroid, complete skin and mucosal assessment, cardiovascular, respiratory, abdomen, neurological, musculoskeletal, lymph nodes and extremities.

6.5.2 Abbreviated Physical Examination

The Investigator will perform the abbreviated physical examination. The extent of the abbreviated examination will be based in the findings of the baseline medical history (including physical examination) and adverse events. This examination must include assessments of baseline abnormalities in physical examination that might have changed, an examination for changes based on adverse events and for changes related to study procedures such as venipuncture and biopsies for example.

6.5.3 ECOG Performance Status

ECOG scoring of general well-being will be assessed as follows:

Grade	ECOG performance status (54)
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, eg, light house work, office work
2	Ambulatory and capable of all self-care but unable to carry out any work activities; up and about more than 50% of waking hours
3	Capable of only limited self-care; confined to bed or chair more than 50% of waking hours
4	Completely disabled; cannot carry on any self-care; totally confined to bed or chair
5	Dead

ECOG=Eastern Cooperative Oncology Group

ECOG grade will be recorded in the eCRF at screening, at the beginning of every cycle and at EOT.

6.5.4 Body Weight and Height

Body weight will be measured in kilograms (kg) and height in meters (m), with patients in light clothing and without shoes.

Body mass index (BMI) will be calculated as follows:

$$BMI = Weight\ (kg)/Height\ (m)^2$$

6.5.5 Adverse Events

Investigators must carefully monitor patients for the occurrence of AEs, including clinical laboratory, vital signs and ECG variables. Assessments must be made of the seriousness, severity and relationship to the administration of study medication (causality). Serious Adverse Events (SAE) and specific Adverse Events of Special Interest (AESI) will require expedited reporting. For details on definitions and reporting procedures see Section 7.

Adverse event assessments must be made by the Investigator or delegated to an appropriately trained and experienced physician. The Investigator is required to record the assessments in the eCRF and patient medical notes. Any AEs already recorded and designated as "continuing" should be reviewed at each subsequent assessment.

During and following a patient's participation in this study, the Investigator has to ensure that adequate medical care is provided to a patient for any AEs, including clinically significant laboratory values, related to the trial.

Patients will be monitored for AEs at all study visits beginning at screening until completion of the 90 day safety follow-up.

6.5.6 Safety Laboratory Tests

All laboratory parameters assessed will be evaluated centrally. However, laboratory tests for safety evaluation, such as hematology, clinical chemistry and coagulation parameters will also be assessed locally at indicated times during each cycle. In exceptional circumstances, the use of local labs may also be considered for assessment of screening laboratory values, after approval by the medical monitor.

Refer to the Schedule of Assessments (Table 6-1, Table 6-2 and Table 6-8) for a summary of the parameters to be evaluated.

More frequent evaluations may be performed at the Investigator's discretion if medically indicated; results should be recorded as unscheduled laboratory assessments.

Laboratory tests will be performed as described below and according to the schedule of assessments.

- All laboratory reports should be reviewed, signed and dated by Investigators. Any clinically significant changes will be recorded as AEs.
- Any single laboratory abnormality without clinical signs or symptoms needs to be repeated before qualifying as an AE.
- All clinically relevant abnormal laboratory tests occurring during the study may be repeated at appropriate intervals until they return to baseline or to a level deemed acceptable by the Investigator or until the abnormality is explained by an appropriate diagnosis.

Full details relating to the methodology of analysis, sample processing, labelling, storage, shipment and destruction procedures will be documented in a laboratory manual.

Table 6-8: Local/Central Clinical Laboratory Parameters Collection Plan

Test category	Test name	Time of assessment	Approx. mL per cycle (central assessment only)
Phase 1 and 2 (unless otherwise specified)			
Hematology	• Hematocrit (HCT), Hemoglobin (Hgb), Reticulocytes, red blood cell count (RBCC), mean cell hemoglobin (MCH), mean hemoglobin concentration (MCHC) and mean cell volume (MCV) • Platelets • White blood cells with Differential (Basophils, Eosinophils, Lymphocytes, Monocytes, Neutrophils)	• Screening [a], • **C 1** [b]**:** D1 pre-dose, D2 [c], D8, D15 • **C 2** [b]**:** D1 pre-dose, D8, D15 • **C 3** [b]**:** D1 pre-dose, D8 • **From Cycle 4** [b]**:** Day 1 pre-dose (CxD1) • EOT	**2 mL/sample** 2 mL = Screening 8 mL = C1 6 mL = C2 4 mL = C3 2 mL = C4 -EOT
	• HbA1c	• Screening [a] • Every 12 weeks: pre-dose (C5D1 etc.). • EOT [d]	
Clinical chemistry	• Alkaline phosphatase (ALP), alanine aminotransferase (ALT), aspartate-aminotransferase (AST), γ-glutamyltransferase (GGT), Total Bilirubin (also measure direct and indirect bilirubin if total bilirubin is >Grade 1), LDH, total CK, CK-MB • High sensitivity CRP (hsCRP) • Amylase, Lipase, • Total protein, Albumin • Bicarbonate, Calcium, Chloride, Sodium, Potassium Inorganic Phosphate, Magnesium, Ferritin, • Iron • Glucose, Cholesterol, Triglycerides, HDL, LDL • Creatinine, Blood Urea Nitrogen (BUN) or Urea	• Screening [a] • **C1- 2** [b]**:** D1 pre-dose, D8, D15 • **C 3** [b]**:** D1 pre-dose, D8 • **From Cycle 4** [b]: Day 1 pre-dose (CxD1) • EOT	**3.5 mL/sample** 3.5 mL = Screening 10.5 mL = C1, C2 7 mL = C3 3.5 mL = C4 -EOT
	• Fasting lipid profile, Glucose, Cholesterol, Triglycerides, HDL, LDL • Creat Clear (Est)	Screening [a]	

Test category	Test name	Time of assessment	Approx. mL per cycle (central assessment only)
Coagulation	• Prothrombin time (PT) or INR, • Activated partial thromboplastin time (aPTT) • Thrombin time • Fibrinogen • D-Dimer	• Screening [a] • Every cycle on Day 1[b] pre-dose (CxD1) • EOT	**4.5 mL/sample:** 4.5 mL per visit
Cardiac markers	• Serum Troponin I	At screening [a] and when clinically indicated	**3.5 mL/sample:**
	• N-terminal pro B-type natriuretic peptide (NT-pro-BNP) (only for patients with previous cardiac history or when clinically indicated)	At screening [a] (for patients with cardiac history only) and when clinically indicated	**2 mL/sample**
Thyroid	• Free T4 • TSH (Thyroid Stimulation Hormone)	• Screening [a] • Every 3 cycles pre-dose (C3D1, C6D1, C9D1 etc.) • EOT	**3.5 mL/sample:** 3.5 mL per visit
Serological exam: Tumor markers [e]	PSA, CEA, CA125, AFP, neuro specific enolase (NSE), CA15-3, CA19-9, serum mesothelin (SMRP)Thyroglobulin, Calcitonin, Chromogranin A, human choriogonadotropin	• Screening [a] • Every cycle on Day 1 pre-dose (CxD1) • EOT	**5 mL/sample:** 5 mL per visit
Serology exam: Auto-antibodies	• Anti-DNA antibodies (abs) • Anti-nuclear abs (ANA) • Anti Cardiolip. IgG, IgM • Anti Cardiolip. IgA (USA only) • Beta2-Glycoprotein I IgG, IgM • Partial thromboplastin time-Lupus anticoagulant (PTT-LA) Screen with Hexagonal Phase Confirm. As reflex (USA only) • Lupus-Anticoagulant and Lupus sens. PTT-LA (EU and APAC only) • Anti-mitochondrial abs (AMA; and AMA titer) • Rheumatoid factor (RF) • Acetyl-choline receptor antibodies (AChR) • Anti-La (Anti-SSB), Anti-Ro (anti-SSA), Anti-Sm-Ab (anti-Smith) (new SmDP assay), anti U1RNP antibodies, anti-Jo-1 (anti-histidyl-tRNA synthetase), Scl-70 (topoisomerase) Ab (only if ANA 1:80 is positive)	• Screening [a] • Every 2 cycles pre-dose until Cycle 6 (C2D1, C4D1, C6D1) • Every 12 weeks thereafter for 48 months of treatment duration • EOT	**18 mL/sample:** 18.0 mL per visit (Rheumatoid factor is part of chemistry sample)

Test category	Test name	Time of assessment	Approx. mL per cycle (central assessment only)
Virology	Serology • (HBeAg, Anti-Hbe, HBcAb, HBsAb, HBsAg, HCV Ab, HIV-1/2 Ab)	• Screening [a]	**3.5 mL/sample**
	• (HIV-Ab, HBV DNA and HCV RNA)	• Screening [a] (if required) • CxD1 pre-dose	**8.5 mL/sample** **8.5 mL per visit**
Pregnancy	• Serum samples only for women of childbearing potential at screening (β-HCG)	• Screening [a]	**Part of the clinical chemistry sample**
Urinalysis	• Bilirubin, Blood (hemoglobin) , Glucose, Ketones, pH, Protein, Specific Gravity, White Blood Cells (Leucocyte Esterase) • Microscopy [f] (WBC, RBC; Hyaline Casts, Granular Casts, Waxy Casts, WBC Casts. RBC Casts, Epithelial Cells, Crystals, Mucous Threads, Bacteria, Yeast) • Urine dipstick pregnancy test (β-HCG) (not at Screening)	• Screening [a] • Every cycle pre-dose (CxD1) • EOT	

a In exceptional circumstances, the use of local labs for screening values may be considered.
b Parameters are also assessed at local laboratories.
c In Phase 2, no sample will be taken at C1D2.
d Only if the previous assessment has not been performed within the last 3 months.
e To be performed in Central laboratory only, where applicable.
f Only if clinically indicated.

6.5.7 Vital Signs

Vital signs, including heart rate (HR), blood pressure (BP), respiratory rate, and temperature will be assessed at the screening visit and periodically during the treatment period as described in the Schedule of Assessments.

Heart rate and BP need to be established as a standard assessment (after 5 minutes in the supine position and after 5 minutes standing) during screening only. For all other visits supine position will be used.

During Cycles 1 and 2, BP and HR will be monitored in the clinic every 15 minutes during the infusions of study treatment and every 30 minutes in between the infusions (for combination therapy) and after the last infusion of study treatment for 1 hour and, during Phase 1, before the patients are discharged from the hospital on C1D2. In Phase 1, if the patient does not stay in the clinic for 24 hours on C1D1 (and instead may be released into after hour care per institutional standard), BP and HR need also to be monitored at 6 to 8 hours after the last infusion and/or before the patient is discharged into after hour care. This schedule maybe altered depending on emerging data.

Any changes from baseline in BPs and HR findings judged to be clinically significant by the Investigator will be recorded as AEs. In such cases, vital signs will be repeated at appropriate intervals until they return to baseline or to a level deemed acceptable by the Investigator or until the abnormality can be explained by an appropriate diagnosis.

6.5.8 12-lead ECG

At the timepoints indicated in Table 6-9, a triplicate 12-lead ECG will be performed at screening and in accordance with PK measurements (the ECG should be recorded as close as possible to the timepoint, when the PK sample is drawn). At each timepoint three ECG recordings should be taken one after another.

Before the ECG, the patient should be supine for at least 10 minutes. All ECGs should be recorded with the patient in the same physical position. ECG traces are to be reviewed by a qualified physician at the study site (physician to sign, date and record interpretation on ECG trace). The Investigator will enter a signed and dated clinical interpretation of the ECG trace in the eCRF.

Any clinically significant abnormalities will be recorded as an AE. In such cases, triplicate ECGs will be repeated at appropriate intervals until they return to baseline or to a level deemed acceptable by the Investigator, or until the abnormality can be explained by an appropriate diagnosis.

Table 6-9: 12-lead ECG Collection Plan for Phase 1 and 2

Cycle	Day	Time[a]
Screening	-28 to -1	Twice[b]
1	1	Pre-infusion
1	1	1.5 hours (±5 min) post-infusion start
3	1	Pre-infusion
3	1	1.5 hours (±5 min) post-infusion start
6	1	Pre-infusion
6	1	1.5 hours (±5 min) post-infusion start
EOT	-	Anytime
Unscheduled[c]	-	Anytime

ECG=electrocardiogram; EOT=end of treatment.

[a] All ECGs will be performed in triplicates
[b] ECGs will be taken twice during the screening period, at least 3 days apart
[c] In case an ECG is performed due to an unexpected cardiac signal then an additional PK sample should be collected at the same time

The Investigator or designated physician will review the ECGs and may refer to a local cardiologist if appropriate. All ECG data will also be collected digitally and will potentially be transferred electronically as described in the ECG manual for central analysis of QTc data.

If an abnormal ECG finding at screening is considered by the Investigator to be clinically significant, it should be reported as a concurrent condition. During the study, clinically significant abnormal ECG findings not present at screening should be reported as an AE.

Troponin I and additionally other cardiac markers, ie, CK, CK-MB, BNP (only for patients with a history of cardiac disease), AST and lactate dehydrogenase (LDH) depending on the Investigators decision and if clinically indicated should also be assessed on identification of abnormal ECG findings, eg, new repolarization abnormalities, found to be possibly clinically significant by Investigators judgement. A repeat cardiac marker assessment should also be performed 24 hours later. The same Troponin isoform I should be assessed at each of the visits.

6.5.9 Virology Tests

Blood samples for HIV and hepatitis virology tests will be taken at screening. For those who have seropositivity of any markers indicating current or previous HBV (any seropositivity of HB s-Antigen, HB s-Antibody, HB c-Antibody, HB e-Antigen or HB e-Antibody, and/or detectability of HBV DNA) and/or HCV infection (seropositivity of HCV antibody and/or detectability of HCV RNA), relevant virology tests (ie, serum HBV DNA load for HBV infected patients and/or serum HCV RNA load for HCV infected patients) will be repeated pre-dose of every cycle, additionally, as clinically indicated (eg, a 2 to 3xULN rise in ALT).

Active HBV infection is defined as HBV viral load ≥2000 IU/mL (10^4 copies/mL). Active HCV infection is defined as anti-HCV positive and detectable HCV RNA.

Methods of assessment

For patients seropositive in HBV and/or HCV, virus replication status will be assessed by serum HBV DNA and/or HCV RNA in International units per milliliter (IU/mL) over time.

Derivation or calculation of outcome variable

For HBV/HCV seropositive patients, changes in virus replication will be measured by changes from baseline in HBV DNA level or in HCV mRNA levels on log scale, and HBV DNA/HCV mRNA status will be further categorized into detectable and undetectable.

6.5.10 Monitoring for Drug Induced Liver Damage

Patients will be monitored for clinical signs of liver impairment according to the FDA guidelines for drug induced liver injury (DILI) (55). The levels of acceptable AST and ALT values must be adapted accordingly for patients with liver metastases or HCC. Re-challenge of patients who developed DILI will be carefully explored by assessing the benefit/risk situation for each individual patient by the Safety Review Committee, taking the FDA guidelines into consideration.

6.5.11 Oxygen Saturation

Oxygen saturation will be measured at screening and when clinically indicated using pulse oximetry.

6.5.12 Imaging for Interstitial Lung Disease (Pneumonitis)

A thorax computed tomography (CT) (or MRI scan) taken at screening as part of the RECIST assessment (see Section 6.2.1) will also be able to document the lung parenchyma status at screening and can be used for comparison with another follow-up scan (with the same methodology as at baseline (CT or MRI), in case clinical symptoms of interstitial lung disease would occur during the trial.

High resolution CT scan/MRI should be performed if clinically indicated by pulmonary symptoms any time during the study.

For any new respiratory symptoms (cough, dyspnea, lower respiratory infection) not clearly explained by other factors (eg, dyspnea associated with substantial drop in hemoglobin), patients should have oxygen saturation measured. If <92%, the high resolution CT /MRI scan of the thorax should be repeated and pulmonary function tests should be performed.

6.6 Total Blood Volume

The maximum volume to be drawn in the 3-week periods for Cycles 1 and 2 will not exceed 200 mL. In screening, later cycles and at EOT, volumes drawn will not exceed 100 mL. At the safety follow-up visit, the volumes drawn will not exceed 50 mL.

7 SAFETY MONITORING AND REPORTING

7.1 Definition of an Adverse Event

The ICH E6(R2) GCP guideline defines an AE as any untoward medical occurrence in a patient or clinical investigation volunteer administered a pharmaceutical product, which does not necessarily have to have a causal relationship with this treatment. An AE can, therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom or disease temporally associated with the use of a medicinal (investigational) product, whether or not considered related to the medicinal (investigational) product.

During the screening period, adverse events include only AEs, which are related to study specific procedures. After enrolment into the study, an AE can include an undesirable medical condition occurring at any time, even if no IMP has been administered. This includes an exacerbation of pre-existing conditions or events, intercurrent illnesses, drug interaction, SARS-CoV-2 vaccines (or any other vaccine) related AEs, or the significant worsening of the indication under investigation that is not recorded elsewhere on the eCRF under specific efficacy assessments. Anticipated fluctuations of pre-existing conditions, including the disease under study, that do not represent a clinically significant exacerbation or worsening will also be considered AEs.

The AE definition includes events occurring from the time of the patient giving informed consent until the safety follow-up 90 days after last study treatment dose.

Any SARSCoV2 vaccine related AEs should be recorded in the Adverse Events eCRF using the following terminology in the verbatim term:

- For general reactions considered to be SARS-CoV-2 vaccine-related, report as “post-SARS-CoV-2 vaccine AEs” (eg, post SARS-CoV-2 vaccine fever).
- For site reactions considered to be SARS-CoV-2 vaccine related, include the words “site” and “post-XX vaccine” (eg, post-SARS-CoV-2 vaccine site pain or post-SARS-CoV-2 vaccine site erythema).

7.1.1 Toxicity Management Algorithms (According to SITC)

Management algorithms have been developed to assist Investigators in assessing and managing specific groups of AEs. The Consensus recommendations from the Society for Immunotherapy of Cancer (SITC) Toxicity management working group will be applied, which will include monitoring of organ systems, known to be potentially affected by immune activation. (See Table 5-5).

7.1.2 Severity of Adverse Events

Adverse events will be classified for severity by the Investigator according to the Common Terminology Criteria for Adverse Events (CTCAE) v5.0 (Table 7-1).

Table 7-1 Common Terminology Criteria for Adverse Events v5.0

Grade	Description of severity
0	No change from normal or reference range
1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
2	Moderate; minimal, local or non-invasive intervention indicated; limiting age-appropriate instrumental activities of daily living
3	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care activities of daily living
4	Life-threatening consequences; urgent intervention indicated.
5	Death related to AE

AE=adverse event

Changes in the severity of an AE should be documented to allow an assessment of the duration of the event at each level of severity to be performed. Adverse events characterized as intermittent require documentation of onset and duration of each episode and their resolution or outcome.

7.1.3 Causality of Adverse Events

The relationship of an AE to administration of IMPs will be classified by the Investigator (or medically qualified designee) according to the following:

- Related: The temporal relationship of the AE to IMP administration makes a causal relationship possible, and other medications, therapeutic interventions, or underlying conditions do not provide a sufficient explanation for the observed event.
- Not related: The temporal relationship of the AE to IMP administration makes a causal relationship unlikely or remote, and other medications, therapeutic interventions, or underlying conditions provide a sufficient explanation for the observed event.

7.1.4 Follow-up of Adverse Events

During the course of the study all AEs/SAEs will be proactively followed-up for each patient. Every effort should be made to obtain a resolution for all events, even if the events continue after the patient discontinued the study.

Patients will undergo safety assessment at the end of study visit 90 days after the last dose of study treatment.

If any AE remains unresolved after the patient's last visit to the study, detailed evaluation and follow-up should be attempted until the AE has been resolved or a reasonable explanation for its persistence is found.

7.1.5 Serious Adverse Event Assessment and Reporting to the Sponsor

The Investigator (or medically qualified designee) must pursue and obtain information adequate both to determine the outcome of the AE and to assess whether it meets criteria for classification as a serious AE (SAE) requiring immediate notification to PRA Drug Safety.

An SAE is any AE that:

- Results in death;
- Is life-threatening (ie, in the opinion of the Investigator, the patient is at immediate risk of death from the AE);
- Results in inpatient hospitalization or prolongation of existing hospitalization (hospitalization is defined as an inpatient admission for 24 hours or longer); hospital admissions for procedures planned before administration of IMP do not need to be reported.

  Hospitalization or prolongation of hospitalization in the absence of a precipitating AE is not in itself an SAE. Examples include:
  - Social admission (eg, patient has no place to sleep)
  - Protocol-specified admission during a clinical study (eg, for a procedure required by the study protocol)
  - Optional admission not associated with a precipitating AE (eg, for elective cosmetic surgery)
  - Surgery that was planned prior to study enrollment (appropriate documentation is required for these cases) and was not caused by worsening of pre-existing condition
  - Hospitalization or prolongation of hospitalization for scheduled therapy of the target malignancy of the study is not considered an SAE
- Results in a persistent or significant disability/incapacity, where disability is a substantial disruption of a person's ability to conduct normal life functions;
- Results in congenital anomaly/birth defect in the offspring of a patient who received IMPs;
- Constitutes an important medical event that may not result in death, be life-threatening, or require hospitalization when, based upon appropriate medical judgement, may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

The Investigator must report all SAEs, regardless of treatment group or suspected relationship to IMPs, in the eCRF **within 24 hours** of knowledge of the event being serious.

In case the eCRF is not accessible for any reason at the required reporting time, the Investigator must report the SAE within 24 hours of knowledge of the event being serious using paper form (fax) or by email.

The contact details for alternative reporting are as follows:

SAE Reporting Contact Details	Fax: [redacted] (Europe/APAC) Fax: [redacted] (North America) or Email: [redacted] (Europe/APAC) Email: [redacted] (North America)

The following information is the minimum that must be provided:

- Investigator/reporter's name and contact details;
- Patient identification number;

- Description of the SAE, including criteria for seriousness.

The additional information included in the SAE form must be provided to PRA Drug Safety as soon as it is available. The Investigator must provide an assessment of causality for each event reported. Upon receipt of the initial report, the Investigator's causality assessment will be requested if it was not provided with the initial report.

The Investigator should report a diagnosis or a syndrome rather than individual signs or symptoms. The Investigator must only report AEs that contribute to the seriousness criterion/criteria. Non serious but medically relevant sequelae and the treatments of AEs must be recorded separately, in the narrative section of the SAE report.

A disease progression will not be considered an SAE and will be reported only as a progressive disease in eCRF, and not as an AE/SAE however if there are adverse events related to disease progression, then they along with disease progression should also be reported and recorded as per AE/SAE reporting conventions for this study.

7.1.6 Adverse Events of Special Interest

Adverse events of special interest (AESIs) for atezolizumab are outlined in Appendix 3.

The Investigator must report AESIs in -atezolizumab treated patients, regardless of suspected relationship to IMPs, to PRA Drug Safety **within 24 hours** of knowledge of the event.

Adverse events of special interest for KY1044: Infusion related reactions (IRRs) of Grade 3 severity or above are deemed as Adverse events of special interest (AESIs) with KY1044 and they must also be reported, regardless of suspected relationship to IMPs, to the PRA Drug Safety within 24 hours of knowledge of the event. All other IRRs (Grade 1 and Grade 2) must also be captured in the eCRF as any other AEs recording and reporting conventions. A periodic reassessment of AEs will be conducted as much as possible.

Overdose (please refer to Section 7.2.2 Guidance for Overdose) and pregnancy are considered AESIs with both IMPs.

7.1.7 Deaths

All deaths and all AEs resulting in death during the study treatment period or 90 days follow-up period must be reported as SAE.

The convention for recording death is as follows:

- S/AE term: the disease or condition directly leading to death including the most precise cause of death such as hepatic failure or any other cause of death (World Health Organization Medical Certification of Cause of Death, 1979)
- Outcome: fatal
- CTCAE v5 Grade 5
- All relevant clinical and safety information related to death including its time

The only exception is if the cause of death is unknown (ie, sudden or unexplained death), in which case the AE term may be "death" or "sudden death" until the cause of death is determined or if the cause of death will not be possible to be determined. In all these cases, every effort must be made to provide appropriate medical history around the event and pertinent records relating to the fatal outcome.

7.1.8 Reporting to Competent Authorities, IECs/IRBs and Other Investigators

The Sponsor will ensure that processes are in place for submission of reports of Suspected Unexpected Serious Adverse Reactions (SUSARs) occurring during the study to the Competent Authorities (CAs), IECs and other Investigators concerned by the IMP.

Suspected AEs are any AEs for which there is a reasonable possibility that the IMPs caused the AE.

As there is no clinical experience yet with KY1044, all SAEs will be reported as unexpected.

Reporting will be done in accordance with the applicable regulatory requirements.

Details of procedures and responsibilities will be documented in the SAE management plan for the study.

7.2 Important Medical Procedures to be Followed

7.2.1 Medical Emergencies and Sponsor Contacts

Each patient will be given a card at the enrolment visit and asked to carry it with them at all times in case of an emergency. The card will include the following study information as a minimum: a patient identifier, IMP name and name and 24-hour telephone number of the Investigator (or medically qualified designee).

If the Investigator needs urgent advice a 24/7 telephone line will be available to contact the Medical Monitor. The phone number will be provided in a separate manual.

7.2.2 Guidance for Overdose

Symptomatic overdose (serious or nonserious) with Investigational Medicinal Products (IMPs)

- An overdose of IMP (KY1044) is defined as: increase of at least 30% of the dose to be administered in the specified duration or if the dose is administered in less than half the recommended duration of administration.
- An overdose (accidental or intentional) with the IMP (atezolizumab) is an event suspected by the Investigator or spontaneously notified by the participant and defined as at least twice the intended dose within the intended therapeutic interval, adjusted according to the tested drug.

In the unlikely event that an overdose of KY1044 is administered, the patient will be observed and treated symptomatically.

KY1044 is expected to have a very slow clearance leading to a half-life ($t_{½}$) of approximately 3 weeks. If severe adverse reactions occur after an overdose of KY1044, then plasmapheresis to reduce the drug exposure may be considered.

There is no information on atezolizumab overdose. Treat as clinically indicated.

Cases of overdose should be documented as protocol deviations in the protocol deviation log.

7.2.3 Protocol Deviations

Any inadvertent protocol deviations that occur during the conduct of the study must be fully documented by the Investigator and the Sponsor notified.

7.2.4 Pregnancy

All pregnancies and their subsequent outcome (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth or congenital abnormality) should be reported to PRA Drug Safety.

7.2.4.1 Maternal Exposure

If a patient becomes pregnant during the course of the study IMP should be discontinued immediately.

Pregnancy itself is not regarded as an adverse event unless there is a suspicion that the study treatment under investigation (IMP), may have interfered with the effectiveness of a contraceptive medication. Congenital abnormalities/birth defects and spontaneous miscarriages will be reported and handled as SAEs. Elective abortions without complications should not be handled as AEs. The outcome of a pregnancy should be followed up and documented even if the patient is withdrawn from the study.

If a pregnancy occurs during exposure to study treatment or in the 90 days after discontinuing study treatment, then Investigators or other site personnel inform PRA Drug Safety **within one day** ie, immediately but no later than the **end of the next business day** of when he or she becomes aware of it.

PRA Drug Safety works with the Investigator to ensure that all relevant information is provided to PRA Drug Safety as soon as it is available for SAEs (see Safety Management Plan) and within 30 days for all other pregnancies not considered to be SAEs.

The same timelines apply when outcome information is available.

7.2.4.2 Paternal Exposure

Pregnancy of a patient's partner is not considered to be an adverse event. However, any conception occurring from the date of dosing until 90 days after dosing will be reported to PRA Drug Safety and followed up for its outcome.

8 WITHDRAWAL OF PATIENTS FROM TREATMENT AND/OR THE STUDY

Patients are free to withdraw from participation in the study at any time, without prejudice to their further care. In some circumstances, patients may be discontinued from study treatment but continue certain study assessments, as described in Section 8.1.

The Investigator should discontinue study treatment for a given patient if, on balance, he/she believes that continuation would be detrimental to the patient's well-being.

Study treatment may be discontinued and/or patients may be withdrawn from the study under the following circumstances:

1. Withdrawal of consent (see Section 8.1.1)
2. Severe non-compliance with the protocol as judged by the Investigator
3. Patients incorrectly initiated on study treatment (eg, patient has been determined to have met one or more of the exclusion criteria for study participation at study entry and continuing study treatment might constitute a safety risk).

4. AEs that, in the opinion of the Investigator or the Medical Monitor, contraindicate further dosing. (Patients on combination therapy who need to discontinue KY1044 due to AEs, also need to discontinue atezolizumab. In the case that a patient needs to discontinue atezolizumab due to acute infusion reactions or ADAs, KY1044 may be continued after discussion with the Medical Monitor)
5. Pregnancy
6. Disease progression, (unless, in the opinion of the Investigator, the patient is still receiving clinical benefit, whereby the patient will be treated until the confirmatory progressive disease per iRECIST (Note: patients with rapid tumor progression or with symptomatic progression that requires urgent medical intervention will not be eligible to continue to receive treatment)
7. Study terminated by the Sponsor (see Section 3.7)
8. 48 months of treatment
9. Lost to follow-up

Regardless of the reason for discontinuation, if possible, all patients should undergo End of Treatment procedures and enter the 90 days safety follow-up period. After the safety follow-up period, patients will have their End of Study visit (Section 8.2). All data available for the patient at the time of withdrawal and all reasons for withdrawal, must be recorded in the eCRF.

8.1 Follow-up of Patients Off Treatment

If a patient needs to withdraw from study treatment for AEs or other safety reasons (reasons 3 and 4 above), but does not have disease progression, they will continue with tumor progression assessments in accordance with the study schedule until they progress as per iRECIST or until they start another anti-cancer therapy or when the overall end of the study is reached. Patients who withdraw consent to treatment but who accept continued monitoring (see Section 6.2.1) will also continue in the same way. Continuation of patients who stop treatment for reasons of non-compliance should be discussed between the Investigator and the Medical Monitor.

All patients (all reasons 1 to 6 listed above) will be followed up at 3 monthly intervals (telephone followup is acceptable) to obtain survival information after the start of treatment. These data will be recorded in eCRF.

8.1.1 Withdrawal of Informed Consent

A patient who withdraws consent will always be asked about the reason(s) and assessed for the presence of any AEs. If possible, AEs will be followed up as described in Section 7. However, it is at the patient's discretion to withdraw from treatment or from the study without giving any reason.

If consent is withdrawn, the patient will not receive any further study treatment. The patient will be specifically asked if they are withdrawing consent to further participation in the study including any further assessment for disease progression or follow-up of survival information.

Note that the patient may be offered additional tests or tapering of certain treatments (co-medication) if withdrawn for safety.

The Sponsor will continue to retain and use all research results that have already been collected for the study evaluation. All biological samples that have already been collected may be

retained and analyzed at a later date for the fulfilment of the assessments defined in this protocol.

8.1.2 Lost to Follow-up

If a patient fails to return for study assessments for unknown reasons, every effort (eg, telephone calls, e-mail, letter) should be made to contact them. Patients will be considered lost to follow-up only if no contact has been established by the time the study is completed such that there is insufficient information to determine the patient's status at that time.

Note: patients who refuse to continue participation in the study, including phone contact, should be documented as "withdrawal of consent" rather than "lost to follow-up." Investigators should document attempts to re-establish contact with missing patients throughout the study period.

8.2 End of Treatment and End of Study Procedures

Patients discontinuing treatment or withdrawing from the study should return for the End of Treatment (EOT) assessments as soon as possible and latest within 21 days of the last dose of study treatment or within 21 days of the decision to discontinue study treatment, and then enter the follow-up period as indicated in (Section 8.2.1).

If the decision to discontinue the patient occurs at a regular scheduled visit, that visit may become the EOT visit rather than having the patient return for an additional visit. The eCRF should be completed, giving the reason for stopping the study treatment.

8.2.1 Safety Follow-up Visit

If possible, all patients will return for the safety follow-up visit 90 days after the last dose of study treatment. Assessments will be performed as per schedule of assessments (see Table 6-1 and Table 6-2).

8.2.2 Follow-up Period

All patients must have 90 days safety follow-up evaluations after the last dose of study treatment, including tumor or survival assessments. Evaluations should be performed according to the schedule of assessments, and data collected added to appropriate eCRF pages.

Patients who discontinue study treatment and do not have progressive disease per RECIST 1.1/iRECIST, but continue with study assessments will return for tumor assessments (Section 6.2.1) according to the study schedule. Any relevant adverse event data reported during study visits will be recorded. No other study procedures will be performed. Tumor assessments will stop when disease progression is confirmed (RECIST 1.1), the patient commences further treatment for their malignancy, or when the overall end of the study is reached. The date at which tumor monitoring is discontinued must be recorded. After discontinuation of tumor assessments patients will continue to be followed up for survival status at 3-monthly intervals.

All patients who do not withdraw consent for the study will be followed up for survival unless they are lost to follow-up or the overall end of the study has been declared.

8.2.3 End of Study for Individual Patients

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, is defined as the date of the last visit of the last participant in the study or last scheduled procedure shown in the Schedule of Activities for the last participant in the trial globally.

The end of the study will be recorded in the eCRF.

8.3 Replacement Policy

8.3.1 Phase 1 Dose Escalation Parts:

Patients will not be replaced on study. However, if a patient is considered to be non-evaluable for the dose escalation, enrolment of a new patient to the current cohort will be considered if there is less than the required number of evaluable patients (see Section 5.4.5.1). Enrolment of new patients may be considered until at least the minimum number or at most the maximum number of evaluable patients is achieved within the cohort. Minimum and maximum numbers of evaluable patients per cohort are defined in Section 4.1.1.

8.3.2 Phase 2 Part:

During the Phase 2 part no replacements of patients will be needed.

9 STATISTICAL CONSIDERATIONS

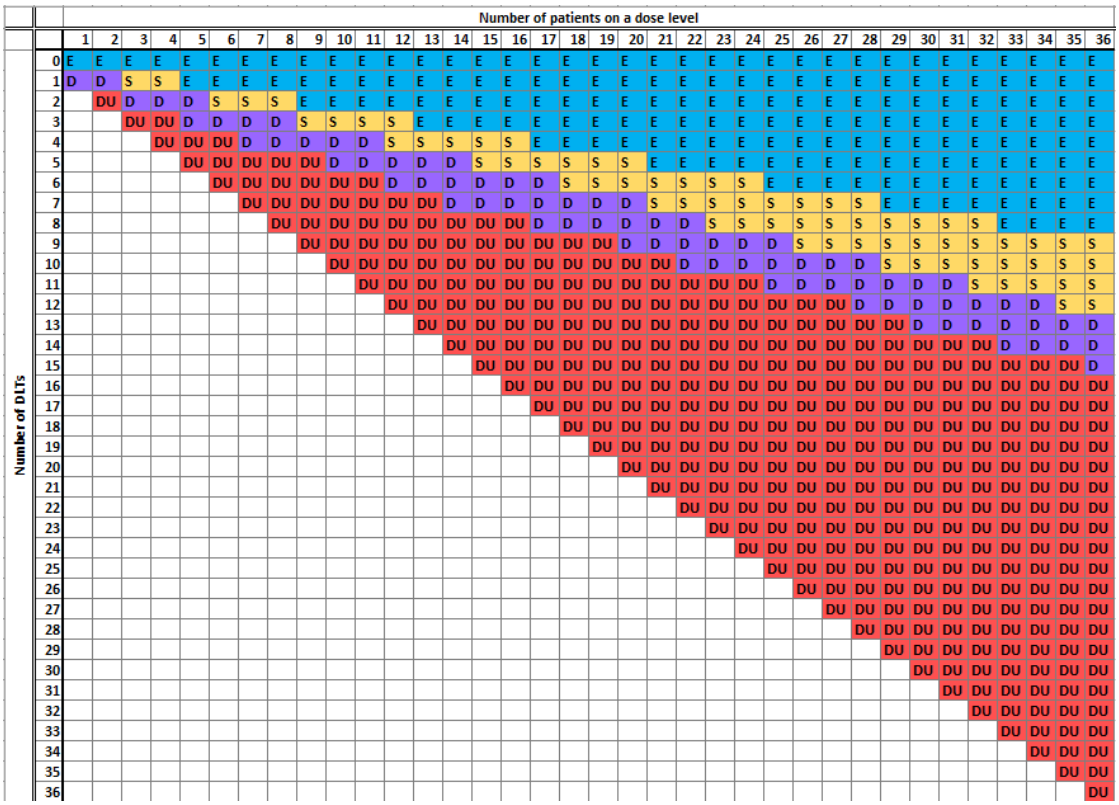
9.1 Modified Toxicity Probability Interval (mTPI-2) Design

9.1.1 Rationale for mTPI-2 Design

The rationale for deciding the starting dose and investigational dose range are discussed in the previous Section 5.4.1. In the trial, dose escalation/de-escalation decisions will use predefined DLT criteria (Section 5.5) and be based on the mTPI-2 design (49) with precalculated decisions that are displayed in Figure 9-1 (obtained via U-Design v1.0, udesign.laiyaconsulting.com). Figure 9-1 consists of all the dose-escalation rules for the trial. The trial is conducted aiming at a target 30% DLT rate (p_T=30%) for the MTD with an acceptable DLT range of 25% to 35%, and a maximum sample size of 36 patients with a cohort size of 3. To begin the trial, treat three patients on the starting dose. After observing all the outcomes of each cohort (or as specified in Section 5.4.3 if cohort modification is required), dose-escalation, de-escalation or staying at the current dose will be guided by the decision table and the SRC.

Figure 9-1: mTPI-2 Decision Table

Sample size=**36**, Target toxicity probability=**0.3**, epsilon 1=**0.05**, epsilon 2=**0.05**



* **Column** indicates the number of patients treated. **Row** indicates the number of patients with DLTs
* **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. Two parameters e1 and e2 are set at default values (Guo. et al. 2017) of 0.05.

The mTPI-2 design is chosen for this trial because it has demonstrated superior operating characteristics when compared with standard methods, such as the 3+3 design, and is easy to implement with precalculated dose decision rules (56).

Section 9.1.2 presents comprehensive simulation results of mTPI-2 and its operating characteristics. See Appendix 4 for the detailed technical summary of the design and simulations.

9.1.2 Simulation Results

Simulations were performed via U-Design v1.0 to assess the performance of mTPI-2 based on the setting of this trial. There are seven prespecified doses and the stating dose is 0.8 mg. The sample size is 36 and patients are enrolled in cohorts of size 3. The MTD target toxicity probability is p_T=0.3 and the choices of e_1 and e_2 are both 0.05. Six different scenarios were investigated in the simulation studies, as shown in Table 9-1 and Figure 9-1. For each scenario, 5000 simulated trials were conducted.

Table 9-1: Six Scenarios Used in Simulation Results

Index	p_T	nsim	Dose (mg)						
			0.24	0.8*	2.4	8	24	80	240
1	0.3	5000	0.001	0.005	0.022	0.0831	0.269	0.599	0.858
2	0.3	5000	0.668	0.832	0.924	0.968	0.987	0.995	0.998
3	0.3	5000	0.002	0.008	0.039	0.168	0.500	0.832	0.961
4	0.3	5000	0.001	0.018	0.269	0.881	0.993	0.9997	0.99998
5	0.3	5000	0.063	0.083	0.109	0.142	0.182	0.231	0.289
6	0.3	5000	0.039	0.083	0.168	0.310	0.500	0.690	0.832

*starting dose

The simulation results are presented in Figure 9-2 and Table 9-2.

Figure 9-2 illustrates the performance of mTPI-2 in terms of the probability of selecting the MTD, probability of toxicity, probability of selecting a dose higher than the MTD, and the probability of no selection.

Table 9-2 provides a summary of these results. The full details of each of the six simulations is presented in Appendix 4.

Figure 9-2: mTPI-2 Performance Across the Six Scenarios

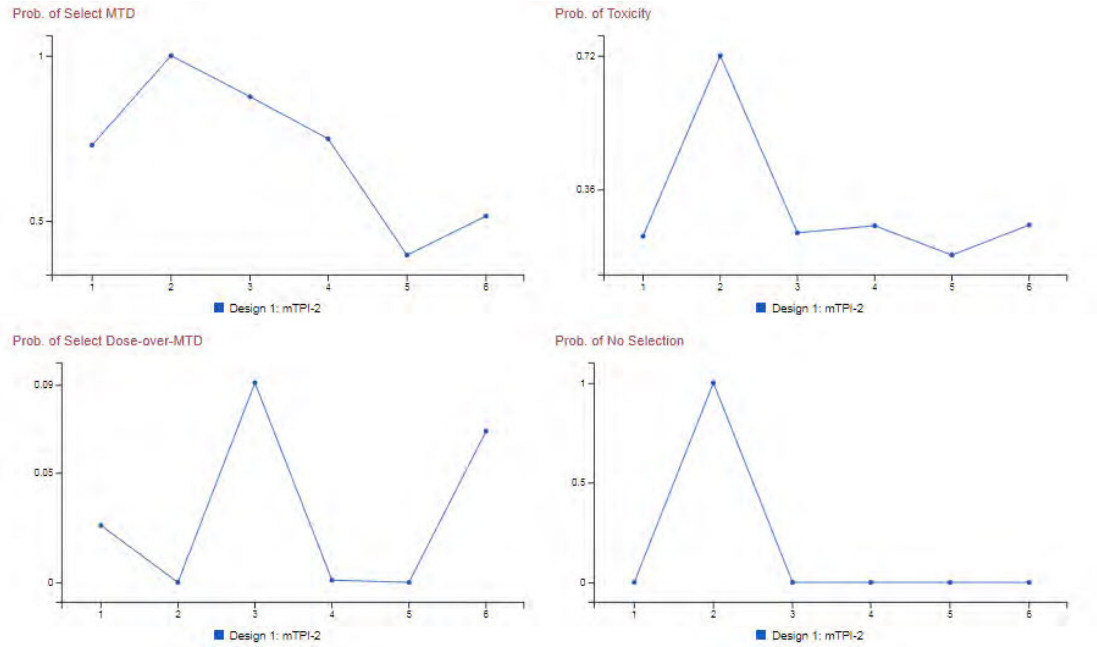


Table 9-2: Summary of mTPI-2 Performance

	mTPI-2
Probability of Selecting the MTD	0.712±0.223
Probability of Toxicity	0.318±0.199
Probability of Selecting Dose-over-MTD	0.031±0.04
Probability of No Selection	0.167±0.408

MTD=maximum tolerated dose; mTPI-2=Modified Toxicity Probability Interval Design No 2

9.2 Sample Size Determination

Sample Size Determination 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) (see Section 3.1.4) will include approximately 20 patients (ie, 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 rates and a target ORR response rate for KY1044 treatment. No formal statistical testing will be performed. Instead, confidence intervals will be constructed around the objective response rate observed in each cohort, and this will enable decisions to be made around the likely success of future studies.

Historical response rates for monotherapy with ICI 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 up to 10 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 patient groups. If signs of efficacy have been observed in at least one patient any of these anti-PD-(L)1 pre-treated indications a further expansion up to 40 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 (Phase 1 and 2).

9.3 Analysis Set

9.3.1 Full Analysis Set

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

9.3.2 Safety Set

The safety set will consist of all patients who take at least one dose of study drug.

Any additional analysis sets will be defined in the Statistical Analysis Plan (SAP).

9.4 Statistical Analyses

Full details of the statistical analyses of the data will be documented in an agreed SAP, which will be finalized prior to locking the database. There will be a preliminary analysis of the study data according to the requirements defined in Section 3.5. Final data analysis will be performed at the end of the study.

Phase 1 will be reported by dose group(s) within KY1044 single agent and KY1044 combination groups.

Phase 2 of the study will be reported 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.

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

In general, continuous variables will be summarized by number of patients, mean, standard deviation (StD), median, and minimum, maximum. Categorical variables will be summarized by frequency counts and percentages.

9.4.1 Demographic and Baseline Characteristics

Demographic variables (age, gender and race), medical history, physical examination and ECOG performance status will be summarized. Body weight, height and BMI will also be summarized.

9.4.2 Efficacy Analysis

9.4.2.1 Analysis of Primary Endpoints

The primary endpoint in Phase 2 is ORR per RECIST 1.1. ORR will be assessed using descriptive statistics for categorical data by indication along with the associated 2-sided exact 80% and 95% CIs . The primary endpoints in Phase 1 are safety endpoints (see Section 9.4.3).

9.4.2.2 Secondary Analysis of Secondary Endpoints

Secondary efficacy endpoints include:

- ORR per RECIST 1.1 (Phase 1 only)
- ORR and PFS per iRECIST (Phase 1 and Phase 2)
- Best Overall Response (BOR), PFS and DOR per RECIST 1.1
- Survival rate at 12 and 24 months

Response endpoints will be summarized using descriptive statistics for categorical data by treatment group along with the associated 2-sided exact 95% CIs.

Time-to-event endpoints (eg, DOR, PFS) will be summarized using the Kaplan-Meier method and displayed graphically where appropriate. Median event times and 2-sided 95% confidence interval for each median will be provided. For survival rate at 12 and 24 months, Kaplan-Meier estimates with 95% CIs will be presented.

Pharmacodynamic endpoints include:

- Presence and/or concentration of anti-KY1044 and anti-atezolizumab antibodies
- Presence of TILs as determined by expression of ICOS, FOXP3 and CD8 cells (IHC)

Continuous endpoints, eg, the concentration of anti-KY1044 and anti-atezolizumab antibodies will be summarized using summary statistics, number of patients (n), mean, StD, median, minimum and maximum values.

Categorical endpoints, eg, Presence of anti-KY1044 and anti-atezolizumab antibodies will be summarized using frequency counts and percentages.

The association between expression of ICOS and other immunological markers with efficacy endpoints will be explored graphically.

9.4.2.3 Analysis of Exploratory Endpoints

The following exploratory endpoints will be evaluated using summary statistics and frequency counts as applicable. Full details of exploratory analyses including graphical presentations will be described in the Statistical Analysis Plan.

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

9.4.3 Safety Analysis

The Phase 1 primary and Phase 2 secondary safety endpoints include:

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

For Phase 1, the primary endpoints will also include:

- 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

All AEs in the clinical trial database will be coded according to the Medical Dictionary for Regulatory Activities (MedDRA) Version 21.0 or higher, which will be used to summarize AEs by primary system organ class (SOC) and preferred term (PT). All AEs will be displayed in listings.

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 (ie, 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. All TEAEs collected during the investigational period will be summarized.

Treatment-related AEs/SAEs coded by primary SOC and PT will be summarized in those receiving at least one infusion of KY1044.

Additional summaries by severity of AEs/SAEs will also be produced.

Actual and change from baseline data for vital signs and ECG parameters will be reported using summary statistics.

When relevant, for laboratory variables, descriptive statistics for results and changes from baseline will be provided during the on-treatment period. These analyses will be performed using local measurements for laboratory variables. Clinical laboratory results will be graded according to NCI CTCAE version 5.0, when applicable. Number (%) of participants with laboratory abnormalities (all grades and by grade) using the worst grade during on-treatment period will be provided for the all-treated population.

When the NCI CTCAE version 5.0 scale is not applicable, the number of participants with laboratory abnormality out-of-normal laboratory range value will be displayed.

The number of dose interruption, reductions and incidence of DLTs will be summarized.

Continuous endpoints, will be summarized using summary statistics, number of patients (n), mean, StD, median, minimum and maximum values.

Categorical endpoints, will be summarized using frequency counts and percentages.

9.4.4 Pharmacokinetic Analysis

The serum PK of KY1044 as a single agent, in combination with atezolizumab and for atezolizumab alone will be characterized using no compartmental analysis. The following PK measures will be calculated, whenever possible, from serum concentrations:

- C_{max}: Maximum concentration (for atezolizumab - only one timepoint of serum concentration at the end of infusion)
- t_{max}: Time of the maximum concentration (obtained without interpolation)
- C_{min}: Trough concentrations
- λz: Terminal elimination rate constant (whenever possible)
- $AUC_{0\text{-}last}$: 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 λz is the apparent terminal elimination rate constant
- Clearance
- Volumes of distribution
- $t_{½}$: Half-life

For both KY1044 and atezolizumab, 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. The summaries will include estimates of not only central tendency but variability such as Standard Error. For concentrations, geomeans will be provided. For t_{max} median (and range) and for half-lives, arithmetic means will be provided. Besides listings of concentrations, noncompartmental analysis (NCA) tables, charts illustrating the concentration-time profiles will be generated.

Additional pharmacokinetic analyses may be undertaken. For instance, if the tables of peak and trough concentration (or anti-drug antibody) indicate some kind of interaction between KY1044 and atezolizumab, pharmacokinetic modelling of these data may be undertaken. Exploratory analyses may also be conducted to estimate dose proportionality and accumulation ratio on relevant parameters.

Population PK analysis may be performed if deemed relevant and applicable, and the results will be summarized in a stand-alone report if deemed relevant. In this context, further exposure-response analyses may also be conducted.

9.4.5 Handling of Withdrawals and Missing Data

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

9.4.6 Protocol Deviations

Any inadvertent protocol deviations that occur during the conduct of the study must be fully documented by the Investigator and the Sponsor notified. The statistical impact of significant protocol deviations will be assessed, and the details provided in the SAP.

10 QUALITY CONTROL AND QUALITY ASSURANCE

10.1 Monitoring

The Sponsor and its selected CRO(s) will ensure the assignment of appropriately qualified monitors who will be responsible for visiting sites at regular intervals throughout the study in order to verify adherence to the protocol, completeness and accuracy of the data entered in the eCRFs and to perform Source Data Verification (SDV) of data recorded in the eCRFs, in accordance with applicable regulations, standard operating procedures (SOPs) and the monitoring plan.

The Investigator is responsible for the validity of all data collected at the site.

The eCRF is expected to be completed an ongoing basis to allow regular review by the study monitor, both remotely and during site visits, and to ensure information is available for safety reviews in a timely fashion.

The monitor will communicate deviations from the protocol, SOPs, GCP and applicable regulations to the Investigator who should ensure that appropriate action designed to prevent recurrence of the detected deviations is taken and documented. Additionally, the monitor will provide a written report, including copies of correspondence with the Investigator and site study staff, to the Sponsor, following each visit.

The frequency and nature of monitoring will be determined by the Sponsor prior to commencement of the study. The monitor must have direct access to patients medical records and other study-related source documents. The Investigator and study staff will be expected to co-operate with the monitor, to be available during the monitoring visit to answer questions and to ensure that any problems detected are resolved in a timely manner.

10.2 Audits and Inspections

In accordance with ICH E6(R2) GCP guidelines and applicable regulations, the Sponsor may decide to conduct audits at investigational sites participating in this study. During the audit, the Sponsor auditors or their representative will assess site's facilities (eg, pharmacy, drug storage areas, laboratory), meet with the Investigator and study personnel and review study-related records in order to evaluate the study compliance with the Sponsor/vendor SOPs, protocol, ICH E6(R2) GCP guideline and applicable parts of 21 CFR and local regulations. The Investigator must also agree to inspection of all study documents by regulatory authorities and the IEC/IRB.

The Investigator and site personnel should be available to provide information and answer questions as necessary. Should the Investigator be notified of a regulatory inspection involving this study, they must notify the Sponsor immediately.

10.3 Data Quality Assurance

The Investigator and study staff are responsible for maintaining a comprehensive and centralized filing system (ISF) of all study-related (essential) documentation, suitable for review and inspection at any time by representatives of the Sponsor and/or applicable regulatory authorities. The ISF must consist of those documents that individually or collectively permit evaluation of the conduct of the study and the quality of the data produced.

Quality assurance and quality control systems will be implemented and maintained using written SOPs to assure that the trial is conducted, and that the data are generated, recorded and reported in compliance with the protocol, GCP and the applicable regulatory requirements.

Quality control procedures will be applied to each stage of data handling to ensure that all data are reliable and have been processed correctly.

11 REGULATORY AND ETHICAL CONSIDERATIONS

This study will be conducted in compliance with the protocol, ICH E6(R2) GCP guideline, the applicable regulatory requirement(s) and the general principles of the Declaration of Helsinki.

11.1 IEC/IEB Approval

The study protocol, Patient Information Sheet, Informed Consent Form, Investigator Brochure, available safety information, patient recruitment procedures (eg, advertisements), information about payments and compensation available to the patients and documentation evidencing the Investigator's qualifications should be submitted to the IEC/IRB for ethical review and approval as required by local regulations, prior to the study start. The written approval should identify all documents reviewed by name and version.

The Investigator/Sponsor will follow all necessary regulations to ensure appropriate, initial, and ongoing, IEC/IRB study review. The Investigator/Sponsor (as appropriate) must submit and, where necessary, obtain approval from the IEC/IRB for all subsequent protocol amendments and changes to the patient information sheet or informed consent documents. Investigators will be advised by the Sponsor whether an amendment is considered substantial or non-substantial and whether it requires submission for approval or notification only to an IEC/IRB.

The Investigator or the Sponsor as applicable will notify the IEC/IRB of the end of the study or early termination if the study within required timelines. A reason for the early termination will be provided.

Safety updates for KY1044 will be prepared by the Sponsor as required, for submission to the relevant IEC/IRB.

11.2 Regulatory Approval

As required by local regulations, the Sponsor will ensure approval of the appropriate regulatory bodies is obtained prior to study initiation. If required, the Sponsor will also ensure that the implementation of substantial amendments to the protocol and other relevant study documents happens only after approval by the relevant regulatory authorities.

The Sponsor will notify the relevant regulatory authorities about end of study or early study termination within required timelines and in case of early termination will provide the reasons for it.

Safety updates for KY1044 will be prepared by the Sponsor as required, for submission to the relevant regulatory authority.

11.3 Patient Confidentiality

An identification code assigned to each patient will be used in lieu of the patient's name to protect the patient's identity when reporting AEs and/or other trial-related data. Personal information will be treated as confidential, but may need to be reviewed by authorized representatives of the Sponsor (eg, monitor or auditor) or the regulatory authorities. The patient's consent to direct access to his/her original medical records for data verification purposes must be obtained prior to a patient's participation in the trial.

For all patients enrolled into the trial, the Investigator must maintain a list of names and identifying information (eg, date of birth, patient identification code, date of study enrollment). The patient identification code list will be kept by the Investigator in the Investigator Site File.

11.4 Protocol Amendments

The Investigator will not implement any changes to the protocol without approval from the Sponsor, the regulatory authority and IRB/IEC (and other approving bodies), if required, except where necessary to eliminate immediate hazards to the trial patients, or when the changes involve only logistical or administrative aspects of the trial.

The Sponsor will not permit or approve any waivers from the approved protocol.

Modifications to the protocol will be made as a protocol amendment.

Substantial amendments to the protocol are those likely to have a significant impact on:

- The safety, or physical or mental integrity of the patients;
- The scientific value of the trial.

Non-substantial amendments (eg, changes in telephone numbers, etc.) will not require prior submission to the regulatory authority and the IRB/IEC or other approving body unless requested.

11.5 Principal Investigator Responsibilities

Principal Investigator (Investigator) responsibilities are set out in the ICH E6(R2) Guideline for GCP and in the local regulations. Sponsor staff or an authorized representative will evaluate and approve all Investigators who in turn will select their staff.

The Investigator must ensure that all persons assisting with the study are adequately informed about the protocol, amendments, study treatments, as well as study-related duties and functions.

The Investigator will maintain a list of sub-Investigators and other appropriately qualified persons to whom he or she has delegated significant study-related duties.

If the Investigator contracts any vendors to work on the study he/she must inform the Sponsor or an authorized Sponsor's representative and ensure appropriate oversight of said vendors.

The Investigator is responsible for the validity, maintenance and archiving of all data collected at site.

12 DATA HANDLING AND RECORD KEEPING

12.1 Data Capture

Data collection is the responsibility of the clinical trial staff at the site under the supervision of the site PI. The PI is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported and should ensure that study staff are adequately trained and have sufficient time to fulfil their responsibilities.

An eCRF Medidata RAVE, Version 2017.2.3, a 21 CFR Part 11-compliant data capture system provided by Medidata will be used for this study.

The results from screening and data collected during the study will be entered into MediData RAVE by the Investigator. The data system includes password protection and internal quality checks, such as automatic range checks, to identify data that appear inconsistent, incomplete, or inaccurate. The Investigator will electronically sign the eCRF indicating that the data in the eCRF have been assessed and agreed.

At the Sponsor's discretion, SDV may be performed on all data items or a percentage thereof.

12.2 Data Management

Detailed data entry instructions will be provided in the eCRF Completion Guidelines.

Computerized data cleaning checks will be used in addition to manual review to check for discrepancies and to ensure consistency of the data. The data entered are subsequently verified.

An electronic audit trail system will be maintained within the data capture system to track all data changes in the database once the data have been saved initially into the system or electronically loaded.

Regular backups of the electronic data will be performed.

12.3 Record Archiving and Retention

All original source documents supporting entries in the eCRF must be included in the patient's medical file and retained so that integrity and accessibility are maintained.

The Sponsor will inform the Investigator of the time period for retaining these records to comply with all applicable regulatory requirements. The minimum retention time will meet the strictest standard applicable to that study center for the study, as dictated by any institutional requirements or local laws or regulations, or the sponsor's standards/procedures; otherwise, the retention period will default to 15 years.

The ISF must be retained in accordance with ICH E6(R2) GCP, 21 CFR 312.62(c) or longer if required by applicable regulatory requirements or by the Sponsor. The PI or his/her institution should retain essential documents until written instructions for their destruction are obtained from the Sponsor. If the PI wishes to assign the study records to another party or to another location, they must obtain prior approval in writing from the Sponsor. Any transfer of records must be fully documented.

13 FINANCING AND INSURANCE

This study will be financed by Kymab Ltd who are the Sponsor of the study. Individual site financing and insurance will be subject to a separate written agreement between the Sponsor and applicable parties.

14 PUBLICATION POLICY

All information provided regarding the study, as well as all information collected/documented during the course of the study, will be regarded as confidential. The Sponsor is committed to publish the data arising from this study at a suitable time irrespective of the study outcome. Results from the study will be published/presented as per the Sponsor's publication policy.

The Sponsor will ensure that any applicable requirements to register the study or publish the results arising are met.

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16 APPENDICES

16.1 Appendix 1 - RECIST 1.1 (Eisenhauer et al., 2009) and Update 2016 (Schwarz et al., 2016)

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New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1)

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Guidelines

ABSTRACT

Background: Assessment of the change in tumour burden is an important feature of the clinical evaluation of cancer therapeutics: both tumour shrinkage (objective response) and disease progression are useful endpoints in clinical trials. Since RECIST was published in 2000, many investigators, cooperative groups, industry and government authorities have adopted these criteria in the assessment of treatment outcomes. However, a number of questions and issues have arisen which have led to the development of a revised RECIST guideline (version 1.1). Evidence for changes, summarised in separate papers in this special issue, has come from assessment of a large data warehouse (>6500 patients), simulation studies and literature reviews.

Highlights of revised RECIST 1.1: Major changes include: *Number of lesions to be assessed:* based on evidence from numerous trial databases merged into a data warehouse for analysis purposes, the number of lesions required to assess tumour burden for response determination has been reduced from a maximum of 10 to a maximum of five total (and from five to two per organ, maximum). *Assessment of pathological lymph* nodes is now incorporated: nodes with a short axis of ≥15 mm are considered measurable and assessable as target lesions. The short axis measurement should be included in the sum of lesions in calculation of tumour response. Nodes that shrink to <10 mm short axis are considered normal. *Confirmation of response* is required for trials with response primary endpoint but is no longer required in randomised studies since the control arm serves as appropriate means of interpretation of data. *Disease progression* is clarified in several aspects: in addition to the previous definition of progression in target disease of 20% increase in sum, a 5 mm absolute increase is now required as well to guard against over calling PD when the total sum is very

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small. Furthermore, there is guidance offered on what constitutes 'unequivocal progression' of non-measurable/non-target disease, a source of confusion in the original RECIST guideline. Finally, a section on detection of new lesions, including the interpretation of FDG-PET scan assessment is included. *Imaging guidance*: the revised RECIST includes a new imaging appendix with updated recommendations on the optimal anatomical assessment of lesions.

Future work: A key question considered by the RECIST Working Group in developing RECIST 1.1 was whether it was appropriate to move from anatomic unidimensional assessment of tumour burden to either volumetric anatomical assessment or to functional assessment with PET or MRI. It was concluded that, at present, there is not sufficient standardisation or evidence to abandon anatomical assessment of tumour burden. The only exception to this is in the use of FDG-PET imaging as an adjunct to determination of progression. As is detailed in the final paper in this special issue, the use of these promising newer approaches requires appropriate clinical validation studies.

1. Background

1.1. History of RECIST criteria

Assessment of the change in tumour burden is an important feature of the clinical evaluation of cancer therapeutics. Both tumour shrinkage (objective response) and time to the development of disease progression are important endpoints in cancer clinical trials. The use of tumour regression as the endpoint for phase II trials screening new agents for evidence of anti-tumour effect is supported by years of evidence suggesting that, for many solid tumours, agents which produce tumour shrinkage in a proportion of patients have a reasonable (albeit imperfect) chance of subsequently demonstrating an improvement in overall survival or other time to event measures in randomised phase III studies (reviewed in [1–4]). At the current time objective response carries with it a body of evidence greater than for any other biomarker supporting its utility as a measure of promising treatment effect in phase II screening trials. Furthermore, at both the phase II and phase III stage of drug development, clinical trials in advanced disease settings are increasingly utilising time to progression (or progression-free survival) as an endpoint upon which efficacy conclusions are drawn, which is also based on anatomical measurement of tumour size.

However, both of these tumour endpoints, objective response and time to disease progression, are useful only if based on widely accepted and readily applied standard criteria based on anatomical tumour burden. In 1981 the World Health Organisation (WHO) first published tumour response criteria, mainly for use in trials where tumour response was the primary endpoint. The WHO criteria introduced the concept of an overall assessment of tumour burden by summing the products of bidimensional lesion measurements and determined response to therapy by evaluation of change from baseline while on treatment.[5] However, in the decades that followed their publication, cooperative groups and pharmaceutical companies that used the WHO criteria often 'modified' them to accommodate new technologies or to address areas that were unclear in the original document. This led to confusion in interpretation of trial results[6] and in fact, the application of varying response criteria was shown to lead to very different conclusions about the efficacy of the same regimen.[7] In response to these problems, an International Working Party was formed in the mid 1990s to standardise and simplify response criteria. New criteria, known as RECIST (Response Evaluation Criteria in Solid Tumours), were published in 2000.[8] Key features of the original RECIST include definitions of minimum size of measurable lesions, instructions on how many lesions to follow (up to 10, a maximum five per organ site), and the use of unidimensional, rather than bidimensional, measures for overall evaluation of tumour burden. These criteria have subsequently been widely adopted by academic institutions, cooperative groups, and industry for trials where the primary endpoints are objective response or progression. In addition, regulatory authorities accept RECIST as an appropriate guideline for these assessments.

1.2. Why update RECIST?

Since RECIST was published in 2000, many investigators have confirmed in prospective analyses the validity of substituting unidimensional for bidimensional (and even three-dimensional)-based criteria (reviewed in [9]). With rare exceptions (e.g. mesothelioma), the use of unidimensional criteria seems to perform well in solid tumour phase II studies.

However, a number of questions and issues have arisen which merit answers and further clarity. Amongst these are whether fewer than 10 lesions can be assessed without affecting the overall assigned response for patients (or the conclusion about activity in trials); how to apply RECIST in randomised phase III trials where progression, not response, is the primary endpoint particularly if not all patients have measurable disease; whether or how to utilise newer imaging technologies such as FDG-PET and MRI; how to handle assessment of lymph nodes; whether response confirmation is truly needed; and, not least, the applicability of RECIST in trials of targeted non-cytotoxic drugs. This revision of the RECIST guidelines includes updates that touch on all these points.

1.3. *Process of RECIST 1.1 development*

The RECIST Working Group, consisting of clinicians with expertise in early drug development from academic research organisations, government and industry, together with imaging specialists and statisticians, has met regularly to set the agenda for an update to RECIST, determine the evidence needed to justify the various changes made, and to review emerging evidence. A critical aspect of the revision process was to create a database of prospectively documented solid tumour measurement data obtained from industry and academic group trials. This database, assembled at the EORTC Data Centre under the leadership of Jan Bogaerts and Patrick Therasse (co-authors of this guideline), consists of >6500 patients with >18,000 target lesions and was utilised to investigate the impact of a variety of questions (e.g. number of target lesions required, the need for response confirmation, and lymph node measurement rules) on response and progression-free survival outcomes. The results of this work, which after evaluation by the RECIST Working Group led to most of the changes in this revised guideline, are reported in detail in a separate paper in this special issue.[10] Larry Schwartz and Robert Ford (also co-authors of this guideline) also provided key databases from which inferences have been made that inform these revisions.[11]

The publication of this revised guideline is believed to be timely since it incorporates changes to simplify, optimise and standardise the assessment of tumour burden in clinical trials. A summary of key changes is found in Appendix I. Because the fundamental approach to assessment remains grounded in the anatomical, rather than functional, assessment of disease, we have elected to name this version RECIST 1.1, rather than 2.0.

1.4. *What about volumetric or functional assessment?*

This raises the question, frequently posed, about whether it is 'time' to move from anatomic unidimensional assessment of tumour burden to either volumetric anatomical assessment or to functional assessment (e.g. dynamic contrast enhanced MRI or CT or (18)F-fluorodeoxyglucose positron emission tomographic (FDG-PET) techniques assessing tumour metabolism). As can be seen, the Working Group and particularly those involved in imaging research, did not believe that there is at present sufficient standardisation and widespread availability to recommend adoption of these alternative assessment methods. The only exception to this is in the use of FDG-PET imaging as an adjunct to determination of progression, as described later in this guideline. As detailed in paper in this special issue[12], we believe that the use of these promising newer approaches (which could either *add to* or *substitute for* anatomical assessment as described in RECIST) requires appropriate and rigorous clinical validation studies. This paper by Sargent et al. illustrates the type of data that will be needed to be able to define 'endpoints' for these modalities and how to determine where and when such criteria/modalities can be used to improve the reliability with which truly active new agents are identified and truly inactive new agents are discarded in comparison to RECIST criteria in phase II screening trials. The RECIST Working Group looks forward to such data emerging in the next few years to allow the appropriate changes to the next iteration of the RECIST criteria.

2. Purpose of this guideline

This guideline describes a standard approach to solid tumour measurement and definitions for objective assessment of change in tumour size for use in adult and paediatric cancer clinical trials. It is expected these criteria will be useful in all trials where objective response is the primary study endpoint, as well as in trials where assessment of stable disease, tumour progression or time to progression analyses are undertaken, since all of these outcome measures are based on an assessment of anatomical tumour burden and its change on study. There are no assumptions in this paper about the proportion of patients meeting the criteria for any of these endpoints which will signal that an agent or treatment regimen is active: those definitions are dependent on type of cancer in which a trial is being undertaken and the specific agent(s) under study. Protocols must include appropriate statistical sections which define the efficacy parameters upon which the trial sample size and decision criteria are based. In addition to providing definitions and criteria for assessment of tumour response, this guideline also makes recommendations regarding standard reporting of the results of trials that utilise tumour response as an endpoint.

While these guidelines may be applied in malignant brain tumour studies, there are also separate criteria published for response assessment in that setting.[13] This guideline is *not* intended for use for studies of malignant lymphoma since international guidelines for response assessment in lymphoma are published separately.[14]

Finally, many oncologists in their daily clinical practice follow their patients' malignant disease by means of repeated imaging studies and make decisions about continued therapy on the basis of both objective and symptomatic criteria. It is not intended that these RECIST guidelines play a role in that decision making, except if determined appropriate by the treating oncologist.

3. Measurability of tumour at baseline

3.1. *Definitions*

At baseline, tumour lesions/lymph nodes will be categorised measurable or non-measurable as follows:

3.1.1. *Measurable*

Tumour lesions: Must be accurately measured in at least one dimension (*longest* diameter in the plane of measurement is to be recorded) with a *minimum* size of:

- 10 mm by CT scan (CT scan slice thickness no greater than 5 mm; see Appendix II on imaging guidance).
- 10 mm caliper measurement by clinical exam (lesions which cannot be accurately measured with calipers should be recorded as non-measurable).
- 20 mm by chest X-ray.

Malignant lymph nodes: To be considered pathologically enlarged *and* measurable, a lymph node must be ≥15 mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed (see Schwartz et al. in this Special Issue[15]). See also notes below on 'Baseline documentation of target and non-target lesions' for information on lymph node measurement.

3.1.2. *Non-measurable*

All other lesions, including small lesions (longest diameter <10 mm or pathological lymph nodes with ≥10 to <15 mm short axis) as well as truly non-measurable lesions. Lesions considered truly non-measurable include: leptomeningeal disease, ascites, pleural or pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, abdominal masses/abdominal organomegaly identified by physical exam that is not measurable by reproducible imaging techniques.

3.1.3. *Special considerations regarding lesion measurability*

Bone lesions, cystic lesions, and lesions previously treated with local therapy require particular comment:

Bone lesions:.

- Bone scan, PET scan or plain films are not considered adequate imaging techniques to measure bone lesions. However, these techniques can be used to confirm the presence or disappearance of bone lesions.
- Lytic bone lesions or mixed lytic-blastic lesions, with *identifiable soft tissue components*, that can be evaluated by cross sectional imaging techniques such as CT or MRI can be considered as measurable lesions if the *soft tissue component* meets the definition of measurability described above.
- Blastic bone lesions are non-measurable.

Cystic lesions:.

- Lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts.
- 'Cystic lesions' thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same patient, these are preferred for selection as target lesions.

Lesions with prior local treatment:

- Tumour lesions situated in a previously irradiated area, or in an area subjected to other loco-regional therapy, are usually not considered measurable unless there has been demonstrated progression in the lesion. Study protocols should detail the conditions under which such lesions would be considered measurable.

3.2. Specifications by methods of measurements

3.2.1. *Measurement of lesions*

All measurements should be recorded in metric notation, using calipers if clinically assessed. All baseline evaluations should be performed as close as possible to the treatment start and never more than 4 weeks before the beginning of the treatment.

3.2.2. *Method of assessment*

The same method of assessment and the same technique should be used to characterise each identified and reported lesion at baseline and during follow-up. Imaging based evaluation should always be done rather than clinical examination unless the lesion(s) being followed cannot be imaged but are assessable by clinical exam.

Clinical lesions: Clinical lesions will only be considered measurable when they are superficial and ≥10 mm diameter as assessed using calipers (e.g. skin nodules). For the case of skin lesions, documentation by colour photography including a ruler to estimate the size of the lesion is suggested. As noted above, when lesions can be evaluated by both clinical exam and imaging, imaging evaluation should be undertaken since it is more objective and may also be reviewed at the end of the study.

Chest X-ray: Chest CT is preferred over chest X-ray, particularly when progression is an important endpoint, since CT is more sensitive than X-ray, particularly in identifying new lesions. However, lesions on chest X-ray may be considered measurable if they are clearly defined and surrounded by aerated lung. See Appendix II for more details.

CT, MRI: CT is the best currently available and reproducible method to measure lesions selected for response assessment. This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. As is described in Appendix II, when CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (e.g. for body scans). More details concerning the use of both CT and MRI for assessment of objective tumour response evaluation are provided in Appendix II.

Ultrasound: Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement. Ultrasound examinations cannot be reproduced in their entirety for independent review at a later date and, because they are operator dependent, it cannot be guaranteed that the same technique and measurements will be taken from one assessment to the next (described in greater detail in Appendix II). If new lesions are identified by ultrasound in the course of the study, confirmation by CT or MRI is advised. If there is concern about radiation exposure at CT, MRI may be used instead of CT in selected instances.

Endoscopy, laparoscopy: The utilisation of these techniques for objective tumour evaluation is not advised. However, they can be useful to confirm complete pathological response when biopsies are obtained or to determine relapse in trials where recurrence following complete response or surgical resection is an endpoint.

Tumour markers: Tumour markers alone cannot be used to assess objective tumour response. If markers are initially above

the upper normal limit, however, they must normalise for a patient to be considered in complete response. Because tumour markers are disease specific, instructions for their measurement should be incorporated into protocols on a disease specific basis. Specific guidelines for both CA-125 response (in recurrent ovarian cancer) and PSA response (in recurrent prostate cancer), have been published.[16–18] In addition, the Gynecologic Cancer Intergroup has developed CA125 progression criteria which are to be integrated with objective tumour assessment for use in first-line trials in ovarian cancer.[19]

Cytology, histology: These techniques can be used to differentiate between PR and CR in rare cases if required by protocol (for example, residual lesions in tumour types such as germ cell tumours, where known residual benign tumours can remain). When effusions are known to be a potential adverse effect of treatment (e.g. with certain taxane compounds or angiogenesis inhibitors), the cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment can be considered if the measurable tumour has met criteria for response or stable disease in order to differentiate between response (or stable disease) and progressive disease.

4. Tumour response evaluation

4.1. *Assessment of overall tumour burden and measurable disease*

To assess objective response or future progression, it is necessary to estimate the *overall tumour burden at baseline* and use this as a comparator for subsequent measurements. Only patients with measurable disease at baseline should be included in protocols where objective tumour response is the primary endpoint. Measurable disease is defined by the presence of at least one measurable lesion (as detailed above in Section 3). In studies where the primary endpoint is tumour progression (either time to progression or proportion with progression at a fixed date), the protocol must specify if entry is restricted to those with measurable disease or whether patients having non-measurable disease only are also eligible.

4.2. *Baseline documentation of 'target' and 'non-target' lesions*

When more than one measurable lesion is present at baseline all lesions up to a maximum of five lesions total (and a maximum of two lesions per organ) representative of all involved organs should be identified as *target lesions* and will be recorded and measured at baseline (this means in instances where patients have only one or two organ sites involved a *maximum* of two and four lesions respectively will be recorded). For evidence to support the selection of only five target lesions, see analyses on a large prospective database in the article by Bogaerts et al.[15]

Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that lend themselves to *reproducible repeated measurements*. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion which can be measured reproducibly should be selected. To illustrate this point see the example in Fig. 3 of Appendix II.

Lymph nodes merit special mention since they are normal anatomical structures which may be visible by imaging even if not involved by tumour. As noted in Section 3, pathological nodes which are defined as measurable and may be identified as target lesions must meet the criterion of a short axis of $\geqslant$15 mm by CT scan. Only the *short axis* of these nodes will contribute to the baseline sum. The short axis of the node is the diameter normally used by radiologists to judge if a node is involved by solid tumour. Nodal size is normally reported as two dimensions in the plane in which the image is obtained (for CT scan this is almost always the axial plane; for MRI the plane of acquisition may be axial, saggital or coronal). The smaller of these measures is the short axis. For example, an abdominal node which is reported as being 20 mm × 30 mm has a short axis of 20 mm and qualifies as a malignant, measurable node. In this example, 20 mm should be recorded as the node measurement (See also the example in Fig. 4 in Appendix II). All other pathological nodes (those with short axis $\geqslant$10 mm but <15 mm) should be considered non-target lesions. Nodes that have a short axis <10 mm are considered non-pathological and should not be recorded or followed.

A *sum of the diameters* (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the *baseline sum diameters*. If lymph nodes are to be included in the sum, then as noted above, only the *short* axis is added into the sum. The baseline sum diameters will be used as reference to further characterise any objective tumour regression in the measurable dimension of the disease.

All other lesions (or sites of disease) including pathological lymph nodes should be identified as *non-target lesions* and should also be recorded at baseline. Measurements are not required and these lesions should be followed as 'present', 'absent', or in rare cases 'unequivocal progression' (more details to follow). In addition, it is possible to record multiple non-target lesions involving the same organ as a single item on the case record form (e.g. 'multiple enlarged pelvic lymph nodes' or 'multiple liver metastases').

4.3. *Response criteria*

This section provides the definitions of the criteria used to determine objective tumour response for target lesions.

4.3.1. *Evaluation of target lesions*

Complete Response (CR): Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm.

Partial Response (PR): At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters.

Progressive Disease (PD): At least a 20% increase in the sum of diameters of target lesions, taking as reference the *smallest sum on study* (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (*Note:* the appearance of one or more new lesions is also considered progression).

Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.

4.3.2. *Special notes on the assessment of target lesions*

Lymph nodes. Lymph nodes identified as target lesions should always have the actual short axis measurement recorded (measured in the same anatomical plane as the baseline examination), even if the nodes regress to below 10 mm on study. This means that when lymph nodes are included as target lesions, the 'sum' of lesions may not be zero even if complete response criteria are met, since a normal lymph node is defined as having a short axis of <10 mm. Case report forms or other data collection methods may therefore be designed to have target nodal lesions recorded in a separate section where, in order to qualify for CR, each node must achieve a short axis <10 mm. For PR, SD and PD, the actual short axis measurement of the nodes is to be included in the sum of target lesions.

Target lesions that become 'too small to measure'. While on study, all lesions (nodal and non-nodal) recorded at baseline should have their actual measurements recorded at each subsequent evaluation, even when very small (e.g. 2 mm). However, sometimes lesions or lymph nodes which are recorded as target lesions at baseline become so faint on CT scan that the radiologist may not feel comfortable assigning an exact measure and may report them as being 'too small to measure'. When this occurs it is important that a value be recorded on the case report form. If it is the opinion of the radiologist that the lesion has likely disappeared, the measurement should be recorded as 0 mm. If the lesion is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned (*Note:* It is less likely that this rule will be used for lymph nodes since they usually have a definable size when normal and are frequently surrounded by fat such as in the retroperitoneum; however, if a lymph node is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned in this circumstance as well). This default value is derived from the 5 mm CT slice thickness (but should not be changed with varying CT slice thickness). The measurement of these lesions is potentially non-reproducible, therefore providing this default value will prevent false responses or progressions based upon measurement error. To reiterate, however, if the radiologist is able to provide an actual measure, that should be recorded, even if it is below 5 mm.

Lesions that split or coalesce on treatment. As noted in Appendix II, when non-nodal lesions 'fragment', the longest diameters of the fragmented portions should be added together to calculate the target lesion sum. Similarly, as lesions coalesce, a plane between them may be maintained that would aid in obtaining maximal diameter measurements of each individual lesion. If the lesions have truly coalesced such that they are no longer separable, the vector of the longest diameter in this instance should be the maximal longest diameter for the 'coalesced lesion'.

4.3.3. *Evaluation of non-target lesions*

This section provides the definitions of the criteria used to determine the tumour response for the group of non-target lesions. While some non-target lesions may actually be measurable, they need not be measured and instead should be assessed only *qualitatively* at the time points specified in the protocol.

Complete Response (CR): Disappearance of all non-target lesions and normalisation of tumour marker level. All lymph nodes must be non-pathological in size (<10 mm short axis).

Non-CR/Non-PD: Persistence of one or more non-target lesion(s) and/or maintenance of tumour marker level above the normal limits.

Progressive Disease (PD): *Unequivocal progression* (see comments below) of existing non-target lesions. (*Note:* the appearance of one or more new lesions is also considered progression).

4.3.4. *Special notes on assessment of progression of non-target disease*

The concept of progression of non-target disease requires additional explanation as follows:

When the patient also has measurable disease. In this setting, to achieve 'unequivocal progression' on the basis of the non-target disease, there must be an overall level of substantial worsening in non-target disease such that, even in presence of SD or PR in target disease, the overall tumour burden has increased sufficiently to merit discontinuation of therapy (see examples in Appendix II and further details below). A modest 'increase' in the size of one or more non-target lesions is usually not sufficient to quality for unequivocal progression status. The designation of overall progression solely on the basis of change in non-target disease in the face of SD or PR of target disease will therefore be extremely rare.

When the patient has only non-measurable disease. This circumstance arises in some phase III trials when it is not a criterion of study entry to have measurable disease. The same general concepts apply here as noted above, however, in this instance there is no measurable disease assessment to factor into the interpretation of an increase in non-measurable disease burden. Because worsening in non-target disease cannot be easily quantified (by definition: if all lesions are truly non-measurable) a useful test that can be applied when assessing patients for unequivocal progression is to consider if the increase in overall disease burden based on the change in non-measurable disease is comparable in magnitude to the increase that would be required to declare PD for measurable disease: i.e. an increase in tumour burden representing an additional 73% increase in 'volume' (which is equivalent to a 20% increase diameter in a measurable lesion). Examples include an increase in a pleural effusion from 'trace' to 'large', an increase in lymphangitic

disease from localised to widespread, or may be described in protocols as 'sufficient to require a change in therapy'. Some illustrative examples are shown in Figs. 5 and 6 in Appendix II. If 'unequivocal progression' is seen, the patient should be considered to have had overall PD at that point. While it would be ideal to have objective criteria to apply to non-measurable disease, the very nature of that disease makes it impossible to do so, therefore the increase must be substantial.

4.3.5. *New lesions*

The appearance of new malignant lesions denotes disease progression; therefore, some comments on detection of new lesions are important. There are no specific criteria for the identification of new radiographic lesions; however, the finding of a new lesion should be unequivocal: i.e. not attributable to differences in scanning technique, change in imaging modality or findings thought to represent something other than tumour (for example, some 'new' bone lesions may be simply healing or flare of pre-existing lesions). This is particularly important when the patient's baseline lesions show partial or complete response. For example, necrosis of a liver lesion may be reported on a CT scan report as a 'new' cystic lesion, which it is not.

A lesion identified on a follow-up study in an anatomical location that was *not* scanned at baseline is considered a new lesion and will indicate disease progression. An example of this is the patient who has visceral disease at baseline and while on study has a CT or MRI brain ordered which reveals metastases. The patient's brain metastases are considered to be evidence of PD even if he/she did not have brain imaging at baseline.

If a new lesion is equivocal, for example because of its small size, continued therapy and follow-up evaluation will clarify if it represents truly new disease. If repeat scans confirm there is definitely a new lesion, then progression should be declared using the date of the initial scan.

While FDG-PET response assessments need additional study, it is sometimes reasonable to incorporate the use of FDG-PET scanning to complement CT scanning in assessment of progression (particularly possible 'new' disease). New lesions on the basis of FDG-PET imaging can be identified according to the following algorithm:

a. Negative FDG-PET at baseline, with a positive[1] FDG-PET at follow-up is a sign of PD based on a new lesion.
b. No FDG-PET at baseline and a positive FDG-PET at follow-up:
   If the positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT, this is PD.
   If the positive FDG-PET at follow-up is not confirmed as a new site of disease on CT, additional follow-up CT scans are needed to determine if there is truly progression occurring at that site (if so, the date of PD will be the date of the initial abnormal FDG-PET scan).
   If the positive FDG-PET at follow-up corresponds to a pre-existing site of disease on CT that is not progressing on the basis of the anatomic images, this is not PD.

[1] A 'positive' FDG-PET scan lesion means one which is FDG avid with an uptake greater than twice that of the surrounding tissue on the attenuation corrected image.

4.4. *Evaluation of best overall response*

The best overall response is the best response recorded from the start of the study treatment until the end of treatment taking into account any requirement for confirmation. On occasion a response may not be documented until after the end of therapy so protocols should be clear if post-treatment assessments are to be considered in determination of best overall response. Protocols must specify how any new therapy introduced before progression will affect best response designation. The patient's best overall response assignment will depend on the findings of both target and non-target disease and will also take into consideration the appearance of new lesions. Furthermore, depending on the nature of the study and the protocol requirements, it may also require confirmatory measurement (see Section 4.6). Specifically, in non-randomised trials where response is the primary endpoint, confirmation of PR or CR is needed to deem either one the 'best overall response'. This is described further below.

4.4.1. *Time point response*

It is assumed that at each protocol specified time point, a response assessment occurs. Table 1 on the next page provides a summary of the overall response status calculation at each time point for patients who have measurable disease at baseline.

When patients have non-measurable (therefore non-target) disease only, Table 2 is to be used.

4.4.2. *Missing assessments and inevaluable designation*

When no imaging/measurement is done at all at a particular time point, the patient is not evaluable (NE) at that time point. If only a subset of lesion measurements are made at an assessment, usually the case is also considered NE at that time point, unless a convincing argument can be made that the contribution of the individual missing lesion(s) would not change the assigned time point response. This would be most likely to happen in the case of PD. For example, if a patient had a baseline sum of 50 mm with three measured lesions and at follow-up only two lesions were assessed, but those gave a sum of 80 mm, the patient will have achieved PD status, regardless of the contribution of the missing lesion.

4.4.3. *Best overall response: all time points*

The best overall response is determined once all the data for the patient is known.

Best response determination in trials where confirmation of complete or partial response IS NOT required: Best response in these trials is defined as the best response across all time points (for example, a patient who has SD at first assessment, PR at second assessment, and PD on last assessment has a best overall response of PR). When SD is believed to be best response, it must also meet the protocol specified minimum time from baseline. If the minimum time is not met when SD is otherwise the best time point response, the patient's best response depends on the subsequent assessments. For example, a patient who has SD at first assessment, PD at second and does not meet minimum duration for SD, will have a best response of PD. The same patient lost to follow-up after the first SD assessment would be considered inevaluable.

Table 1 – Time point response: patients with target (+/– non-target) disease.

Target lesions	Non-target lesions	New lesions	Overall response
CR	CR	No	CR
CR	Non-CR/non-PD	No	PR
CR	Not evaluated	No	PR
PR	Non-PD or not all evaluated	No	PR
SD	Non-PD or not all evaluated	No	SD
Not all evaluated	Non-PD	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

CR = complete response, PR = partial response, SD = stable disease, PD = progressive disease, and NE = inevaluable.

Table 2 – Time point response: patients with non-target disease only.

Non-target lesions	New lesions	Overall response
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD[a]
Not all evaluated	No	NE
Unequivocal PD	Yes or No	PD
Any	Yes	PD

CR = complete response, PD = progressive disease, and NE = inevaluable.
a 'Non-CR/non-PD' is preferred over 'stable disease' for non-target disease since SD is increasingly used as endpoint for assessment of efficacy in some trials so to assign this category when no lesions can be measured is not advised.

Best response determination in trials where confirmation of complete or partial response IS required: Complete or partial responses may be claimed only if the criteria for each are met at a subsequent time point as specified in the protocol (generally 4 weeks later). In this circumstance, the best overall response can be interpreted as in Table 3.

4.4.4. *Special notes on response assessment*

When nodal disease is included in the sum of target lesions and the nodes decrease to 'normal' size (<10 mm), they may still have a measurement reported on scans. This measurement should be recorded even though the nodes are normal in order not to overstate progression should it be based on increase in size of the nodes. As noted earlier, this means that patients with CR may not have a total sum of 'zero' on the case report form (CRF).

In trials where confirmation of response is required, repeated 'NE' time point assessments may complicate best response determination. The analysis plan for the trial must address how missing data/assessments will be addressed in determination of response and progression. For example, in most trials it is reasonable to consider a patient with time point responses of PR-NE-PR as a confirmed response.

Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as 'symptomatic deterioration'. Every effort should be made to document objective progression even after discontinuation of treatment. Symptomatic deterioration is not a descriptor of an objective response: it is a reason for stopping study therapy. The objective response status of such patients is to be determined by evaluation of target and non-target disease as shown in Tables 1–3.

Conditions that define 'early progression, early death and inevaluability' are study specific and should be clearly described in each protocol (depending on treatment duration, treatment periodicity).

In some circumstances it may be difficult to distinguish residual disease from normal tissue. When the evaluation of complete response depends upon this determination, it is recommended that the residual lesion be investigated (fine

Table 3 – Best overall response when confirmation of CR and PR required.

Overall response First time point	Overall response Subsequent time point	BEST overall response
CR	CR	CR
CR	PR	SD, PD or PR[a]
CR	SD	SD provided minimum criteria for SD duration met, otherwise, PD
CR	PD	SD provided minimum criteria for SD duration met, otherwise, PD
CR	NE	SD provided minimum criteria for SD duration met, otherwise NE
PR	CR	PR
PR	PR	PR
PR	SD	SD
PR	PD	SD provided minimum criteria for SD duration met, otherwise, PD
PR	NE	SD provided minimum criteria for SD duration met, otherwise NE
NE	NE	NE

CR = complete response, PR = partial response, SD = stable disease, PD = progressive disease, and NE = inevaluable.
a If a CR is truly met at first time point, then any disease seen at a subsequent time point, even disease meeting PR criteria relative to baseline, makes the disease PD at that point (since disease must have reappeared after CR). Best response would depend on whether minimum duration for SD was met. However, sometimes 'CR' may be claimed when subsequent scans suggest small lesions were likely still present and in fact the patient had PR, not CR at the first time point. Under these circumstances, the original CR should be changed to PR and the best response is PR.

needle aspirate/biopsy) before assigning a status of complete response. FDG-PET may be used to upgrade a response to a CR in a manner similar to a biopsy in cases where a residual radiographic abnormality is thought to represent fibrosis or scarring. The use of FDG-PET in this circumstance should be prospectively described in the protocol and supported by disease specific medical literature for the indication. However, it must be acknowledged that both approaches may lead to false positive CR due to limitations of FDG-PET and biopsy resolution/sensitivity.

For equivocal findings of progression (e.g. very small and uncertain new lesions, cystic changes or necrosis in existing lesions), treatment may continue until the next scheduled assessment. If at the next scheduled assessment, progression is confirmed, the date of progression should be the earlier date when progression was suspected.

4.5. *Frequency of tumour re-evaluation*

Frequency of tumour re-evaluation while on treatment should be protocol specific and adapted to the type and schedule of treatment. However, in the context of phase II studies where the beneficial effect of therapy is not known, follow-up every 6–8 weeks (timed to coincide with the end of a cycle) is reasonable. Smaller or greater time intervals than these could be justified in specific regimens or circumstances. The protocol should specify which organ sites are to be evaluated at baseline (usually those most likely to be involved with metastatic disease for the tumour type under study) and how often evaluations are repeated. Normally, all target and non-target sites are evaluated at each assessment. In selected circumstances certain non-target organs may be evaluated less frequently. For example, bone scans may need to be repeated only when complete response is identified in target disease or when progression in bone is suspected.

After the end of the treatment, the need for repetitive tumour evaluations depends on whether the trial has as a goal the response rate or the time to an event (progression/death). If 'time to an event' (e.g. time to progression, disease-free survival, progression-free survival) is the main endpoint of the study, then routine scheduled re-evaluation of protocol specified sites of disease is warranted. In randomised comparative trials in particular, the scheduled assessments should be performed as identified on a calendar schedule (for example: every 6–8 weeks on treatment or every 3–4 months after treatment) and should not be affected by delays in therapy, drug holidays or any other events that might lead to imbalance in a treatment arm in the timing of disease assessment.

4.6. *Confirmatory measurement/duration of response*

4.6.1. *Confirmation*

In non-randomised trials where response is the primary endpoint, confirmation of PR and CR is required to ensure responses identified are not the result of measurement error. This will also permit appropriate interpretation of results in the context of historical data where response has traditionally required confirmation in such trials (see the paper by Bogaerts et al. in this Special Issue[10]). However, in all other circumstances, i.e. in randomised trials (phase II or III) or studies where stable disease or progression are the primary endpoints, confirmation of response is not required since it will not add value to the interpretation of trial results. However, elimination of the requirement for response confirmation may increase the importance of central review to protect against bias, in particular in studies which are not blinded.

In the case of SD, measurements must have met the SD criteria at least once after study entry at a minimum interval (in general not less than 6–8 weeks) that is defined in the study protocol.

4.6.2. *Duration of overall response*

The duration of overall response is measured from the time measurement criteria are first met for CR/PR (whichever is first recorded) until the first date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded on study).

The duration of overall complete response is measured from the time measurement criteria are first met for CR until the first date that recurrent disease is objectively documented.

4.6.3. *Duration of stable disease*

Stable disease is measured from the start of the treatment (in randomised trials, from date of randomisation) until the criteria for progression are met, taking as reference the *smallest sum on study* (if the baseline sum is the smallest, this is the reference for calculation of PD).

The clinical relevance of the duration of stable disease varies in different studies and diseases. If the proportion of patients achieving stable disease for a minimum period of time is an endpoint of importance in a particular trial, the protocol should specify the minimal time interval required between two measurements for determination of stable disease.

Note: The duration of response and stable disease as well as the progression-free survival are influenced by the frequency of follow-up after baseline evaluation. It is not in the scope of this guideline to define a standard follow-up frequency. The frequency should take into account many parameters including disease types and stages, treatment periodicity and standard practice. However, these limitations of the precision of the measured endpoint should be taken into account if comparisons between trials are to be made.

4.7. *Progression-free survival/proportion progression-free*

4.7.1. *Phase II trials*

This guideline is focused primarily on the use of objective response endpoints for phase II trials. In some circumstances, 'response rate' may not be the optimal method to assess the potential anticancer activity of new agents/regimens. In such cases 'progression-free survival' (PFS) or the 'proportion progression-free' at landmark time points, might be considered appropriate alternatives to provide an initial signal of biologic effect of new agents. It is clear, however, that in an uncontrolled trial, these measures are subject to criticism since an apparently promising observation may be related to biological factors such as patient selection and not the impact of the intervention. Thus, phase II screening trials utilising these endpoints are best designed with a randomised control. Exceptions may exist

where the behaviour patterns of certain cancers are so consistent (and usually consistently poor), that a non-randomised trial is justifiable (see for example van Glabbeke et al.[20]). However, in these cases it will be essential to document with care the basis for estimating the expected PFS or proportion progression-free in the absence of a treatment effect.

4.7.2. *Phase III trials*

Phase III trials in advanced cancers are increasingly designed to evaluate progression-free survival or time to progression as the primary outcome of interest. Assessment of progression is relatively straightforward if the protocol requires all patients to have measurable disease. However, restricting entry to this subset of patients is subject to criticism: it may result in a trial where the results are less likely to be generalisable if, in the disease under study, a substantial proportion of patients would be excluded. Moreover, the restriction to entry will slow recruitment to the study. Increasingly, therefore, trials allow entry of both patients with measurable disease as well as those with non-measurable disease only. In this circumstance, care must be taken to explicitly describe the findings which would qualify for progressive disease for those patients *without* measurable lesions. Furthermore, in this setting, protocols must indicate if the maximum number of recorded target lesions for those patients with measurable disease may be relaxed from five to three (based on the data found in Bogaerts et al.[10] and Moskowitz et al.[11]). As found in the 'special notes on assessment of progression', these guidelines offer recommendations for assessment of progression in this setting. Furthermore, if available, validated tumour marker measures of progression (as has been proposed for ovarian cancer) may be useful to integrate into the definition of progression. Centralised blinded review of imaging studies or of source imaging reports to verify 'unequivocal progression' may be needed if important drug development or drug approval decisions are to be based on the study outcome. Finally, as noted earlier, because the date of progression is subject to ascertainment bias, timing of investigations in study arms should be the same. The article by Dancey et al. in this special issue[21] provides a more detailed discussion of the assessment of progression in randomised trials.

4.8. *Independent review of response and progression*

For trials where *objective response* (CR + PR) is the primary endpoint, and in particular where key drug development decisions are based on the observation of a minimum number of responders, it is recommended that all claimed responses be reviewed by an expert(s) independent of the study. If the study is a randomised trial, ideally reviewers should be blinded to treatment assignment. Simultaneous review of the patients' files and radiological images is the best approach.

Independent review of progression presents some more complex issues: for example, there are statistical problems with the use of central-review-based progression time in place of investigator-based progression time due to the potential introduction of informative censoring when the former precedes the latter. An overview of these factors and other lessons learned from independent review is provided in an article by Ford et al. in this special issue.[22]

4.9. *Reporting best response results*

4.9.1. *Phase II trials*

When response is the primary endpoint, and thus all patients must have measurable disease to enter the trial, all patients included in the study must be accounted for in the report of the results, even if there are major protocol treatment deviations or if they are not evaluable. Each patient will be assigned one of the following categories:

1. Complete response
2. Partial response
3. Stable disease
4. Progression
5. Inevaluable for response: specify reasons (for example: early death, malignant disease; early death, toxicity; tumour assessments not repeated/incomplete; other (specify)).

Normally, *all eligible* patients should be included in the denominator for the calculation of the response rate for phase II trials (in some protocols it will be appropriate to include all treated patients). It is generally preferred that 95% two-sided confidence limits are given for the calculated response rate. Trial conclusions should be based on the response rate for all eligible (or all treated) patients and should *not* be based on a selected 'evaluable' subset.

4.9.2. *Phase III trials*

Response evaluation in phase III trials may be an indicator of the relative anti-tumour activity of the treatments evaluated and is almost always a secondary endpoint. Observed differences in response rate may not predict the clinically relevant therapeutic benefit for the population studied. If objective response is selected as a primary endpoint for a phase III study (only in circumstances where a direct relationship between objective tumour response and a clinically relevant therapeutic benefit can be unambiguously demonstrated for the population studied), the same criteria as those applying to phase II trials should be used and all patients entered should have at least one measurable lesion.

In those many cases where response is a secondary endpoint and not all trial patients have measurable disease, the method for reporting overall best response rates must be pre-specified in the protocol. In practice, response rate may be reported using either an 'intent to treat' analysis (all randomised patients in the denominator) or an analysis where only the subset of patients with measurable disease at baseline are included. The protocol should clearly specify how response results will be reported, including any subset analyses that are planned.

The original version of RECIST suggested that in phase III trials one could write protocols using a 'relaxed' interpretation of the RECIST guidelines (for example, reducing the number of lesions measured) but this should no longer be done since these revised guidelines have been amended in such a way that it is clear how these criteria should be applied for all trials in which anatomical assessment of tumour response or progression are endpoints.

Appendix I. Summary of major changes RECIST 1.0 to RECIST 1.1

	RECIST 1.0	RECIST 1.1	Rationale	Reference in special issue (if applicable)
Minimum size measurable lesions	CT: 10 mm spiral 20 mm non-spiral	CT: 10 mm; delete reference to spiral scan	Most scans used have 5 mm or less slice thickness Clearer to give instruction based on slice interval if it is greater than 5 mm	
	Clinical: 20 mm	Clinical: 10 mm (must be measurable with calipers)	Caliper measurement will make this reliable	
	Lymph node: not mentioned	CT: ⩾15 mm short axis for target ⩾10–<15 mm for non-target <10 mm is non-pathological	Since nodes are normal structure need to define pathological enlargement. Short axis is most sensitive	Schwartz et al.[15]
Special considerations on lesion measurability	–	Notes included on bone lesions, cystic lesions	Clarify frequently asked questions	
Overall tumour burden	10 lesions (5 per organ)	5 lesions (2 per organ)	Data warehouse analysis shows no loss of information if lesion number reduced from 10 to 5. A maximum of 2 lesions per organ yields sufficient representation per disease site	Bogaerts et al.[30]
Response criteria target disease	CR lymph node not mentioned	CR lymph nodes must be <10 mm short axis	In keeping with normal size of nodes	Schwartz et al.[15]
	PD 20% increase over smallest sum on study or new lesions	PD 20% increase over smallest sum on study (including baseline if that is smallest) and at least 5 mm increase or new lesions	Clarification that if baseline measurement is smaller than any on study measurement, it is reference against which PD is assessed 5 mm absolute increase to guard against over calling PD when total sum is very small and 20% increase is within measurement error	
Response criteria non-target disease	'unequivocal progression' considered as PD	More detailed description of 'unequivocal progression' to indicate that it should not normally trump target disease status. It must be representative of overall disease status change, not a single lesion increase	Confusion with RECIST 1.0 where some were considering PD if 'increase' in any non-target lesion, even when target disease is stable or responding	
New lesions	–	New section on New lesions	To provide guidance on when a lesion is considered new (and thus PD)	
Overall response	Table integrated target and non-target lesions	Two tables: one integrating target and non-target and the other of non-target only	To account for the fact that RECIST criteria are now being used in trials where PFS is the endpoint and not all patients have measurable (target) disease at baseline	Dancey et al.[21]

		Special notes: How to assess and measure lymph nodes CR in face of residual tissue Discussion of 'equivocal' progression	Frequently asked questions on these topics	
Confirmatory measure	For CR and PR: criteria must be met again 4 weeks after initial documentation	Retain this requirement ONLY for non-randomised trials with primary endpoint of response	Data warehouse shows that response rates rise when confirmation is eliminated, but the only circumstance where this is important is in trials where there is no concurrent comparative control and where this measure is the primary endpoint	Bogaerts et al.[20]
Progression-free survival	General comments only	More specific comments on use of PFS (or proportion progression-free) as phase II endpoint Greater detail on PFS assessment in phase III trials	Increasing use of PFS in phase III trials requires guidance on assessment of PD in patients with non-measurable disease	Dancey et al.[21]
Reporting of response results	9 categories suggested for reporting phase II results	Divided into phase II and phase III 9 categories collapsed into 5 In phase III, guidance given about reporting response	Simplifies reporting and clarifies how to report phase II and III data consistently	
Response in phase III trials	More relaxed guidelines possible if protocol specified	This section removed and referenced in section above: no need to have different criteria for phase II and III	Simplification of response assessment by reducing number of lesions and eliminating need for confirmation in randomised studies where response is not the primary endpoint makes separate 'rules' unnecessary	
Imaging appendix	Appendix I	Appendix II: updated with detailed guidance on use of MRI, PET/CT Other practical guidance included	Evolving use of newer modalities addressed. Enhanced guidance in response to frequent questions and from radiology review experience	
New appendices		Appendix I: comparison of RECIST 1.0 and 1.1 Appendix III: frequently asked questions		

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Conflict of interest statement

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Appendix II. Specifications for standard anatomical radiological imaging

These protocols for image acquisition of computed tomography (CT) and magnetic resonance imaging (MRI) are recommendations intended for patients on clinical trials where RECIST assessment will be performed. Standardisation of imaging requirements and image acquisition parameters is ideal to allow for optimal comparability of subjects within a study and results between studies. These recommendations are designed to balance optimised image acquisition protocols with techniques that should be feasible to perform globally at imaging facilities in all types of radiology practices. These guidelines are not applicable to functional imaging techniques or volumetric assessment of tumour size.

Scanner quality control is highly recommended and should follow standard manufacturer and facility maintenance schedules using commercial phantoms. It is likely that for RECIST unidimensional measurements this will be adequate to produce reproducible measurements. Imaging quality control for CT includes an analysis of image noise and uniformity and CT number as well as spatial resolution. The frequency of quality control analysis is also variable and should focus on clinically relevant scanning parameters. Dose analysis is always important and the use of imaging should follow the ALARA principle, 'As Low As Reasonably Achievable', which refers to making every reasonable effort to maintain radiation exposures as far below the dose limits as possible.

Specific notes

Chest X-ray measurement of lesions surrounded by pulmonary parenchyma is feasible, but not preferable as the measurement represents a summation of densities. Furthermore, there is poor identification of new lesions within the chest on X-ray as compared with CT. Therefore, measurements of pulmonary parenchymal lesions as well as mediastinal disease are optimally performed with CT of the chest. MRI of the chest should only be performed in extenuating circumstances. Even if IV contrast cannot be administered (for example, in the situation of allergy to contrast), a non-contrast CT of the chest is still preferred over MRI or chest X-ray.

CT scans: CT scans of the chest, abdomen, and pelvis should be contiguous throughout all the anatomic region of interest. As a general rule, the minimum size of a measurable lesion at baseline should be no less than double the slice thickness and also have a minimum size of 10 mm (see below for minimum size when scanners have a slice thickness more than 5 mm). While the precise physics of lesion size and partial volume averaging is complex, lesions smaller than 10 mm may be difficult to accurately and reproducibly measure. While this rule is applicable to baseline scans, as lesions potentially decrease in size at follow-up CT studies, they should still be measured. Lesions which are reported as 'too small to measure' should be assigned a default measurement of 5 mm if they are still visible.

The most critical CT image acquisition parameters for optimal tumour evaluation using RECIST are *anatomic coverage, contrast administration, slice thickness, and reconstruction interval*.

a. *Anatomic coverage*: Optimal anatomic coverage for most solid tumours is the chest, abdomen and pelvis. Coverage should encompass all areas of known predilection for metastases in the disease under evaluation and

should additionally investigate areas that may be involved based on signs and symptoms of individual patients. Because a lesion later identified in a body part not scanned at baseline would be considered as a new lesion representing disease progression, careful consideration should be given to the extent of imaging coverage at baseline and at subsequent follow-up time points. This will enable better consistency not only of tumour measurements but also identification of new disease.

b. *IV contrast administration*: Optimal visualisation and measurement of metastases in solid tumours requires consistent administration (dose and rate) of IV contrast as well as timing of scanning. Typically, most abdominal imaging is performed during the portal venous phase and (optimally) about the same time frame after injection on each examination (see Fig. 1 for impact of different phase of IV contrast on lesion measurement). Most solid tumours may be scanned with a single phase after administration of contrast. While triphasic CT scans are sometimes performed on other types of vascular tumours to improve lesion conspicuity, for consistency and uniformity, we would recommend triphasic CT for hepatocellular and neuroendocrine tumours for which this scanning protocol is generally standard of care, and the improved temporal resolution of the triphasic scan will enhance the radiologists' ability to consistently and reproducibly measure these lesions. The precise dose and rate of IV contrast is dependent upon the CT scanning equipment, CT acquisition protocol, the type of contrast used, the available venous access and the medical condition of the patient. Therefore, the method of administration of intravenous contrast agents is variable. Rather than try to institute rigid rules regarding methods for administering contrast agents and the volume injected, it is appropriate to suggest that an adequate volume of a suitable contrast agent should be given so that the metastases are demonstrated to best effect and a *consistent method* is used on subsequent examinations for any given patient (ideally, this would be specified in the protocol or for an institution). It is very important that the same technique be used at baseline and on follow-up examinations for a given patient. This will greatly enhance the reproducibility of the tumour measurements. If prior to enrolment it is known a patient is not able to undergo CT scans with IV contrast due to allergy or renal insufficiency, the decision as to whether a non-contrast CT or MRI (with or without IV contrast) should be used to evaluate the subject at baseline and follow-up should be guided by the tumour type under investigation and the anatomic location of the disease. For patients who develop contraindications to contrast after baseline contrast CT is done, the decision as to whether non-contrast CT or MRI (enhanced or non-enhanced) should be performed should also be based on the tumour type, anatomic location of the disease and should be optimised to allow for comparison to the prior studies if possible. Each case should be discussed with the radiologist to determine if substitution of these other approaches is possible and, if not, the patient should be considered not evaluable from that point forward. Care must be taken in measurement of target lesions on a different modality and interpretation of non-target disease or new lesions, since the same lesion may appear to have a different size using a new modality (see Fig. 2 for a comparison of CT and MRI of the same lesion). Oral contrast is recommended to help visualise and differentiate structures in the abdomen.

c. *Slice thickness and reconstruction interval*: RECIST measurements may be performed at most clinically obtained slice thicknesses. It is recommended that CT scans be performed at 5 mm contiguous slice thickness or less and indeed this guideline presumes a minimum 5 mm thickness in recommendations for measurable lesion definition. Indeed, variations in slice thickness can have an impact on lesion measurement and on detection of new lesions. However, consideration should also be given for minimising radiation exposure. With these parameters, a minimum 10 mm lesion is considered measurable at baseline. Occasionally, institutions may perform medically acceptable scans at slice thicknesses *greater than* 5 mm. If this occurs, the minimum size of measurable lesions at baseline should be *twice the slice*

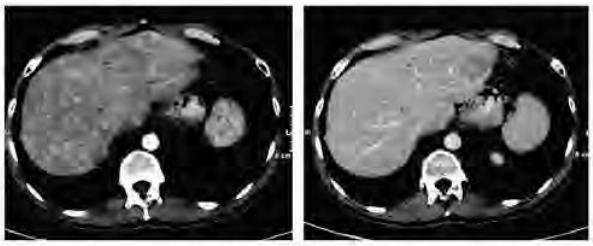

Fig. 1 – Difference in measurement/visualisation with different phases of IV contrast administration. Hypervascular metastases imaged in the arterial phase (left) and the portal venous phase (right). Note that the number of lesions visible differs greatly between the two phases of contrast administration as does any potential lesion measurement. Consistent CT scan acquisition, including phase of contrast administration, is important for optimal and reproducible tumour

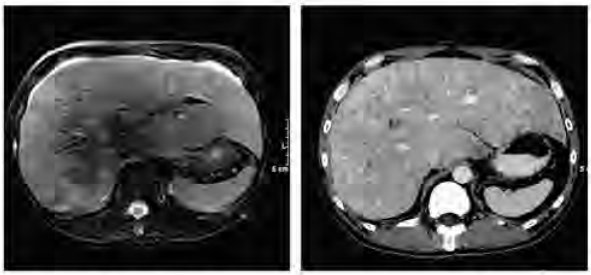

Fig. 2 – CT versus MRI of same lesions showing apparent 'progression' due only to differing method of measurement.

thickness of the baseline scans. Most contemporary CT scanners are multidetector which have many imaging options for these acquisition parameters.[23] The equipment vendor and scanning manual should be reviewed if there are any specific system questions.

d. *Alternative contrast agents*: There are a number of other, new contrast agents, some organ specific.[24] They may be used as part of patient care for instance, in liver lesion assessment, or lymph node characterisation[25], but *should not as yet be used in clinical trials*.

FDG-PET has gained acceptance as a valuable tool for detecting, staging and restaging several malignancies. Criteria for incorporating (or substituting) FDG-PET into anatomical assessment of tumour response in phase II trials are not yet available, though much research is ongoing. Nevertheless, FDG-PET is being used in many drug development trials both as a tool to assess therapeutic efficacy and also in assessment of progression. If FDG-PET scans are included in a protocol, by consensus, an FDG uptake period of 60 min prior to imaging has been decided as the most appropriate for imaging of patients with malignancy.[26] Whole-body acquisition is important since this allows for sampling of all areas of interest and can assess if new lesions have appeared thus determining the possibility of interval progression of disease. Images from the base of the skull to the level of the mid-thigh should be obtained 60 min post injection. PET camera specifications are variable and manufacturer specific, so every attempt should be made to use the same scanner, or the same model scanner, for serial scans on the same patient. Whole-body acquisitions can be performed in either 2- or 3-dimensional mode with attenuation correction, but the method chosen should be consistent across all patients and serial scans in the clinical trial.

PET/CT scans: Combined modality scanning such as with PET–CT is increasingly used in clinical care, and is a modality/technology that is in rapid evolution; therefore, the recommendations in this paper may change rather quickly with time. At present, low dose or attenuation correction CT portions of a combined PET–CT are of limited use in anatomically based efficacy assessments and it is therefore suggested that they should not be substituted for dedicated diagnostic contrast enhanced CT scans for anatomically based RECIST measurements. However, if a site can document that the CT performed as part of a PET–CT is of identical diagnostic quality to a diagnostic CT (with IV and oral contrast) then the CT portion of the PET–CT can be used for RECIST measurements. Note, however, that the PET portion of the CT introduces additional data which may bias an investigator if it is not routinely or serially performed.

Ultrasound examinations should not be used in clinical trials to measure tumour regression or progression of lesions because the examination is necessarily subjective and operator dependent. The reasons for this are several: Entire examinations cannot be reproduced for independent review at a later date, and it must be assumed, whether or not it is the case, that the hard-copy films available represent a true and accurate reflection of events. Furthermore, if, for example, the only measurable lesion is in the para-aortic region of the abdomen and if gas in the bowel overlies the lesion, the lesion will not be detected because the ultrasound beam cannot penetrate the gas. Accordingly, the disease staging (or restaging for treatment evaluation) for this patient will not be accurate.

While evaluation of lesions by *physical examination* is also of limited reproducibility, it is permitted when lesions are superficial, at least 10 mm size, and can be assessed using calipers. In general, it is preferred if patients on clinical trials have at least one lesion that is measurable by CT. Other skin or palpable lesions may be measured on physical examination and be considered target lesions.

Use of *MRI* remains a complex issue. MRI has excellent contrast, spatial and temporal resolution; however, there are many image acquisition variables involved in MRI, which greatly impact image quality, lesion conspicuity and measurement. Furthermore, the availability of MRI is variable globally. As with CT, if an MRI is performed, the technical specifications of the scanning sequences used should be optimised for the evaluation of the type and site of disease. Furthermore, as with CT, the modality used at follow-up should be the same as was used at baseline and the lesions should be measured/assessed on the same pulse sequence. Generally, axial imaging of the abdomen and pelvis with T1 and T2 weighted imaging along with gadolinium enhanced imaging should be performed. The field of view, matrix, number of excitations, phase encode steps, use of fat suppression and fast sequences should be optimised for the spe-

cific body part being imaged as well as the scanner utilised. It is beyond the scope of this document or appendix to prescribe specific MRI pulse sequence parameters for all scanners, body parts and diseases. Ideally, the same type of scanner should be used and the image acquisition protocol should be followed as closely as possible to prior scans. Body scans should be performed with breath-hold scanning techniques if possible.

Selection of target lesions: In general, the *largest* lesions representative of involved organs (up to a maximum of two per organ and five total) are selected to follow as target lesions. However, in some cases, the largest lesions may not be easily measured and are not suitable for follow-up because of their configuration. In these cases, identification of the largest *most reproducible* lesions is advised. Fig. 3 provides an illustrative example where the largest lesion is not the most reproducible and another lesion is better to select and follow:

Measurement of lesions

The longest diameter of selected lesions should be measured in the plane in which the images were acquired. For body CT, this is the axial plane. In the event isotropic reconstructions are performed, measurements can be made on these reconstructed images; however, it should be cautioned that not all radiology sites are capable of producing isotropic reconstructions. This could lead to the undesirable situation of measurements in the axial plane at one assessment point and in a different plane at a subsequent assessment. There are some tumours, for instance paraspinal lesions, which are better measured in the coronal or sagittal plane. It would be acceptable to measure these lesions in these planes if the reconstructions in those planes were isotropic or the images were acquired with MRI in those planes. Using the same plane of evaluation, the maximal diameter of each target lesion should always be measured at subsequent follow-up time points even if this results in measuring the lesion at a different slice level or in a different orientation or vector compared with the baseline study. Software tools that calculate the maximal diameter for a perimeter of a tumour may be employed and may even reduce variability.

The only exception to the longest diameter rule is lymph node measurement. Because malignant nodes are identified by the length of their short axis, this is the guide used to determine not only whether they are pathological but is also the dimension measured for adding into the sum of target lesions. Fig. 4 illustrates this point: the large arrow identifies a malignant node: the shorter perpendicular axis is $\geqslant$15 mm and will be recorded. Close by (small arrow) there is a normal node: note here the long axis is greater than 10 mm but the short axis is well below 10 mm. This node should be considered non-pathological.

If a lesion disappears and reappears at a subsequent time point it should continue to be measured. However, the patient's response at the point in time when the lesion reappears will depend upon the status of his/her other lesions. For example, if the patient's tumour had reached a CR status and the lesion reappeared, then the patient would be considered PD at the time of reappearance. In contrast, if the tumour status was a PR or SD and one lesion which had disappeared then reappears, its maximal diameter should be added to the sum of the remaining lesions for a calculated response: in other words, the reappearance of an apparently 'disappeared' single lesion amongst many which remain is not in itself en-

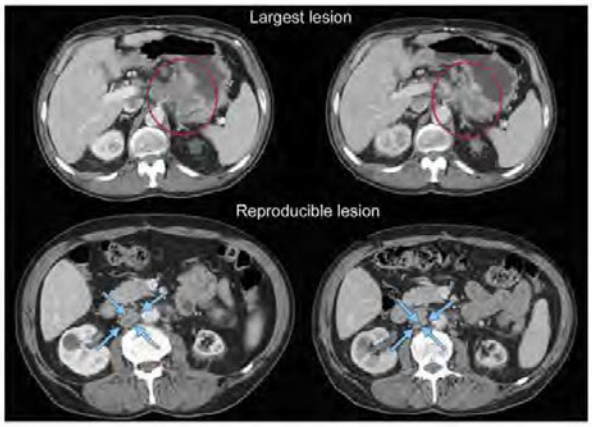

Fig. 3 – Largest lesion may not be most reproducible: most reproducible should be selected as target. In this example, the primary gastric lesion (circled at baseline and at follow-up in the top two images) may be able to be measured with thin section volumetric CT with the same degree of gastric distention at baseline and follow-up. However, this is potentially challenging to reproduce in a multicentre trial and if attempted should be done with careful imaging input and analysis. The most reproducible lesion is a lymph node (circled at baseline and at follow-up in the bottom two images).

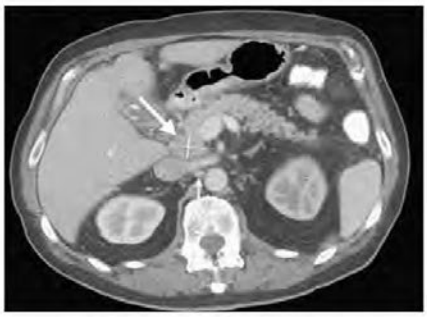

Fig. 4 – Lymph node assessment: large arrow illustrates a pathological node with the short axis shown as a solid line which should be measured and followed. Small arrow illustrates a non-pathological node which has a short axis <10 mm.

ough to qualify for PD: that requires the sum of all lesions to meet the PD criteria. The rationale for such a categorisation is based upon the realisation that most lesions do not actually 'disappear' but are not visualised because they are beyond the resolving power of the imaging modality employed.

The identification of the precise boundary definition of a lesion may be difficult especially when the lesion is embedded in an organ with a similar contrast such as the liver, pancreas, kidney, adrenal or spleen. Additionally, peritumoural oedema may surround a lesion and may be difficult to distinguish on certain modalities between this oedema and actual tumour. In fact, pathologically, the presence of tumour cells within the oedema region is variable. Therefore, it is most critical that the measurements be obtained in a reproducible manner from baseline and all subsequent follow-up timepoints. This is also a strong reason to consistently utilise the same imaging modality.

When lesions 'fragment', the individual lesion diameters should be added together to calculate the target lesion sum. Similarly, as lesions coalesce, a plane between them may be maintained that would aid in obtaining maximal diameter measurements of each individual lesion. If the lesions have truly coalesced such that they are no longer separable, the vector of the longest diameter in this instance should be the maximal longest diameter for the 'merged lesion'.

Progression of non-target lesions

To achieve 'unequivocal progression' there must be an *overall* level of substantial worsening in non-target disease that is of a magnitude that, even in the presence of SD or PR in target disease, the treating physician would feel it important to change therapy. Examples of unequivocal progression are shown in Figs. 5 and 6.

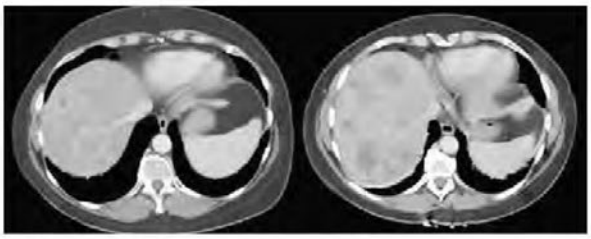

Fig. 5 – Example of unequivocal progression in non-target lesions in liver.

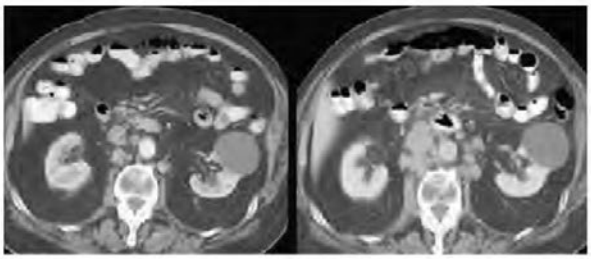

Fig. 6 – Example of unequivocal progression in non-target lesion (nodes).

Appendix III. Frequently asked questions

Question	Answer
What should be done if several unique lesions at baseline become confluent at a follow-up evaluation?	Measure the longest diameter of the confluent mass and record to add into the sum of the longest diameters
How large does a new lesion have to be to count as progression? Does any small subcentimetre lesion qualify, or should the lesion be at least measurable?	New lesions do not need to meet 'measurability criteria' to be considered valid. If it is clear on previous images (with the same technique) that a lesion was absent then its definitive appearance implies progression. If there is any doubt (because of the techniques or conditions) then it is suggested that treatment continue until next scheduled assessment when, generally, all should be clear. Either it gets bigger and the date of progression is the date of the first suspicion, or it disappears and one may then consider it an artefact with the support of the radiologists
How should one lesion be measured if on subsequent exams it is split into two?	Measure the longest diameter of each lesion and add this into the sum
Does the definition of progression depend on the status of all target lesions or only one?	As per the RECIST 1.1 guideline, progression requires a 20% increase in the sum of diameters of all target lesions AND a minimum absolute increase of 5 mm in the sum
Are RECIST criteria accepted by regulatory agencies?	Many cooperative groups and members of pharma were involved in preparing RECIST 1.0 and have adopted them. The FDA was consulted in their development and supports their use, though they don't require it. The European and Canadian regulatory authorities also participated and the RECIST criteria are now integrated in the European note for guidance for the development of anticancer agents. Many pharmaceutical companies are also using them. RECIST 1.1 was similarly widely distributed before publication
What is the criterion for a measurable lesion if the CT slice thickness is >5 mm?	RECIST 1.1 recommends that CT scans have a maximum slice thickness of 5 mm and the minimum size for a measurable lesion is twice that: 10 mm (even if slice thickness is <5 mm). If scanners with slice thickness >5 mm are used, the minimum lesion size must have a longest diameter twice the actual slice thickness
What should we record when target lesions become so small they are below the 10 mm 'measurable' size?	Target lesion measurability is defined at baseline. Thereafter, actual measurements, even if <10 mm, should be recorded. If lesions become very small, some radiologists indicate they are 'too small to measure'. This guideline advises that when this occurs, if the lesion is actually still present, a default measurement of 5 mm should be applied. If in fact the radiologist believes the lesion has gone, a default measurement of 0 mm should be recorded
If a patient has several lesions which have decreased in size to meet PR criteria and one has actually disappeared, does that patient have PD if the 'disappeared' lesion reappears?	Unless the sum meets the PD criteria, the reappearance of a lesion in the setting of PR (or SD) is not PD. The lesion should simply be added into the sum. If the patients had had a CR, clearly reappearance of an absent lesion would qualify for PD
When measuring the longest diameter of target lesions in response to treatment, is the same axis that was used initially used subsequently, even if there is a shape change to the lesion that may have produced a new longest diameter?	The longest diameter of the lesion should always be measured even if the actual axis is different from the one used to measure the lesion initially (or at different time point during follow-up) The only exception to this is lymph nodes: as per RECIST 1.1 the short axis should always be followed and as in the case of target lesions, the vector of the short axis may change on follow-up
Target lesions have been selected at baseline and followed but then one of these target lesions then becomes non-evaluable (i.e. different technique used) What is the effect this has on the other target lesions and the overall response?	What may be done in such cases is one of the following: (a) If the patient is still being treated, call the centre to be sure that future evaluations are done with the baseline technique so at least SOME courses are fully evaluable (b) If that is not possible, check if there IS a baseline exam by the same technique which was used to follow patients...in which case if you retrieve the baseline measures from that technique you retrieve the lesion evaluability (c) If neither (a) nor (b) is possible then it is a judgement call about whether you delete the lesion from all forms or consider the impact of the lesion overall is so important that its being non-evaluable makes the overall response interpretation inevaluable without it. Such a decision should be discussed in a review panel It is NOT recommended that the lesion be included in baseline sums and then excluded from follow-up sums since this biases in favour of a response

(continued on next page)

Appendix III – *continued*

Question	Answer
What if a single non-target lesion cannot be reviewed, for whatever reason; does this negate the overall assessment?	Sometimes the major contribution of a single non-target lesion may be in the setting of CR having otherwise been achieved: failure to examine one non-target in that setting will leave you unable to claim CR. It is also possible that the non-target lesion has undergone such substantial progression that it would override the target disease and render patient PD. However, this is very unlikely, especially if the rest of the measurable disease is stable or responding
A patient has a 32% decrease in sum cycle 2, a 28% decrease cycle 4 and a 33% decrease cycle 6. Does confirmation of PR have to take place in sequential scans or is a case like this confirmed PR?	It is not infrequent that tumour shrinkage hovers around the 30% mark. In this case, most would consider PR to have been confirmed looking at this overall case. Had there been two or three non-PR observations between the two time point PR responses, the most conservative approach would be to consider this case SD
In the setting of a breast cancer neoadjuvant study, would mammography not be used to assess lesions? Is CT preferred in this setting?	Neither CT nor mammography are optimal in this setting. MRI is the preferred modality to follow breast lesions in a neoadjuvant setting
A patient has a lesion measurable by clinical exam and by CT scan. Which should be followed?	CT scan. Always follow by imaging if that option exists since it can be reviewed and verified
A lesion which was solid at baseline has become necrotic in the centre. How should this be measured?	The longest diameter of the entire lesion should be followed. Eventually, necrotic lesions which are responding to treatment decrease in size. In reporting the results of trials, you may wish to report on this phenomenon if it is seen frequently since some agents (e.g. angiogenesis inhibitors) may produce this effect
If I am going to use MRI to follow disease, what is minimum size for measurability?	MRI may be substituted for contrast enhanced CT for some sites, but not lung. The minimum size for measurability is the same as for CT (10 mm) as long as the scans are performed with slice thickness of 5 mm and no gap. In the event the MRI is performed with thicker slices, the size of a measurable lesion at baseline should be two times the slice thickness. In the event there are inter slice gaps, this also needs to be considered in determining the size of measurable lesions at baseline
Can PET–CT be used with RECIST?	At present, the low dose or attenuation correction CT portion of a combined PET–CT is not always of optimal diagnostic CT quality for use with RECIST measurements. However, if your site has documented that the CT performed as part of a PET–CT is of the same diagnostic quality as a diagnostic CT (with IV and oral contrast) then the PET–CT can be used for RECIST measurements. Note, however, that the PET portion of the CT introduces additional data which may bias an investigator if it is not routinely or serially performed

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RECIST 1.1 – Update and Clarification: From the RECIST Committee

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Abstract

The Response Evaluation Criteria in Solid Tumors (RECIST) were developed and published in 2000, based on the original World Health Organization (WHO) guidelines first published in 1981. In 2009, revisions were made (RECIST 1.1) incorporating major changes, including a reduction in the number of lesions to be assessed, a new measurement method to classify lymph nodes as pathologic or normal, the clarification of the requirement to confirm a complete response (CR) or partial response (PR) and new methodologies for more appropriate measurement of disease

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progression. The purpose of this paper is to summarize the questions posed and the clarifications provided as an update to the 2009 publication.

Keywords

RECIST; clarifications; tumor response

Introduction

World Health Organization (WHO) response guidelines were first published in 1981 [1,2]. The RECIST criteria were based on those criteria, and were themselves updated in a 2009 in the European Journal of Cancer (RECIST 1.1) [3]. The revised guidelines incorporated major changes to the original RECIST criteria [2], including a reduction in the number of lesions to be assessed, a new measurement method to classify lymph nodes as pathologic or normal, the clarification of the requirement to confirm a complete response (CR) or partial response (PR) and new recommendations for the assessment of disease progression. Supplementary information provided included imaging guidelines, which better defined image acquisition and interpretation.

The RECIST criteria have gained widespread adoption and are widely used in oncology clinical trials. The RECIST 1.1 paper has been cited 3881 times as of December 2015 Web of Science. Endpoints categorized by the RECIST criteria have been used as either primary or supportive data for regulatory approval of new therapeutics by both the FDA and EMA [4]. RECIST provides a standardized set of rules for response assessment using tumour shrinkage, based upon imaging modalities that are globally available and interpretable by most clinicians. This standardisation, and the rules and criteria established, provide a framework for reproducible analysis and reporting of changes in tumour size. The reproducibility of these criteria and the correlations with historical trial results serve an important purpose in drug discovery.

Despite the widespread acceptance of RECIST, the RECIST Working Group continues its work. RECIST and RECIST 1.1 were developed and tested using data from clinical trials testing cytotoxic drugs. In the last decade, there have been substantial changes in the mechanism of action of cancer therapeutics (targeted agents, immunotherapies), as well as advances in imaging and clinical trial design and endpoints. Although the majority of clinical trials continue to use RECIST as an adjunct to the gold standard endpoints of survival and quality of life, the RECIST Working Group continues to build data warehouses (e.g. data from clinical trials involving targeted agents and immunotherapies, FDG PET/CT data) to review the criteria, update them periodically as required and validate any changes in a standardized, methodical manner in response to both therapeutic and imaging technology advances. Critically, the global oncology community must be able to implement and adopt any changes proposed to RECIST in a timely and cost effective manner.

Since the original publication, users have submitted questions on the use and interpretation of the guidelines through the RECIST website (http://www.eortc.org/recist/). These questions are reviewed by the Steering Committee and replies provided based on the 2009

publication. If not addressed in the publication, the Working Group is consulted to prepare appropriate replies. Relevant and/or frequently asked questions (FAQs) are posted on a regular basis on the RECIST website.

Here we summarize the questions and clarifications posed as an update to the 2009 publication.

Commonly asked questions regarding RECIST 1.1

1. What is the frequency of tumour evaluation?

   The schedule and frequency of tumour response re-evaluation is protocol-specific and is based on the therapeutic, the disease, the anticipated time to response and progression as well as practical considerations such as cost and patient convenience.

   However, in the context of phase II studies where the beneficial effect of therapy is not known, follow-up every 6–8 weeks (timed to coincide with the end of a cycle) is reasonable. Shorter or longer time intervals than these could be justified in specific regimens or circumstances. The protocol should specify which areas (chest, abdomen) and organs are to be evaluated at baseline (usually those most likely to be involved with metastatic disease for the tumour type under study) and how often evaluations should be repeated [2]. The method of assessment should be stated and, ideally, repeated using the same imaging technique, equipment and assessor each time. Additional assessments should be performed if there is suspicion of new site of metastasis, or of disease progression based upon clinical symptoms. The presence of a new lesion(s) should be documented on an imaging study. All potential sites of metastases should be evaluated at each time point rather than following only sites of disease identified at baseline.

2. Should lesions smaller than 5 mm be reported as the actual size or reported as a default value of 5 mm?

   All lesions, both nodal and non-nodal, must be evaluated, accurately measured (if measurable/target) and recorded at all timepoints. If a lesion is no longer seen, it should be recorded as zero (or absent if non-measurable /non-target). If a lesion is smaller than 5 mm and the radiologist believes the lesion can be accurately measured then the actual size should be recorded.

   It is recognized that lesions become small and ill-defined on a CT scan such that the radiologist cannot accurately measure them. Some radiologists use the term "too small to measure" to describe this phenomena. When this occurs, the radiologist may decide that the lesion is present but he/she does not feel comfortable providing the oncologist with a precise measurement. If this occurs, the radiologist may assign the lesion a value of 5 mm by default. This default value is nominally derived from the 5 mm CT slice thickness (but should not be changed with varying CT slice thickness). The measurement of this type of lesion is potentially non-reproducible, and providing this default value will

prevent a false assessment of response or progressive disease due to measurement error.

3. If there are three or more measurable lesions in one organ, and we select two of them as target lesions, how should the third lesion be considered?

   The third lesion should be considered a non-target lesion and should be recorded and followed as part of the non-target disease.

4. Is a single target lesion measurable if a patient has multiple non-target non-measurable disease?

   Yes, a single target lesion is considered measurable disease provided the lesion meets the definition of measurability as described in RECIST 1.1.

5. How should the limitation of two target lesions per organ be applied to lymph nodes? Can individual chains/regions be considered one organ or are lymph nodes (all locations included) a single organ?

   Lymph nodes are considered one organ. Only two lymph nodes should be measured per patient as target lesions. Other involved lymph nodes should be assessed and followed as non-target lesions. The analysis of data from the RECIST warehouse was performed in this manner.

6. Should double the slice thickness/interval be applied to lymph nodes as well when a CT slice thickness of 10 mm is used?

   It is strongly recommended that CT slice thickness of 5 mm be used. Although RECIST 1.1 (2009) recommends the following: "As is described in Appendix II, when CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness", in 2016 contemporary CT scanners globally should be able to acquire images with a slice thickness of 5 mm or less. This is recommended by the Quantitative Imaging Biomarkers Alliance (QIBA) guidelines for standardizing image acquisition for CT (http://rsna.org/QIBA_.aspx) [5]. There are many disadvantages and no real advantages in obtaining 10 mm slices. Not only are lesions more difficult to measure, but new lesion conspicuity is significantly less at 10 mm [6, 7].

7. When lymph nodes coalesce forming a conglomerate mass, which axis should be measured to assess the response: short or long axis?

   The short axis of lymph nodes should always be measured. As nodal lesions coalesce, a plane between them may be maintained that would aid in obtaining maximal short axis diameter measurements of each individual lesion. If the nodal lesions have truly coalesced such that they are no longer separable, the vector of the longest diameter in this instance should be used to determine the perpendicular vector for the maximal short axis diameter of the coalesced lesion (Fig. 1). Non-nodal lesions that coalesce should similarly be assessed by the longest diameter.

8. Clarification of the definition of Stable Disease (SD)

The definition of stable disease is clarified as follows: "Neither sufficient shrinkage (compared to baseline) to qualify for partial or complete response (CR or PR) nor sufficient increase (taking as reference the smallest sum of diameters at baseline or while on study, whichever is smallest) to qualify for progressive disease (PD)".

It is important to recognize that the classification of a response (either CR or PR) occurs in comparison to the sum of diameters at *baseline*, while progression is based on a comparison to the smallest of the sum of diameters at *baseline* or the smallest sum of diameters during the trial (*nadir*). Most protocols require the criteria for SD for a specified period (for example at least 4 weeks) before SD can be concluded. Thus, if imaging is conducted at 2 weeks and 4 weeks on-study, and at 2 weeks the criteria for CR, PR or PD are not met, but at 4 weeks meets the criteria for PD, the best overall response is PD, not SD as the subject was not on-study long enough to qualify for SD.

9. If an abnormal lymph node (or non-nodal disease) 'disappears' but then 'reappears' should this considered to be PD?

In general, significant lesions that completely regress and then reappear are indicative of PD. However, it is important to consider the patient's entire tumor burden in order to make certain that the patient is not falsely classified as having PD based upon a single measurement or lesion, especially when those lesions are small or there is a change in optimal imaging assessment. This holds true for all types of metastases (Fig 2)

If the response was previously considered to be CR, with resolution of all sites of disease, then the reappearance of any lesion, or the development of a new lesion considered to be malignant, would generally be considered PD (see comments below regarding lymph nodes).

In the case of PR or SD, if a previously resolved lesion reappears, then PD should not be assigned purely based on the reappearance of the lesion; rather, other criteria for PD must be met as well, such as the appearance of new lesions or a sum measurement of target lesions that has increased more than 20%.

It is important to remember that lymph nodes must meet the criteria for malignancy (defined pragmatically as ≥ 10mm) in order to be considered to have reappeared. A node which is less than 10 mm is considered benign and is not PD. In a subject with CR, a new node that meets the size criteria for a pathologic node is considered a new site of disease and is therefore consistent with PD. In subjects with PR or SD:

a. A previously abnormal target node that became normal and subsequently enlarged in size meeting the criteria for a pathologic and measurable node (a short axis of ≥ 15 mm) should be added to the Sum of the Diameters (SOD) to determine if the criteria for PD are met based on target lesions.

b. A previously abnormal non-target node that became normal and subsequently recurred must meet the criteria for PD based on NT lesions to call progression.

c. A normal node at baseline that subsequently becomes pathologic is considered a new lesion and results in PD.

In the circumstances illustrated above, where a single pathologic node is driving the progression event, continuation of treatment/follow-up and confirmation by a subsequent exam should be contemplated. If it becomes clear that the "new node" has not resolved, or has significantly increased in size, and truly represents PD, the date of PD would be the date the new node was *first* documented.

10. How should patients be classified who have had surgery/radiotherapy during trials for which they are being followed by RECIST?

For most clinical trials using RECIST, surgery or radiotherapy after trial inclusion and prior to disease progression is a protocol deviation, and if a target lesion has been surgically removed or treated with radiotherapy, then the patient's response is not evaluable. If surgery or radiotherapy is part of the clinical trial, then the protocol must define in advance how response and progression will be handled and 'censored' in the analyses. If the treatment has resulted in inoperable lesions being suitable for resection, the researcher may wish to capture that separately as an indicator of 'activity".

11. The section on FDG-PET mentions that correlation with CT is warranted for new lesions, and that PD should be declared if the hot spot on PET corresponds to a progressing lesion on CT. How should this correlation be made if the hot spot on PET corresponds to a target lesion that has increased in size but the sum of the measurements does not show an increase that is sufficient for PD (other target lesions have not enlarged or have actually decreased). Is this PD?

The RECIST 1.1 guidelines state "a. Negative FDG-PET at baseline, with a positive FDG-PET at follow-up is a sign of PD based on a new lesion. b. No FDG-PET at baseline and a positive FDG-PET at follow- up: If the positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT, this is PD. If the positive FDG-PET at follow-up is not confirmed as a new site of disease on CT, additional follow-up CT scans are needed to determine if there is truly progression occurring at that site (if so, the date of PD will be the date of the initial abnormal FDG-PET scan). If the positive FDG-PET at follow-up corresponds to a pre-existing site of disease on CT that is not progressing on the basis of the anatomic images, this is not PD".

Therefore, the scenario is not PD. Currently PET scanning is considered a complementary modality primarily to assess for new tumor lesions. Therefore, if a target lesion is FDG avid and even if the standardized uptake value (SUV) on PET has increased, the patient would only be considered to be PD if the CT metrics for progression were met, including a greater than 20% increase in the

sum measurement of lesions, non-target unequivocal PD or new lesions on CT (regardless of their presence or SUV on PET).

12. If there is a hot spot on FDG-PET (baseline PET is not available) that is not associated with a new CT (or MRI) lesion, the article states that PD should not be declared. What should the response be, not evaluable (NE)?

FDG-PET is a complementary modality and should be used in adjunct to the CT or MRI. Therefore, in this example, the patient's response should be based solely upon the measurements and findings on CT and/or MRI. Since there is no PET at baseline and no corresponding new lesion on CT or MRI then the patient can only be assessed on the existing lesions and their change from baseline to follow-up on CT or MRI. Providing the scan was evaluable and all lesions visible/measurable, the response would therefore be CR, PR or SD as no new lesions were seen on CT/MRI.

13. Can the CT information from PET-CT be used as the basis of CT assessments? Is the technical quality of such images sufficient for quantification as required in RECIST?

At present, the low dose or the attenuation correction CT portion of a combined PET-CT is not of optimal diagnostic CT quality for use with RECIST measurements. However, if the site has documented that a CT with appropriate radiation dose for diagnostic quality and IV and oral contrast was used (if not medically contraindicated) the CT portion of the PET-CT can be used for RECIST measurements.

14. Can we use coronal or sagittal imaging to measure lesions in CT if the largest diameter is in a plane other than axial?

It is recommended that the axial imaging plane be used in all cases on CT scans for consistency and for ease of measurement especially since reconstructions or advanced workstations are not always available globally. It is recognized that the other planes may represent the true long axis of the tumor but depending on the CT acquisition parameters across timepoints this may be difficult to consistently and reproducibly measure.

Conclusions

The RECIST Working Group is currently testing the Criteria for their applicability with modern therapeutics, imaging techniques and trial endpoints. The current RECIST 1.1 criteria remain widely used. A number of users have asked questions regarding the interpretation of the 2009 Criteria and we have attempted to summarize those questions, and the answers, in this update. For further updates on the criteria, please visit the RECIST website at http://www.eortc.org/recist/

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Highlights

- Clarification on how to select target lesions and what to do with measurable lesions which are not selected for target disease response assessment
- Clarification on the definition of stable disease
- Clarification on the role of FDG-PET/PET-CT in the context of RECIST 1.1

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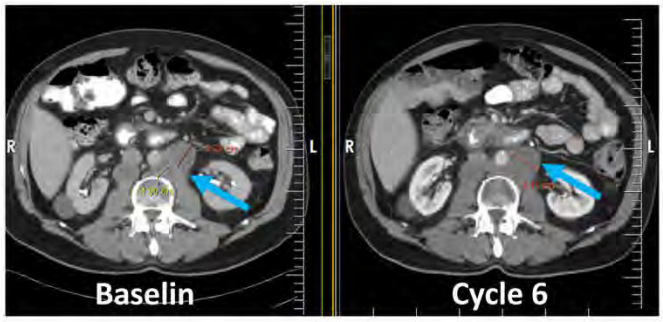

Fig 1.
Note optimal manner for measuring the short axis of coalescing lymph nodes (blue arrow). At baseline, there are two distinct nodes, therefore the short axis is measured for each (red and yellow lines) and at cycle 6 the single short axis of the coalesced node is now measured as a single line (red).

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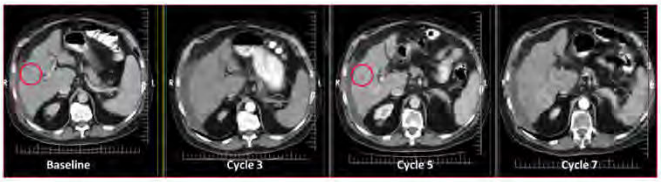

Fig. 2.

Patient with colorectal cancer. Liver metastases at baseline (red circle) appear to resolved at cycle 3 with "reappearance" at cycle 5 (red circle). However, notice that the imaging techniques are different and the cycle 3 is of poor image quality to visualize these metastases. Therefore, these lesions have not truly reappeared and the patient should not be considered to have progressive disease at cycle 5. There is true progression at cycle 7.

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16.2 Appendix 2 - iRECIST

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iRECIST: guidelines for response criteria for use in trials testing immunotherapeutics

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For the **EORTC RECIST data warehouse** see www.eortc.org/RECIST

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Abstract

Tumours respond differently to immunotherapies compared with chemotherapeutic drugs, raising questions about the assessment of changes in tumour burden—a mainstay of evaluation of cancer therapeutics that provides key information about objective response and disease progression. A consensus guideline—iRECIST—was developed by the RECIST working group for the use of modified Response Evaluation Criteria in Solid Tumours (RECIST version 1.1) in cancer immunotherapy trials, to ensure consistent design and data collection, facilitate the ongoing collection of trial data, and ultimate validation of the guideline. This guideline describes a standard approach to solid tumour measurements and definitions for objective change in tumour size for use in trials in which an immunotherapy is used. Additionally, it defines the minimum datapoints required from future trials and those currently in development to facilitate the compilation of a data warehouse to use to later validate iRECIST. An unprecedented number of trials have been

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done, initiated, or are planned to test new immune modulators for cancer therapy using a variety of modified response criteria. This guideline will allow consistent conduct, interpretation, and analysis of trials of immunotherapies.

Introduction

Changes in tumour burden (termed response) are often used as surrogates of survival or quality of life;[1] consequently, validated and consistent criteria for defining response to treatment are crucial. In 2000, the Response Evaluation Criteria in Solid Tumours (RECIST) working group simplified the 1981 WHO response criteria[2] after validation in a large data warehouse.[3] In 2009, RECIST was refined to RECIST version 1.1.[4] The RECIST working group ensures that RECIST undergoes continuous testing, validation, and updates.[5–7]

Immune modulators are one of the most important classes of new anticancer therapeutics.[8–10] Cytotoxic T-lymphocyte antigen-4 (CTLA-4), programmed death-1 (PD-1), and programmed death ligand-1 (PD-L1) pathways are the most intensively studied,[11–17] and drugs that are active in these pathways have, since 2011, received marketing authorisation (for some drugs the authorisation is conditional, pending the completion of other studies) for melanoma, lung, bladder, renal, and head and neck cancer.[18–23] The novel mechanism of action of these drugs, with immune and T-cell activation, is postulated to lead to unusual patterns of response that resemble tumour flare but are more pronounced and more frequent than previously described responses. In early trials of immune-based therapeutics in melanoma, investigators described unique response patterns, termed pseudoprogression. Some patients whose disease met the criteria for disease progression based on traditional response criteria such as RECIST (an increase in the sum of measures of target lesions, unequivocal increase in non-target disease, or the appearance of new lesions) were noted to have late but deep and durable responses.[24–28] In 2009, modified response criteria based on WHO criteria (which include the collection of bidimensional measurements of target lesions) were proposed—the immune-related response criteria (irRC).[29] The major modification involved the inclusion of the measurements of new target lesions (each must be at least 5 × 5 mm in size; with a maximum of ten visceral lesions in total, up to five new lesions per organ, and five new cutaneous lesions) into disease assessments. In 2013, researchers published revised irRC using unidimensional measurements based on the original RECIST.[30] Subsequent recommendations, some published in abstract form, seem to incorporate RECIST 1.1 recommendations.[31–33] These recommendations are often referred to as irRECIST, but have not always been consistently applied, leading to concerns about the comparability of data and results across trials, difficulty with pooling databases, and poor clarity regarding whether new lesions were measured, and if so, how many were captured, and whether measures were incorporated into tumour burden. Recent trials (since 2010) have generally used RECIST-based immune criteria to assess responses to immunotherapies.

Because of the need to standardise and validate response criteria, the RECIST working group prospectively planned to create a warehouse of data from trials of immunotherapeutics to test and validate RECIST 1.1 and suggest modifications if required. During the planning

and initial collection of the immunotherapeutic warehouse, it was apparent that most trials testing these drugs have typically used RECIST 1.1 to define the primary and secondary efficacy-based endpoints, and reserved irRC or their modified definition of RECIST for exploratory endpoints.[31,32] Additionally, substantial variability in which criteria were used was seen across clinical trials within pharmaceutical companies and cooperative groups, leading to serious concerns about interpretation of pooled datasets. Finally, most trials that used immune-modified criteria used independent imaging review by a commercial entity for those criteria, rather than investigator assessments. We think that response criteria should be applicable across all cancer clinical trials, including those done in the academic sector, where costly independent review is not feasible.

On the basis of these observations, the RECIST working group decided to develop a guideline for the use of a modified RECIST to ensure consistent design and data collection that would facilitate the ongoing collection of clinical trial data and ultimate validation, if indicated, of a modified RECIST 1.1 for immune-based therapeutics (termed iRECIST). These guidelines are not intended to define or guide clinical practice or treatment decisions, but rather to provide a consistent framework for the management of data collected in clinical trials of immune-based therapies. Treatment decisions rest with the patient and their health-care team.

Terminology

iRECIST is based on RECIST 1.1. Responses assigned using iRECIST have a prefix of "i" (ie, immune)—eg, "immune" complete response (iCR) or partial response (iPR), and unconfirmed progressive disease (iUPD) or confirmed progressive disease (iCPD) to differentiate them from responses assigned using RECIST 1.1. Similar nomenclature is used for stable disease (iSD). New lesions are assessed and subcategorised into those that qualify as target lesions (new lesion, target) or non-target lesions (new lesion, non-target).

Development of the guideline

The RECIST working group formed a subcommittee and held a series of conference calls and face-to-face meetings in 2015 and 2016 to discuss plans for the development and validation of iRECIST (figure 1) and to review existing approaches to assess response in immune modulator trials, and also to identify points of consensus and items that needed further discussion. Members of the subcommittee included clinical, statistical, and imaging experts in methodology and immunotherapy, representatives from the pharmaceutical companies developing immunotherapeutics, and key regulatory authorities (appendix p 1). On June 2, 2016, a formal meeting was held in Chicago (IL, USA), with invited presentations from regulatory authorities, pharmaceutical companies with immune modulator drugs in development, and academic groups, followed by a structured discussion. Before the meeting, the 52 invited participants were polled to enable the identification of questions that needed to be addressed, as well as the response criteria routinely used by participants. Ten respondents provided responses before the meeting (including some pooled responses) and all eight presenters identified additional areas of interest in their presentations. After review and discussion during the meeting, the group identified a list of

important questions to be addressed by iRECIST (panel 1). Notably, all participants confirmed that RECIST 1.1 was used for primary endpoints, with immune-modified response criteria being used in an exploratory manner, with very few exceptions; in one instance, immune-modified criteria were used as a coprimary endpoint. The most commonly used immune-modified criteria were variations of irRECIST. There was more variability in independent imaging review and the period of time during which response data were collected after RECIST 1.1 progression or cessation of protocol therapy. Further calls and meetings were held to develop and plan the full validation of iRECIST (figure 1).

iRECIST

The continued use of RECIST 1.1 is recommended to define whether tumour lesions, including lymph nodes, are measurable or non-measurable, as well as for the management of bone lesions, cystic lesions, and lesions with previous local treatment (eg, radiotherapy; table 1). Similarly, no changes have been made to the recommendations regarding the method of measurement, although clinical examination and chest radiograph are rarely used, with the availability of more modern imaging techniques (eg, CT scans and MRI). The principles used to establish objective tumour response are largely unchanged from RECIST 1.1, but the major change for iRECIST is the concept of resetting the bar if RECIST 1.1 progression is followed at the next assessment by tumour shrinkage.

iRECIST defines iUPD on the basis of RECIST 1.1 principles; however, iUPD requires confirmation, which is done on the basis of observing either a further increase in size (or in the number of new lesions) in the lesion category in which progression was first identified in (ie, target or non-target disease), or progression (defined by RECIST 1.1) in lesion categories that had not previously met RECIST 1.1 progression criteria. However, if progression is not confirmed, but instead tumour shrinkage occurs (compared with baseline), which meets the criteria of iCR, iPR, or iSD, then the bar is reset so that iUPD needs to occur again (compared with nadir values) and then be confirmed (by further growth) at the next assessment for iCPD to be assigned. If no change in tumour size or extent from iUPD occurs, then the timepoint response would again be iUPD. This approach allows atypical responses, such as delayed responses that occur after pseudoprogression, to be identified, further understood, and better characterised (tables 1–3, figure 2, appendix pp 2–4). Sample case record forms and protocol sections are included in the appendix pp 5–19. In the next few paragraphs, we only briefly summarise sections of RECIST 1.1 that are unchanged; readers should refer to RECIST 1.1 for full descriptions.[4]

Assessment of target, non-target, and new lesions

Most RECIST 1.1 recommendations are unchanged for timepoint response, including the management of lymph nodes, lesions that become too small to measure, lesions that split or coalesce, and the definition of complete response, partial response, stable disease, and progressive disease. Each timepoint response is based on the assessment of target lesions, non-target lesions, and new lesions.

For target lesions, iCR, iPR, and iSD can all be assigned after iUPD has been documented, as long as iCPD was not confirmed. iUPD is defined by RECIST 1.1 criteria for progressive

disease; iUPD can be assigned multiple times as long as iCPD is not confirmed at the next assessment. Progression is confirmed in the target lesion category if the next imaging assessment after iUPD (4–8 weeks later) confirms a further increase in sum of measures of target disease from iUPD, with an increase of at least 5 mm. However, the criteria for iCPD (after iUPD) are not considered to have been met if complete response, partial response, or stable disease criteria (compared with baseline and as defined by RECIST 1.1) are met at the next assessment after iUPD. The status is reset (unlike RECIST 1.1, in which any progression precludes later complete response, partial response, or stable disease). iCR, iPR, or iSD should then be assigned; and if no change is detected, then the timepoint response is iUPD.

The assessment of non-target lesions at each timepoint follows similar principles. iUPD (but not iCPD) can have been documented before iCR or when the criteria for neither CR nor PD have been met (referred to as non-iCPD/non-iUPD) and can be assigned several times, as long as iCPD was not confirmed. iUPD is defined by RECIST 1.1 criteria; however, iUPD can be assigned multiple times as long as iCPD is not confirmed at the next assessment. Progressive disease in the non-target lesion category is confirmed if subsequent imaging, done 4–8 weeks after iUPD, shows a further increase from iUPD. The criteria for iCPD are not judged to have been met if RECIST 1.1 criteria for complete response or non-iCR/non-iUPD are met after a previous iUPD. The status is reset (unlike RECIST 1.1) and iCR, or non-iCR/non-iUPD is assigned; if no change is detected, the timepoint response is iUPD.

RECIST 1.1 defines the appearance of new malignant lesions as denoting true disease progression, providing that other lesions (artefacts or benign intercurrent disease) are appropriately assessed and discounted if not malignant. These principles of RECIST 1.1 remain useful and clearly identify the management of new lesions that are considered to be potentially artefactual: "If a new lesion is equivocal, for example because of its small size, continued therapy and follow-up assessment will clarify whether it represents truly new disease. If repeat scans confirm there is definitely a new lesion, then progression should be declared using the date of the initial scan".[4]

However, many aspects of new lesion assessment are unique to iRECIST. If a new lesion is identified (thus meeting the criteria for iUPD) and the patient is clinically stable, treatment should be continued. New lesions should be assessed and categorised as measurable or non-measurable using RECIST 1.1 principles. Five lesions (no more than two per organ) should be measured and recorded as a new lesion target, but should not be included in the sum of measures of the original target lesions identified at baseline (appendix p 17). Other measurable and non-measurable lesions are recorded as new lesion non-target. Trialists might choose to measure and record more than five new lesions for research purposes, but this method is not believed to be practical for general use. New lesions do not need to meet the criteria for new lesion target to result in iUPD (or iCPD); new lesion non-target can also drive iUPD or iCPD. Progressive disease is confirmed (iCPD) in the new lesion category if the next imaging assessment, done at 4–8 weeks after iUPD, confirms additional new lesions or a further increase in new lesion size from iUPD (sum of measures increase in new lesion target ≥5 mm, any increase for new lesion non-target).

Notably, if iUPD criteria were met on the basis of progression in the target or non-target disease, or the appearance of new lesions, then RECIST 1.1-assigned progression in another lesion category in the confirmatory scan also confirms iCPD.

Continued treatment after iUPD

The existing literature describes pseudoprogression as an increase in the size of lesions, or the visualisation of new lesions, followed by a response, which might be durable. Although well described, differentiating transient pseudoprogression from true progression, potentially requiring a change in therapy, can be challenging. Although early discontinuation of an effective drug is not desirable, continued long-term treatment with a non-effective drug past true progression might delay the initiation of potentially effective salvage therapy.

We recommend that clinical trials in which treatment beyond initial RECIST 1.1-defined progression (ie, iUPD) is permitted should only allow patients who are clinically stable to continue on treatment until the next assessment (≥4 weeks later); this next imaging assessment should be no longer than 8 weeks later, to ensure that patients remain fit for salvage therapies. A longer timeframe before the next assessment might be reasonable if pseudoprogression is well described in the tumour type (eg, melanoma treated with a CTLA4 inhibitor), especially if no effective salvage therapies are available (eg, *BRAF* wild-type melanoma) but should be justified in the trial protocol. All decisions regarding continuation or discontinuation of therapy should be made by the patient and their health-care provider; iRECIST describes what data are to be collected, submitted, and analysed in clinical trials of immune-based therapies.

An assignment of clinical stability requires that no worsening of performance status has occurred, that no clinically relevant increases in disease-related symptoms such as pain or dyspnoea occur that are thought to be associated with disease progression (these symptoms are generally understood to mean a requirement for increased palliative intervention), and that no requirement for intensified management of disease-related symptoms exists, including increased analgesia, radiotherapy, or other palliative care.

The imaging findings and the recommendation to continue with treatment despite iUPD should be discussed with the patient before a decision is made about whether or not to continue therapy. Patients who have iUPD and are not clinically stable should be designated as not clinically stable in the case report form. This designation will allow the best overall response to be calculated and the date of iUPD to be used in estimates of progression-free survival.

If the confirmatory scan confirms iCPD, but the investigator or patient believes that continued treatment is appropriate, imaging should continue and data should be collected to allow further elucidation of tumour growth dynamics with immune modulators. For the same reason, and if feasible, even patients who discontinue therapy for iCPD are recommended to continue to have disease assessments until they start other systemic or local therapies.

Timepoint and best overall response

Although the principles of the assignment of the timepoint response and best overall response closely follow RECIST 1.1, and reflect assessment of target and non-target lesions as well as the presence of new lesions, the possibility of pseudoprogression adds complexity (tables 1–3, panel 2, appendix pp 2–4). The timepoint response is calculated using the response assigned for each category of lesion (as for RECIST 1.1), but takes into account the last timepoint response.

The algorithm for patients with no previous iUPD is identical to RECIST 1.1. For patients with iUPD at the last timepoint response, the next timepoint response is dependent on the status of all lesions, including target, non-target, new lesion target, and new lesion non-target; on whether any increase in size has occurred (either a further increase in size or a sufficient increase to assign a new iUPD if the criteria were not previously met); or the appearance of additional new lesions.

For iRECIST, the best overall response (iBOR) is the best timepoint response recorded from the start of the study treatment until the end of treatment, taking into account any requirement for confirmation. iUPD will not override a subsequent best overall response of iSD, iPR, or iCR (tables 1–3, appendix pp 2–4), meaning that iPR or iSD can be assigned (timepoint response or iBOR) even if new lesions have not regressed, or if unequivocal progression (non-target lesions) remains unchanged, providing that the criteria for iCPD are not met.

Confirmation of response is not required when using RECIST 1.1, except in non-randomised trials, and this approach is also recommended for iRECIST. The duration of iCR and iPR is from the timepoint when the criteria for iCR or iPR are first met, whereas the duration of iSD is still calculated from baseline.

The protocol should establish how missing response assessments will be handled. Assessments that are not done or are not evaluable should be disregarded. For example, an iUPD followed by an assessment that was not done or not evaluable, and then another unconfirmed progressive disease, would be indicative of iCPD. Protocols should clearly specify whether assessments done after protocol therapy is discontinued can be considered in identification of iBOR; it might be reasonable to include assessments done several weeks or months after protocol treatment has been discontinued if late responses are anticipated (such as with a CTLA4 inhibitor) and patients have not received other systemic or local therapies. Protocols should also specify how any new therapy introduced before progression (eg, radiotherapy or surgery) will affect iBOR designation. Other RECIST 1.1 recommendations, including the management of missing assessments, remain unchanged, including requiring that the statistical analysis plan should indicate how missing data or assessments will be addressed in the determination of response and progression.

Frequency of tumour reassessment

In general, follow-up response assessment every 6–12 weeks is recommended for iRECIST, depending on the frequency of treatment visits, as recommended for RECIST 1.1. The protocol should specify which anatomical locations are assessed at baseline and follow-up,

and whether bone scans should be repeated at each response assessment, only to confirm iPR or iCR, or when clinically indicated. For all trials, especially comparative ones, response assessments should be done on a calendar schedule and not be affected by delays in therapy or the requirement for earlier confirmatory scans, which might be done to confirm iUPD or in some trials, to confirm complete or partial response.

Tumour reassessment can be done earlier than originally planned (but only between 4 and 8 weeks after iUPD) to confirm iUPD (or, in non-randomised trials, to confirm iCR or iPR ≥4 weeks after the scan showing complete or partial response). If progression is not confirmed, reassessment should continue as originally planned (ie, if scans were to be done at 8, 16, and 24 weeks, and a scan was done at 12 weeks to confirm response, then the next scans should be done at 16 weeks and 24 weeks, as planned). If patients continue on treatment per protocol after iCPD, assessments should continue to be done, at the same planned schedule, until protocol treatment is discontinued.

Ideally, all imaging done after protocol treatment has been discontinued should continue to be recorded on the case report form until subsequent therapies are initiated, as the protocol and informed consent document permit. These data will allow further refinement of iRECIST.

Statistical and protocol considerations

The event date to be used for calculation of progression-free survival (iPFS) should be the first date at which progression criteria are met (ie, the date of iUPD) provided that iCPD is confirmed at the next assessment (appendix pp 2–4 and 19). If iUPD occurs, but is disregarded because of later iSD, iPR, or iCR, that iUPD date should not be used as the progression event date.

If progression is not confirmed and there is no subsequent iSD, iPR, or iCR, then the iUPD date should still be used in the following scenarios: if the patient stops protocol treatment because they were not judged to be clinically stable, or no further response assessments are done (because of patient refusal, protocol noncompliance, or patient death); the next timepoint responses are all iUPD, and iCPD never occurs; or the patient dies from their cancer. The case report form collects the reason why confirmatory response assessment was not done at any timepoint, such as not clinically stable, centre error, patient refusal, or patient death.

For protocols that permit crossover, or if intermittent schedules are being tested, the protocol should clearly specify whether iUPD or iCPD would be used for a treatment decision leading to crossover and how data subsequent to crossover will be managed and analysed. In general, we suggest that iCPD be used especially for scenarios with immunotherapy in both treatment groups and when pseudoprogression is anticipated.

Adjuvant trials of immune modulators given after curative surgery for melanoma or lung cancer are ongoing (NCT 02437279, 02388906, 02595944, 02504372, and 02273375) but have yet to report their results. Suspected new lesions in the curative setting should always be investigated thoroughly and preferably have a biopsy taken before the designation of

relapse is assigned. If taking a biopsy sample is not technically feasible, then it would seem to be reasonable to follow the principles of iRECIST, with a follow-up scan to confirm relapse in patients who are clinically stable.

The collection of anonymised imaging (even if centralised blinded review of imaging studies is not planned) is recommended for all studies using an imaging-based endpoint (ie, response or progression-free survival) if feasible. Although the iRECIST guideline requires the recording of the measurements of up to five new lesions, it might eventually be necessary to record additional lesions to obtain a more precise estimate of progression. Central collection of images will allow further assessment by an independent radiologist if necessary. If real-time central review is planned, the protocol should clearly explain how treatment decisions will be made.

We recommend that phase 3 clinical trials continue to incorporate both RECIST 1.1 and iRECIST (table 1) and that RECIST 1.1 should continue to be used to define the primary efficacy outcomes (progression-free survival, disease progression, and best overall response). Exploratory analyses using the iPD date (ie, the first date of iUPD that is subsequently confirmed) can be defined in the statistical analysis plan. Early-phase trials can consider using iRECIST as the primary criteria. The protocol should carefully explain which will be the primary criteria used to assess response, and which would be exploratory. This information is especially important for trials that compare an immune modulator treatment with a non-immune modulator treatment.

Discussion: next steps and validation

Immunotherapeutics are a major advance in the treatment of an escalating number of cancers. The increasing testing and use of these drugs in multiple clinical settings, including adjuvant, first, second, and subsequent lines of therapy will require the use of progression-based endpoints. RECIST 1.1 might not always adequately capture the unique patterns of response that have been well described in clinical trials of these drugs in a low proportion of patients, typically reported as 10% or less, mainly in melanoma studies.[32–34] The true frequency in trials of other malignancies (including non-small-cell lung cancer) is unclear because most trials have reported RECIST 1.1-based response rates,[35] but might be less common based on anecdotal reports. Similarly, whether this pattern is unique to drugs active in the CTLA4–PD-1–PD-L1 pathway is currently unknown. Trials testing immunotherapeutics in combination with standard therapies, especially when they are compared with these standard therapies alone, further confound the assessment of progression-based endpoints.

RECIST 1.1 already addresses the management of equivocal progression, including suspected new lesions, which might explain, at least in part, the continued use of RECIST 1.1 to define response-based primary endpoints. RECIST 1.1 deals with mainly technical differences in scans that give the appearance that new lesions might have developed, or the concept of the isodense lesion at baseline that becomes more visible after the start of therapy since it becomes internally more necrotic as opposed to a true new lesion. However, the

intention was never to use those recommendations to manage pseudoprogression described with immune modulators.

Although modified response criteria have been used, a formal guideline is clearly needed, with robust plans for prospective testing and consistent data collection and validation. Trials have not always been consistent in the definition of the response criteria to be used, have used trial-specific modifications of response criteria in which new lesion measurements can or cannot be included in the assessment of response, and response assessments after progression defined by RECIST 1·1 are not always done. Those data are crucial to understand the dynamics of tumour response to immunotherapeutics, including whether immunotherapeutics with different mechanisms of action have varying effects.

Although some progress has been made in understanding tumour dynamics with immunotherapeutics, progress in this area has undoubtedly been limited by reluctancy toward data sharing across trials, companies, and immunotherapeutics. Publications have been based on trials done by individual pharmaceutical companies or commercial organisations. In the development of this guideline, virtually all major pharmaceutical companies developing immunotherapeutics participated and have shared their experiences, protocols, response criteria, and, most importantly, their data. The iRECIST team also included members of the European Medicines Agency and the US Food and Drug Administration.

Although this guideline is consensus based, it is not yet validated because the data warehouse is still being created with initial trial data already in place. The guideline includes all available knowledge on response dynamics, allowing appropriate management of true pseudoprogression, but importantly, it also safeguards patients: although pseudoprogression is now well described, it still only occurs in fewer than one in ten patients. Treatment past radiographic progression might be appropriate only in a small number of patients, and the continuation of treatment past true progression could reduce subsequent effective therapies if the patient is no longer fit enough to tolerate any further treatment.

iRECIST requires the confirmation of progression to rule out or confirm pseudoprogression. Although this recommendation is in keeping with that of RECIST 1.1 to continue treatment and repeat imaging in the case of a mixed response or equivocal findings, if pseudoprogression is common, patients might be exposed to a higher risk (of continuing ineffective therapy or increasing exposure to radiotherapy) or cost (for the potentially ineffective therapy or the costs of imaging). We recommend that these criteria are used for clinical trial protocols rather than to guide clinical practice. Treatment beyond RECIST 1.1-based progression should be considered only in carefully selected scenarios in which the patient is stable (or improving) symptomatically and if there is just a short period remaining before reassessment.

Although at first glance the recommendation to collect measurements of new lesions as defined in this guideline seems onerous, the collection of these measurements and the recording of both RECIST 1.1 and iRECIST for timepoint response and best overall response have several benefits. The association between the site of the new lesion and

progression-free survival and the value of adding new lesion measurements to the sum of measures can be explored. Continuing to record RECIST 1.1 allows comparison with reported immunotherapy trials that have used RECIST 1.1, as well as chemotherapy trials, while also allowing treatment past progression and collecting data that will allow further testing and validation of iRECIST. Differences in trial outcomes using RECIST 1.1 versus iRECIST could occur, and the interpretation will be informative. Our proposed plan will enable identification of such situations, and hopefully clarification of the underlying mechanisms. Additionally, in the future, quantification of the differences in outcome estimation between RECIST 1.1 and iRECIST will be possible, enabling better informed decisions for future changes to RECIST guidelines.

This strategy will also be useful for trials comparing immunotherapy-based with non-immunotherapy-based therapeutics. RECIST 1.1 and iRECIST should yield almost identical results for non-immunotherapy treatments, based on the RECIST warehouses; whereas an immune modulator warehouse and associated sensitivity analysis of endpoints will enable the quantification of potential added benefit for the immunotherapy component. Although comparison of iRECIST in such situations incorporates an element of bias by construction, confirmation and validation of the guideline by overall survival results might gain additional importance.

Our recommendation for the design of randomised studies planned for licensing applications is to continue to use RECIST 1.1 as the primary criteria for response-based endpoints. iRECIST should be regarded as exploratory in such trials, although earlier phase trials might consider using primarily iRECIST.

The creation of a data warehouse is underway and updates are available from EORTC where the warehouse is held. Meanwhile the implementation of this guideline, and the continued sharing of anonymised, patient-level data will allow the formal validation of iRECIST, ensuring that response-based guidelines remain robust and enable the rapid and robust future development of new cancer therapeutics to improve treatments for patients.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Panel 1: **Key questions identified by the RECIST working group**

- How to define the date of progression in scenarios in which initial progression by RECIST 1.1 is followed by response and later progression
- How to define best overall response when initial progression is established with RECIST 1.1
- How to manage response and progression in trials comparing standard non-immunotherapy drugs against immunotherapeutics
- Whether or not progression should be confirmed with a second scan; and if so, which timepoint denotes the date of progression?
- New lesions: when to measure, how many to measure, and whether all should be measured at each subsequent assessment
- Optimal timing of frequency of response assessment
- How to manage therapeutic interventions such as surgery or radiotherapy after response

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***Panel 2:* Key principles to be considered**

- If the criteria for iUPD have never been met, principles follow RECIST 1.1
- However, if the criteria for iUPD have been met, the next timepoint response could be:
- iUPD: no change noted in any category of lesion
- iSD, iPR, or iCR. Here, iUPD (followed by iCPD) should occur again
- iCPD, if the category in which iUPD was met at the last timepoint response shows a further increase in tumour burden as evidenced (as applicable) by a ≥5 mm increase in sum of measures of target or new target lesions, further increase in non-target or new non-target lesions, or an increase in the number of new lesions

iCPD of a category which did not meet criteria for iUPD now meets the criteria for RECIST 1.1 progression Prefix "i" indicates immune responses assigned using iRECIST. RECIST=Response Evaluation Criteria in Solid Tumours. iCR=complete response. iCPD=complete progression. iPR=partial response. iSD=stable disease. iUPD=unconfirmed progression.

Search strategy and selection criteria

This paper describes a consensus guideline, rather than a formal literature review. However, a database search was done using PubMed in August, 2016, with the following search terms: "immune response criteria" (limited to cancer, clinical trials, and publications in English language; 234 citations), "irRC" (23 citations), and "pseudoprogression" (limited to cancer, clinical trials, and pubications in English language; 39 citations).

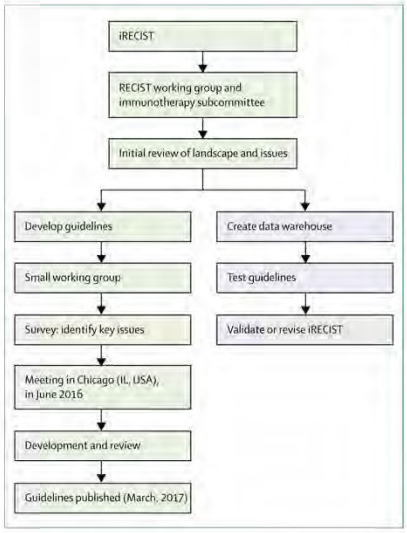


Figure 1. Process for developing and validating iRECIST consensus guidelines
Blue shaded boxes represent steps still in progress. RECIST=Response Evaluation Criteria in Solid Tumours.

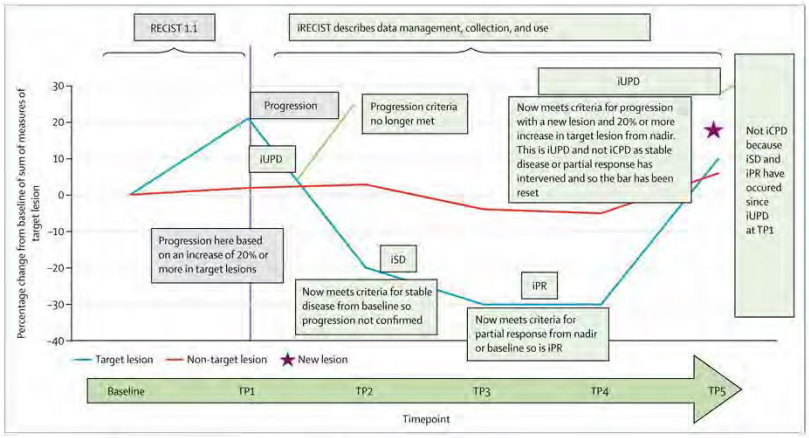


Figure 2. RECIST 1.1 and iRECIST: an example of assessment

Prefix "i" indicates immune responses assigned using iRECIST; others without "i" are confirmed by RECIST 1.1. RECIST=Response Evaluation Criteria in Solid Tumours. iCR=complete response. iCPD=complete progression. iPR=partial response. iSD=stable disease. iUPD=unconfirmed progression. TP=timepoint.

Table 1

Comparison of RECIST 1.1 and iRECIST

	RECIST 1.1	iRECIST
Definitions of measurable and non-measurable disease; numbers and site of target disease	Measurable lesions are ≥10 mm in diameter (≥15 mm for nodal lesions); maximum of five lesions (two per organ); all other disease is considered non-target (must be ≥10 mm in short axis for nodal disease)	No change from RECIST 1.1; however, new lesions are assessed as per RECIST 1.1 but are recorded separately on the case report form (but not included in the sum of lesions for target lesions identified at baseline)
Complete response, partial response, or stable disease	Cannot have met criteria for progression before complete response, partial response, or stable disease	Can have had iUPD (one or more instances), but not iCPD, before iCR, iPR, or iSD
Confirmation of complete response or partial response	Only required for non-randomised trials	As per RECIST 1.1
Confirmation of stable disease	Not required	As per RECIST 1.1
New lesions	Result in progression; recorded but not measured	Results in iUPD but iCPD is only assigned on the basis of this category if at next assessment additional new lesions appear or an increase in size of new lesions is seen (≥5 mm for sum of new lesion target or any increase in new lesion non-target); the appearance of new lesions when none have previously been recorded, can also confirm iCPD
Independent blinded review and central collection of scans	Recommended in some circumstances —eg, in some trials with progression-based endpoints planned for marketing approval	Collection of scans (but not independent review) recommended for all trials
Confirmation of progression	Not required (unless equivocal)	Required
Consideration of clinical status	Not included in assessment	Clinical stability is considered when deciding whether treatment is continued after iUPD

"i" indicates immune responses assigned using iRECIST. RECIST=Response Evaluation Criteria in Solid Tumours. iUPD=unconfirmed progression. iCPD=confirmed progression. iCR=complete response. iPR=partial response. iSD=stable disease.

Table 2

Assignment of timepoint response using iRECIST

	Timepoint response with no previous iUPD in any category	Timepoint response with previous iUPD in any category*
Target lesions: i CR; non-target lesions: iCR; new lesions: no	iCR	iCR
Target lesions: iCR; non-target lesions: non-iCR/non-iUPD; new lesions: no	iPR	iPR
Target lesions: iPR; non-target lesions: non-iCR/non-iUPD; new lesions: no	iPR	iPR
Target lesions: iSD; non-target lesions: non-iCR/non-iUPD; new lesions: no	iSD	iSD
Target lesions: iUPD with no change, or with a decrease from last timepoint; non-target lesions: iUPD with no change, or decrease from last timepoint; new lesions: yes	Not applicable	New lesions confirm iCPD if new lesions were previously identified and they have increased in size (≥5 mm in sum of measures for new lesion target or any increase for new lesion non-target) or number; if no change is seen in new lesions (size or number) from last timepoint, assignment remains iUPD
Target lesions: iSD, iPR, iCR; non-target lesions: iUPD; new lesions: no	iUPD	Remains iUPD unless iCPD is confirmed on the basis of a further increase in the size of non-target disease (does not need to meet RECIST 1.1 criteria for unequivocal progression)
Target lesions: iUPD; non-target lesions: non-iCR/non-iUPD, or iCR; new lesions: no	iUPD	Remains iUPD unless iCPD is confirmed on the basis of a further increase in sum of measures ≥5 mm; otherwise, assignment remains iUPD
Target lesions: iUPD; non-target lesions: iUPD; new lesions: no	iUPD	Remains iUPD unless iCPD is confirmed based on a further increase in previously identified target lesion iUPD in sum of measures >5 mm or non-target lesion iUPD (previous assessment need not have shown unequivocal progression)
Target lesions: iUPD; non-target lesions: iUPD; new lesions: yes	iUPD	Remains iUPD unless iCPD is confirmed on the basis of a further increase in previously identified target lesion iUPD sum of measures ≥5 mm, previously identified non-target lesion iUPD (does not need to be unequivocal), or an increase in the size or number of new lesions previously identified
Target lesions: non-iUPD or progression; non-target lesions: non-iUPD or progression; new lesions: yes	iUPD	Remains iUPD unless iCPD is confirmed on the basis of an increase in the size or number of new lesions previously identified

Target lesions, non-target lesions, and new lesions defined according to RECIST 1.1 principles; if no pseudoprogression occurs, RECIST 1.1 and iRECIST categories for complete response, partial response, and stable disease would be the same.

*Previously identified in assessment immediately before this timepoint. "i" indicates immune responses assigned using iRECIST. iCR=complete response. iPR=partial response. iSD=stable disease. iUPD=unconfirmed progression. non-iCR/non-iUPD=criteria for neither CR nor PD have been met. iCPD=confirmed progression. RECIST=Response Evaluation Criteria in Solid Tumours.

Table 3

Scenarios of assignments of best overall response using iRECIST

	Timepoint response 1	Timepoint response 2	Timepoint response 3	Timepoint response 4	Timepoint response 5	iBOR
Example 1	iCR	iCR, iPR, iUPD, or NE	iCR, iPR, iUPD, or NE	iUPD	iCPD	iCR
Example 2	iUPD	iPR, iSD, or NE	iCR	iCR, iUPD, or NE	iCR, iPR, iSD, iUPD, iCPD, or NE	iCR
Example 3	iUPD	iPR	iPR, iSD, iUPD, or NE	iPR, iSD, iUPD, NE, or iCPD	iPR, iSD, iUPD, NE, or iCPD	iPR
Example 4	iUPD	iSD or NE	iPR	iPR, iSD, iUPD, or NE	iPR, iSD, iUPD, iCPD, or NE	iPR
Example 5	iUPD	iSD	iSD, iUPD, or NE	iSD, iUPD, iCPD, or NE	iSD, iUPD, iCPD, or NE	iSD
Example 6	iUPD	iCPD	Any	Any	Any	iCPD
Example 7	iUPD	iUPD (no iCPD)	iCPD	Any	Any	iCPD
Example 8	iUPD	NE	NE	NE	NE	iUPD

Eight examples are presented for patients with target disease at baseline, but many more scenarios exist following the same principles. Table assumes a randomised study in which confirmation of complete response or partial response is not required. For patients with non-target disease only at baseline, only iCR or non-complete response or non-progression of disease can be assigned at each timepoint (not shown in the table for ease of presentation). "i" indicates immune responses assigned using iRECIST. iBOR=best overall response. iCR=complete response. iPR=partial response. NE=not evaluable. iUPD=unconfirmed progression. iCPD=confirmed progression. iSD=stable disease. RECIST=Response Evaluation Criteria in Solid Tumours.

16.3 Appendix 3 - Adverse Events of Special Interest

Atezolizumab Adverse Events of Special Interest

Adverse Events of Special Interest (Immediately Reportable to the Sponsor):

Adverse events of special interest are required to be reported by the investigator to the Sponsor immediately (ie, no more than 24 hours after learning of the event). Adverse events of special interest for this study are as follows:

- Cases of potential drug-induced liver injury that include an elevated alanine aminotransferase (ALT) or aspartate aminotransferase (AST) in combination with either an elevated bilirubin or clinical jaundice, as defined by Hy's Law (see reference and definition of Hy's Law in KY1044-CT01 protocol, Section 6.5.10):
- Suspected transmission of an infectious agent by the study treatment, as defined below:

  Any organism, virus, or infectious particle (eg, prion protein transmitting transmissible spongiform encephalopathy), pathogenic or non-pathogenic, is considered an infectious agent. A transmission of an infectious agent may be suspected from clinical symptoms or laboratory findings that indicate an infection in a patient exposed to a medicinal product. This term applies only when a contamination of study treatment is suspected.
- Pneumonitis
- Colitis
- Endocrinopathies: diabetes mellitus, pancreatitis, adrenal insufficiency, hyperthyroidism, and hypophysitis
- Hepatitis, including AST or ALT >10 × ULN
- Systemic lupus erythematosus
- Neurological disorders: Guillain-Barré syndrome, myasthenic syndrome or myasthenia gravis and meningoencephalitis
- Events suggestive of hypersensitivity, infusion-related reactions, cytokine release syndrome, influenza-like illness, systemic inflammatory response syndrome and immune-mediated reactions
- Nephritis
- Ocular toxicities (eg, uveitis, retinitis, optic neuritis)
- Myositis
- Myopathies, including rhabdomyolysis
- Grade ≥2 cardiac disorders (eg, atrial fibrillation, myocarditis, pericarditis)
- Vasculitis
- Autoimmue hemolytic anemia
- Severe cutaneous reactions (eg, Stevens-Johnson syndrome, dermatitis bullous, toxic epidermal necrolysis)

16.4 Appendix 4 - Modified Toxicity Probability Interval Design No 2 (mTPI2) Design and Simulations

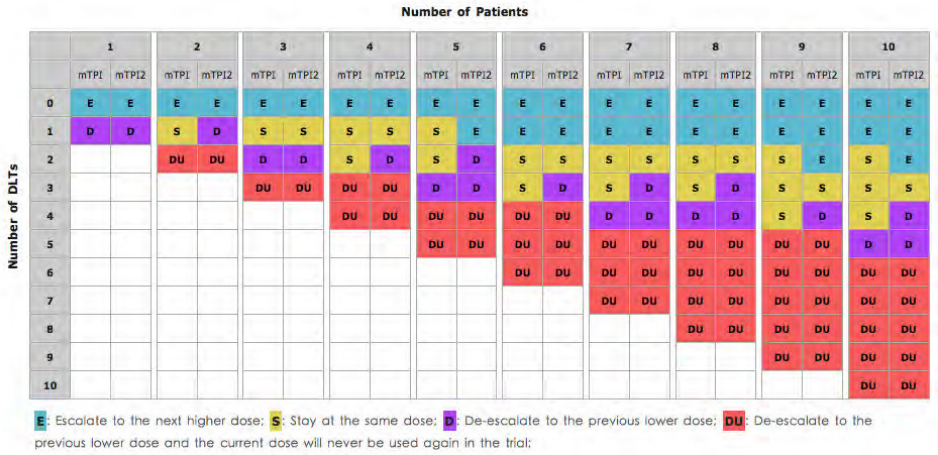
The mTPI-2 design

The modified toxicity probability interval design no 2 (mTPI-2) design[1] is an extension of the modified toxicity probability interval design (mTPI) design[2], which uses a Bayesian hierarchical model and a decision framework for dose finding. In mTPI, decision rules are based on calculating the unit probability mass (UPM) of three intervals $(0, p_T - e_1)$, $(p_T - e_1, p_T + e_2)$ and $(p_T + e_2, 1)$ that correspond to under-, proper-, and over-dosing intervals, respectively. Here, p_T is the target toxicity probability, and e_1 and e_2 are small fractions, such as 0.05, to account for the uncertainty around the true target toxicity. The proper-dosing interval $(p_T - e_1, p_T + e_2)$ is also called the equivalence interval. Assume at a given moment of the trial, a dose is used to treat patients. That dose is referred to as the "current dose". Given an interval and a probability distribution, the unit probability mass (UPM) of that interval is defined as the probability of the interval divided by the length of the interval. Under an optimal Bayesian decision framework[2], the mTPI design calculates the UPMs for the three dosing intervals given the observed toxicity data at the current dose and selects the one with the largest UPM. The selected interval is associated with a decision of escalation (E), stay (S), or de-escalation (D), respectively, if it is the under-dosing interval, the equivalence interval, or the over-dosing interval.

Because of its simplicity and transparency as 3+3 (all decisions could be pre-tabulated for examination as 3+3), and also its better performance than 3+3[3], the mTPI design has been applied in real-world trials, including trials sponsored by Merck[4,5], Pfizer[6], and Bristol-Myers Squibb[7].

The mTPI-2 design extends mTPI with a refined decision framework[1]. It further partitions the under-dosing interval $(0, p_T - e_1)$ and the over-dosing interval $(p_T + e_2, 1)$ into adjacent subintervals with equal length of $(e_1 + e_2)$, the length of the equivalence interval. As a result, it is nimbler, with fewer "Stay" decisions than mTPI (Figure 16-1). For example, mTPI gives decision "Stay" when three out of six patients have dose limiting toxicity (DLT) and if p_T=0.3; whereas, mTPI-2 gives decision "De-escalation". As a result, mTPI-2 yields safer and more ethical decisions, with similar accuracy in identifying the maximal tolerated dose (MTD) compared to mTPI[1].

Figure 16-1: Example mTPI-2 Decision Table



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.

mTPI-2 Simulation Results

Simulations were performed via [redacted] to assess the performance of mTPI-2 based on the setting of this trial. There are seven prespecified doses and the stating dose is 0.8 mg. The sample size is 36 and patients are enrolled in cohorts of size 3. The MTD target toxicity probability is p_T=0.3 and the choices of e_1 and e_2 are both 0.05. Six different scenarios were investigated in the simulation studies, as shown below (Table 16-1). For each scenario, 5000 simulated trials were conducted.

Table 16-1: Six Scenarios used in Simulation Results

Index	p_T	nsim	Dose (mg)						
			0.24	0.8*	2.4	8	24	80	240
1	0.3	5000	0.001	0.005	0.022	0.0831	0.269	0.599	0.858
2	0.3	5000	0.668	0.832	0.924	0.968	0.987	0.995	0.998
3	0.3	5000	0.002	0.008	0.039	0.168	0.500	0.832	0.961
4	0.3	5000	0.001	0.018	0.269	0.881	0.993	0.9997	0.99998
5	0.3	5000	0.063	0.083	0.109	0.142	0.182	0.231	0.289
6	0.3	5000	0.039	0.083	0.168	0.310	0.500	0.690	0.832

*starting dose

The results for each of the six scenarios are presented below:

Scenario 1

p_T=0.3, n_{sim}=5000		Selection Prob.	# of Patients Treated	# of Toxicities
Dose Level	**True Tox prob.**	**mTPI-2**	**mTPI-2**	**mTPI-2**
1	0.001	0	0	0
2	0.005	0	3.052	0.015
3	0.022	0.002	3.347	0.076
4	0.0831	0.242	7.467	0.621
5	0.269	0.73	16.945	4.548
6	0.599	0.026	4.973	2.98
7	0.858	0	0.216	0.186
		mTPI-2		
Prob. of Select MTD		0.73		
Prob. of Toxicity		0.234		
Prob. of Select Dose-over-MTD		0.026		
Prob. of No Selection		0		

Scenario 2

p_T=0.3, n_{sim}=5000		Selection Prob.	# of Patients Treated	# of Toxicities
Dose Level	**True Tox prob.**	**mTPI-2**	**mTPI-2**	**mTPI-2**
1	0.668	0	7.064	4.716
2	0.832	0	3.304	2.743
3	0.924	0	0.015	0.013
4	0.968	0	0.001	0.001
5	0.987	0	0	0
6	0.995	0	0	0
7	0.998	0	0	0
		mTPI-2		
Prob. of Select MTD		1		
Prob. of Toxicity		0.72		
Prob. of Select Dose-over-MTD		0		
Prob. of No Selection		1		

Scenario 3

p_T=0.3, n_{sim}=5000		Selection Prob.	# of Patients Treated	# of Toxicities
Dose Level	**True Tox prob.**	**mTPI-2**	**mTPI-2**	**mTPI-2**
1	0.002	0	0	0
2	0.008	0	3.091	0.024
3	0.039	0.033	4.393	0.176
4	0.168	0.876	17.987	3.036
5	0.500	0.09	9.847	4.935
6	0.832	0	0.678	0.568
7	0.961	0	0.004	0.003
		mTPI-2		
Prob. of Select MTD		0.876		
Prob. of Toxicity		0.243		
Prob. of Select Dose-over-MTD		0.091		
Prob. of No Selection		0		

Scenario 4

p_T=0.3, n_{sim}=5000		Selection Prob.	# of Patients Treated	# of Toxicities
Dose Level	**True Tox prob.**	**mTPI-2**	**mTPI-2**	**mTPI-2**
1	0.001	0	0.003	0
2	0.018	0.25	8.058	0.144
3	0.269	0.749	25.09	6.791
4	0.881	0.001	2.845	2.503
5	0.993	0	0.004	0.004
6	0.9997	0	0	0
7	0.99998	0	0	0
		mTPI-2		
Prob. of Select MTD		0.749		
Prob. of Toxicity		0.262		
Prob. of Select Dose-over-MTD		0.001		
Prob. of No Selection		0		

Scenario 5

p_T=0.3, n_{sim}=5000		Selection Prob.	# of Patients Treated	# of Toxicities
Dose Level	**True Tox prob.**	**mTPI-2**	**mTPI-2**	**mTPI-2**
1	0.063	0	0.125	0.009
2	0.083	0.005	4.301	0.35
3	0.109	0.021	5.137	0.57
4	0.142	0.082	6.128	0.855
5	0.182	0.187	6.955	1.275
6	0.231	0.306	6.505	1.505
7	0.289	0.398	6.848	2.009
		mTPI-2		
Prob. of Select MTD		0.398		
Prob. of Toxicity		0.183		
Prob. of Select Dose-over-MTD		0		
Prob. of No Selection		0		

Scenario 6

p_T=0.3, n_{sim}=5000		Selection Prob.	# of Patients Treated	# of Toxicities
Dose Level	**True Tox prob.**	**mTPI-2**	**mTPI-2**	**mTPI-2**
1	0.039	0	0.115	0.005
2	0.083	0.029	5.055	0.412
3	0.168	0.386	11.426	1.925
4	0.310	0.516	14.052	4.4
5	0.500	0.066	4.835	2.416
6	0.69	0.002	0.503	0.346
7	0.832	0	0.014	0.011
		mTPI-2		
Prob. of Select MTD		0.516		
Prob. of Toxicity		0.264		
Prob. of Select Dose-over-MTD		0.069		
Prob. of No Selection		0		

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16.5 Appendix 5 - Protocol Amendments

This is the seventh version of the protocol. To date, there have been six protocol amendments. Details of the key changes made in each version are provided in the table below.

Protocol version	Effective date	Section	Change
1.0	**24th Aug 2018**	**All**	No change - new protocol
2.0	**14th Nov 2018**	**FDA requested changes**	
		Section 1.6.2	Start of corticosteroid therapy was clarified
		Section 4.2	Clarification of terminology "standard therapy" and protocol in and exclusion criteria (#4)
			Clarification if patients will be enrolled who are eligible to receive therapies with known clinical benefit
		Section 5.5	Update DLT criteria
		Section 3.3	Define pre-specified stopping rules to pause enrolment
		Section 5	Revise protocol to align management of toxicities according to Appendix 1 and Table 5-5 of protocol
		Section 5	Table 5-2 revised for administration sets
		Section 6	Addition of antiacetyl-choline receptor (AChR) autoantibodies to autoantibody panel
		IRB requested changes	
		Section 3.1.2	Consistency of description of antitumor activity
		Section 9.2	Consistency of number of patients enrolled throughout the entire study
		Section 4.2	Change age of participants to ≥18 years for all countries (excluding Taiwan)
		Kymab internal changes	
			Various changes for correction of typographical errors and clarifications
3.0	**24th Jan 2019**	**MHRA requested changes**	
		Section 5.2.3	The observation period of the sentinel patient in the combination cohort 1 of KY1044 with atezolizumab has been prolonged to 72 hours instead of 48 hours.
		Section 3.3	Specific wording has been added to clarify the detailed communication process, in the event that the study needs to be put on hold
		Section 5.7	Table 5-6 has been updated to clarify the duration for when and how long, life attenuated vaccines are prohibited
		Protocol synopsis **Section 4.2** **Section 5.8**	The duration required for contraception of females and males (barrier contraception) have been changed to at least 5 months after discontinuing study treatment, or longer if the half-life of KY1044 is observed to exceed that of atezolizumab.

Protocol version	Effective date	Section	Change
		Kymab internal changes	
		Section 4.1.1	The number of patients required in each cohort in Phase 1 has been clarified
		Section 5.4.2	Table 5-2 has been updated and corrected for dose level -1
		Section 5.4.4	The requirements for the assessment of DLT data based on three patients has been clarified
		Section 6	Table 6-8 has been amended according to the changes in the Lab manual
			Table 6-1 and Table 6-2 have been amended according to changes in Table 6-8
			Section 6.5.8 has been amended to specify Troponin I according to changes in the laboratory manual
4.0	**08 May 2019**	**Section 1.4.3.1**	Updated date relating to atezolizumab approvals.
		Section 4.3	Updated to clarify the requirements for use of anticoagulant treatment.
		Section 5.6.3	Updated as Appendix 5 atezolizumab guidance for investigators removed.
		Section 6	Section 6.5.6 revised to enable use of local labs if necessary
		Appendix 3	Updated list of atezolizumab adverse events of special interest.
		Appendix 5	Atezolizumab guidance for investigators removed.
5.0	**28 Jul 2020**	**Protocol Synopsis: Study design; Protocol Synopsis: Study population; Sections 1.5.2; 3.1; 3.1.2; 3.1.4; 5.2.1; 5.9; 9.2**	The study design for Phase 2 has been changed to introduce an initial Phase 2 dose assessment part in one or more specific indication(s) 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 patient population.
		Protocol Synopsis: Sample size; Sections 1.5.2; 3.1.3; 4.1; 9.2	The number of patients in Phase 1 has been increased from 112 to approximately 150. The number of patients in Phase 2 has been decreased from a maximum of 300 to a maximum of 262.
		Protocol Synopsis: Study population; Protocol synopsis: Key inclusion criteria; Sections 1.5.2; 3.1.4; 4.2; 5.4.7	Clarification that patients will be treated with KY1044 as single agent in Phase 2 only if evidence of anti-tumor activity is detected in the dose escalation/enrichment Phase 1 parts.
		Protocol Synopsis: Key exclusion criteria; Section 4.3	Update to Exclusion criterion 5 in the Protocol Synopsis and Exclusion criterion 6 in Section 4.3 to exclude patients with any severe infection within 4 weeks of initiation of study treatment to align with the atezolizumab required exclusion criteria.

Protocol version	Effective date	Section	Change
		Protocol Synopsis: Statistical analysis; Protocol Section 9.4	Text was updated to account for multiple dose groups and schedules. It was clarified that Phase 2 will be reported by dose group(s) in addition to indication.
		Section 1.6.5	Addition of benefit/risk of KY1044 as single agent and in combination with atezolizumab regarding potential infections with SARS-Cov-2.
		Section 3.1.4	Amendments have been made to the study design figure to include the total patients in Phase 1 and Phase 2, to clarify that approximately 36 patients will be enrolled in the Phase 1 dose escalation part (KY1044 monotherapy and in combination with atezolizumab), and to increase the number of patients in the enrichment pool from 40 to approximately 78. An initial Phase 2 dose assessment part has been added, and it has been clarified that patients will be treated with KY1044 as a single agent in Phase 2 only if evidence of anti-tumor activity is observed in the Phase 1 dose escalation/enrichment parts. A footnote has been added to clarify that, for the tumor types selected for Phase 2, the number of patients enrolled per group could be reduced, depending on enrolment feasibility in the ongoing study.
		Section 3.3; 5.4.4	It was clarified that, in addition to continuing until identification of the MTD and/or the RP2D, dose escalation may also continue until completion of all defined dose levels, or a decision that further increase of dose is not warranted.
		Section 5.2.2	The infusion schedule has been updated so that, when given in combination, both IMPs are to be administered within 24 hours.
		Section 5.2.4	A sentence has been added to clarify that if an infusion reaction is caused by KY1044, the atezolizumab infusion may be delayed until the next day and/or until recovery from the event.
		Section 5.6.1	Active SARS-Cov-2 infections should be treated as AEs, as should any other concurrent illnesses, and treatment interruption should be considered on an individual patient basis.
		Section 5.6.3; Appendix 3	In alignment with Addendum 2 of the atezolizumab IB Version 15, "Systemic immune activation" has been amended to 'immune-mediated reactions'.
		Section 6	The atezolizumab PK sampling schedule was clarified in Table 6-1 for Phase 1 and Table 6-2 for Phase 2.
		Section 6.3.1	Safety analysis has been added to the alternative biomarkers to be able to explore biomarkers for infusion reactions. Blood volumes for PBMCs for pharmacogenomic testing, immunoprofiling and receptor occupancy have been clarified in Table 6-4.
		Section 6.4.2	A sentence has been added to allow PK samples to be used for analysis of alternative biomarkers of safety and efficacy. The PK sampling timetable has been clarified in Table 6-5.

Protocol version	Effective date	Section	Change
		Section 6.5.8	The electrocardiogram collection plan timetable has been clarified in Table 6-9.
		Addendum 1	A finalized addendum dated 21 April 2020 summarizing potential adjustments for protocol visits and assessments due to circumstances created by the COVID-19 pandemic has been incorporated into the protocol.
6.0	**07 May 2021**	**Protocol Synopsis: Study design; Protocol Synopsis: Duration of the Study; Sections 3.1, 3.2, 3.4, 3.6, 5.3, 6, 6.2.1, 6.5.6, 8.1, 8.2.2, 8.2.3**	The study has been amended to allow study treatment beyond 24 months up to 48 months for patients that are deriving clinical benefit without safety concerns. The requirements for survival follow-up have been updated accordingly.
		Protocol Synopsis: Key exclusion criteria; Sections 4.3, 5.7, 6, 6.1.5, 7.1	The study design has been updated with respect to the management of SARS-CoV-2 vaccination in subjects participating in non-COVID-19 clinical trials.
7.0	**10 Nov 2021**	See Section Protocol Amendment Summary of Changes	

17 ADDENDA

17.1 Addendum 1

This addendum is applicable only where national/local restrictions due to COVID-19 are implemented and may therefore be in force at variable times and in certain sites only.

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

PROTOCOL IDENTIFIER: KY1044-CT01

Addendum version 1.0 Date: 21 April 2020

SUMMARY

This document is an addendum to the existing protocol KY1044-CT01, summarizing potential adjustments for protocol visits and assessments due to circumstances created by the current COVID-19 pandemic.

Recruitment to the study is being reviewed continuously to allow detailed assessments of the impact of the COVID-19 pandemic per country and site. Visits of patients and study monitors to hospitals have been restricted in most countries due to requirements for social distancing and also travel restrictions related to the COVID-19 pandemic. Additionally, scheduling of study visits and assessments may be impacted by the lack of, or availability of, study staff. The impact of COVID-19 differs at different sites, depending on the situation in each country, patient recruitment and internal site-specific procedures. These circumstances necessitate the set-up of new procedures to ensure that study oversight by the sponsor and the CRO can still be maintained.

The expectation is that the full protocol must be followed at each site wherever possible. New patients will not be started on the study unless there is an expectation that all protocol required assessments can be performed. However, for study assessments for ongoing patients at sites where restrictions due to COVID-19 are implemented, the absolute minimum requirements for safety, pharmacokinetic (PK) and biomarker analysis to allow collection of essential data on safety, drug exposure and biological activity, are summarized in this addendum.

This addendum is therefore relevant to the following sections of the protocol:

- Section 6.3 Assessment of Pharmacodynamics
- Section 6.4 Pharmacokinetic and Anti-drug Antibody Procedures
- Section 6.5.6 Safety Laboratory Tests
- Section 7 Safety Monitoring and Reporting
- Section 7.2 Important Medical Procedures to be Followed.

For study assessments for ongoing patients at sites with restrictions due to COVID-19:

Protocol section 6.3 Assessment of Pharmacodynamics

All efforts should be made to collect all samples as per protocol, however, if this is not possible:

- Blood biomarker samples **(protocol section 6.3.3 and table 6-4)** C1D2 samples may be taken at C1D1 – at the latest timepoint possible (6-8h after dosing together with the PK sample). C1D8 samples can be taken together with the safety assessments as per safety samples section below
- Tumor biopsies **(protocol section 6.3.2)** (as per protocol to be taken on C2D8) can be scheduled together with the safety assessment as described below
    - If this is not possible, then the biopsy may be taken at the next subsequent opportunity around 8 days after the last infusion, as an unscheduled biopsy

Protocol section 6.4 Pharmacokinetic and Anti-drug Antibody Procedures

6.4.1 Pharmacokinetic Procedures:

For patients who cannot attend the scheduled PK follow-up visits (C1D2, C1D8, C1D11, C1D15, C3D8, C3D11, C3D15) PK sampling at those time points may be omitted, although every effort should be made to collect C1D8 samples together with the safety assessments as per safety samples section below

- If, following removal of any restrictions due to the COVID-19 pandemic, patients remain on treatment and are ongoing in the study, any missed PK samples should be taken during later cycles, after discussion with the medical monitor/SRMO
- PK sample tubes from the unscheduled visit kits should be used for collection of these samples

Protocol section 6.5.6 Safety Laboratory Tests (Table 6-8)

Minimum requirements for safety analysis

- Safety blood samples should be collected prior to dosing (approximately every 3 weeks at every cycle) as per protocol
- Collection of follow-up blood safety samples may be reduced to once in each of Cycle 1 and Cycle 2 (approximately in the middle of the cycle between D3 and D19). The C1D8/C2D8 samples should be collected at this visit.. The C3D8 samples may be omitted or performed when the patient comes into the clinic for restaging scans (RECIST assessment).

If due to COVID-19 related issues, it is not possible to collect this minimum set of safety samples, the Kymab SRMO or PRA Medical Director will discuss the situation with the Principal Investigator and assess if the situation can be improved or if discontinuation of the dosing will need to be considered.

- If the full safety analyses per table 6-8 of the protocol cannot be collected, the following analyses are an absolute minimum requirement:
  - Haematology: WBC with differential, HgB, platelets
  - Biochemistry: (AST, ALT, bilirubin, glucose, sodium, potassium, creatinine, amylase or lipase)
  - Coagulation: aPTT, PT
- In exceptional COVID-19 related circumstances section 6.5.6 of the protocol is extended to allow the use of local laboratory results for all assessment timepoints where central labs absolutely cannot be collected. Local laboratory results must be entered into the EDC as soon as possible and not later than 2 weeks after the date of the sample. Exceptionally, if entry cannot be performed within 2 weeks, anonymized reports must be sent to the PRA medical monitor for oversight purposes.

Protocol section 7 Safety Monitoring and Reporting

Minimum requirements for safety reporting

- AE review in accordance with section 7 of the protocol must be performed at least once per cycle
- SAE reporting and follow up must be performed per protocol

Protocol section 7.2 Important Medical Procedures to be Followed

7.2.3 Protocol Deviations

It is expected that more deviations than usual will be reported. Deviations related to the COVID-19 pandemic must be documented as such (COVID included in the deviation description). All deviations to the full protocol must be documented; local requirements for reporting of deviations covered by this addendum should be followed.

Signature Page for VV-CLIN-0621509 v2.0
tcd17370-ky1044-ct01-16-1-1-amended-protocol07

Approve & eSign	[redacted]
Approve & eSign	[redacted]