**Official Title:** A 3-Arm, Randomized, Blinded, Active-Controlled, Phase II Study of RO7121661, a PD1-TIM3 Bispecific Antibody and RO7247669, a PD1-LAG3 Bispecific Antibody, Compared with Nivolumab in Participants with Advanced or Metastatic Squamous Cell Carcinoma of the Esophagus

**NCT Number:** NCT04785820

**Document Date:** Protocol Amendment Version 3: 02-Feb-2022

# PROTOCOL

| | |
|---|---|
| **TITLE:** | **A 3-ARM, RANDOMIZED, BLINDED, ACTIVE-CONTROLLED, PHASE II STUDY OF RO7121661, A PD1-TIM3 BISPECIFIC ANTIBODY AND RO7247669, A PD1-LAG3 BISPECIFIC ANTIBODY, COMPARED WITH NIVOLUMAB IN PARTICIPANTS WITH ADVANCED OR METASTATIC SQUAMOUS CELL CARCINOMA OF THE ESOPHAGUS** |
| **PROTOCOL NUMBER:** | BP42772 |
| **VERSION:** | 3 |
| **EUDRACT NUMBER:** | 2020-004606-60 |
| **IND NUMBER:** | 142906 (LAG3), 142844 (TIM3) |
| **TEST PRODUCT:** | RO7121661, RO7247669, Nivolumab |
| **SPONSOR:** | F. Hoffmann-La Roche Ltd |
| **DATE FINAL:** | 08 December 2020 |
| **DATE AMENDED:** | See electronic stamp below |

## FINAL PROTOCOL APPROVAL

| Date and Time (UTC) | Title | Approver's Name |
|---|---|---|
| 02-Feb-2022 15:45:22 | Company Signatory | [redacted] |

## PROTOCOL ACCEPTANCE FORM

| | |
|---|---|
| **TITLE:** | **A 3-ARM, RANDOMIZED, BLINDED, ACTIVE-CONTROLLED, PHASE II STUDY OF RO7121661, A PD1-TIM3 BISPECIFIC ANTIBODY AND RO7247669, A PD1-LAG3 BISPECIFIC ANTIBODY, COMPARED WITH NIVOLUMAB IN PARTICIPANTS WITH ADVANCED OR METASTATIC SQUAMOUS CELL CARCINOMA OF THE ESOPHAGUS** |
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| **TEST PRODUCT:** | RO7121661, RO7247669, Nivolumab |
| **SPONSOR:** | F. Hoffmann-La Roche Ltd |

**I agree to conduct the study in accordance with the current protocol.**

_____

Principal Investigator's Name (print)

_____ _____

Principal Investigator's Signature Date

Please keep the signed original form in your study files and return a copy to your local Site Monitor.

# PROTOCOL AMENDMENT, VERSION 3
# RATIONALE

Protocol BP42772 Version 2 has been mainly amended to stop recruitment into the RO7121661 arm. Changes to the protocol, along with a rationale for each change, are summarized below.

- Sections 1.2, 3, 4.1, 6.3, 9.1, 9.3.2, and 9.4 have been amended to reflect the decision to stop recruitment into the RO7121661 arm. The decision to stop recruitment for RO7121661 was based on strategic considerations and not based on emerging safety and/or efficacy data. The benefit/risk assessment for RO7121661 remains unchanged. The study will not be unblinded and participants already randomized to the RO7121661 arm prior to this decision will continue to receive treatment with RO7121661 as long as participants are experiencing clinical benefit, as assessed by the Investigator, in the absence of unacceptable toxicity or symptomatic deterioration attributed to disease progression after an integrated assessment of radiographic data, biopsy results (if available), and clinical status for a maximum of 24 months. Participants who meet the criteria for disease progression per RECIST v1.1 will be permitted to continue study treatment if they meet all criteria for treatment beyond progression.

- Sections 3, 4.1, 8.1.1, and 9.3.2 have been amended to remove the endpoint of iRECIST from the protocol since tumor assessment data are no longer planned to be analyzed according to iRECIST criteria.

- In Section 5.1 (Inclusion Criteria), inclusion criterion #4 has been amended to improve clarity.

- In Section 5.2 (Exclusion Criteria), exclusion criterion #5 has been amended to clarify that not all patients with a risk of fistula need to be excluded.

- Table 6 in the Guidelines for Management of Immune-Mediated Myocarditis events (Appendix 7) has been updated following a health authorities request to include all grades immune-mediated myocarditis in the Guidelines for Management of Immune-Mediated Myocarditis events.

Additional minor changes have been made to improve clarity and consistency. Substantial new information appears in *Book Antiqua* italics. This amendment represents cumulative changes to the original protocol.

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## LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

| Abbreviation | Definition |
|---|---|
| **2L** | Second-line |
| **ADA** | Anti-drug antibody |
| **AE** | Adverse event |
| **ALP** | Alkaline phosphatase |
| **ALT** | Alanine aminotransferase |
| **aPTT** | Activated partial thromboplastin time |
| **AST** | Aspartate aminotransferase |
| **BML** | Below measurable limit |
| **BP** | Blood pressure |
| **BsAb** | Bispecific antibody |
| **C1D1** | Cycle 1 Day 1 |
| **CNS** | Central nervous system |
| **COVID-19** | Coronavirus disease 2019 |
| **CPI** | Checkpoint inhibitor |
| **CR** | Complete response |
| **CT** | Computed tomography |
| **CTCAE** | Common terminology criteria for adverse events |
| **DCR** | Disease control rate |
| **DLT** | Dose-limiting toxicities |
| **DNA** | Deoxyribonucleic acid |
| **DoR** | Duration of response |
| **EC** | Ethics Committee |
| **ECG** | Electrocardiogram |
| **eCRF** | Electronic case report form |
| **EDC** | Electronic data capture |
| **EEA** | European Economic Area |
| **eCOA** | Electronic clinical outcome assessment |
| **ECOG** | Eastern Cooperative Oncology Group |
| **EIH** | Entry-into-human |
| **EORTC** | European Organisation for Research and Treatment of Cancer |
| **ESCC** | Esophageal squamous-cell carcinoma |
| **EU** | European Union |

| Abbreviation | Definition |
|---|---|
| **FDA** | Food and Drug Administration |
| **FFPE** | Formaldehyde fixed-paraffin-embedded |
| **FPI** | First participant in |
| **FSH** | Follicle-stimulating hormone |
| **GHS** | Global health status |
| **HBsAg** | Hepatitis B surface antigen |
| **HBcAb** | Total hepatitis B core antibody |
| **HCV** | Hepatitis C |
| **HIPAA** | Health Insurance Portability and Accountability Act |
| **HLH** | Hemophagocytic lymphohistiocytosis |
| **HIV** | Human immunodeficiency virus |
| **ICF** | Informed Consent Form |
| **ICH** | International Council on Harmonisation |
| **IEC** | Independent Ethics Committee |
| **IgA** | Immunoglobulin A |
| **IgE** | Immunoglobulin E |
| **IgG** | Immunoglobulin G |
| **IgM** | Immunoglobulin M |
| **IL97** | Item library 97 |
| **IMP** | Investigational medicinal product |
| **imAE** | Immune-mediated adverse event |
| **IND** | Investigational New Drug (application) |
| **INR** | International normalized ratio |
| **IRB** | Institutional Review Board |
| **iRECIST** | Immune response evaluation criteria in solid tumors |
| **IRR** | Infusion-related reaction |
| **ITT** | Intent-to-treat |
| **IUD** | Intrauterine device |
| **IV** | Intravenous |
| **IxRS** | Interactive (voice/web) response system |
| **JMC** | Joint Monitoring Committee |
| **LAG3** | Lymphocyte-activation gene 3 |
| **LDH** | Lactate dehydrogenase |
| **LDL** | Low-density lipoproteins |
| **LH** | Luteinizing hormone |
| **MAS** | Macrophage activation syndrome |

| Abbreviation | Definition |
|---|---|
| **MRI** | Magnetic resonance imaging |
| **MTD** | Maximum tolerated dose |
| **MUGA** | Multiple-gated acquisition scans |
| **NCI** | National Cancer Institute |
| **NGS** | Next generation sequencing |
| **NK** | Natural killer |
| **NSAESI** | Non-serious adverse event of special interest |
| **NYHA** | New York Heart Association |
| **ORR** | Objective response rate |
| **OS** | Overall survival |
| **OTC** | Over-the-counter |
| **PD** | Pharmacodynamic |
| **PD1** | Anti–programmed death-1 |
| **PFS** | Progression-free survival |
| **PGI-CI** | Patient Global Impression of Change and its Importance |
| **PGI-S** | Patient Global Impression of Severity |
| **PK** | Pharmacokinetic |
| **PR** | Partial response |
| **PRO** | Patient-reported outcome (also refers to participants) |
| **PRO-CTCAE** | Patient-Reported Outcomes Common Terminology Criteria for Adverse Events |
| **PT** | Prothrombin time |
| **Q2W** | Every 2 weeks |
| **QLQ-C30** | Quality-of-life questionnaire |
| **QLQ-OES18** | Quality-of-life questionnaire for esophageal cancer |
| **QRS** | QRS complex |
| **QT** | QT interval |
| **QTc** | QT corrected for heart rate |
| **QTcF** | QT corrected for heart rate using the Fridericia's correction factor |
| **RBR** | Research biosample repository |
| **RECIST** | Response evaluation criteria in solid tumors |
| **RNA** | Ribonucleic acid |
| **RR** | RR interval |
| **SAE** | Serious adverse event |
| **SARS-CoV-2** | Sudden acute respiratory syndrome coronavirus 2 |

| Abbreviation | Definition |
|---|---|
| **SDR** | Stable disease rate |
| **SoA** | Schedule of activities |
| **TIM3** | T cell immunoglobulin and mucin domain 3 |
| **TMB** | Tumor mutational burden |
| **TnI** | Troponin I |
| **TnT** | Troponin T |
| **TSH** | Thyroid-stimulating hormone |
| **TTE** | Transthoracic echocardiogram |
| **ULN** | Upper limit of normal |
| **U.S.** | United States |
| **WES** | Whole exome sequencing |
| **WMS** | Whole metagenomic sequencing |
| **WGS** | Whole genome sequencing |
| **WOCBP** | Women of childbearing potential |

# 1. PROTOCOL SUMMARY

## 1.1 SYNOPSIS

| | |
|---|---|
| **PROTOCOL TITLE:** | **A 3-ARM, RANDOMIZED, BLINDED, ACTIVE-CONTROLLED, PHASE II STUDY OF RO7121661, A PD1-TIM3 BISPECIFIC ANTIBODY AND RO7247669, A PD1-LAG3 BISPECIFIC ANTIBODY, COMPARED WITH NIVOLUMAB IN PARTICIPANTS WITH ADVANCED OR METASTATIC SQUAMOUS CELL CARCINOMA OF THE ESOPHAGUS** |
| **SHORT TITLE** | **A PHASE II STUDY OF RO7121661 AND RO7247669 COMPARED WITH NIVOLUMAB IN ADVANCED OR METASTATIC SQUAMOUS CELL CARCINOMA OF THE ESOPHAGUS** |
| **PROTOCOL NUMBER:** | BP42772 |
| **VERSION:** | 3 |
| **TEST PRODUCT:** | RO7121661, RO7247669, Nivolumab |
| **PHASE:** | II |

**RATIONALE**

Cancer remains a major cause of death worldwide despite several new agents providing survival benefits to patients. Many cancer indications have a poor prognosis and the management of most advanced solid tumors remains challenging because of the high rate of tumor recurrence or the development of distant metastases.

Despite the effectiveness of PD1/L1 checkpoint inhibitor (CPI) therapy in various tumor types including esophageal squamous-cell carcinoma (ESCC), additional treatment options targeting immune checkpoints are needed, because the majority of patients eventually progress after an initial response or fail to respond to PD1/L1 checkpoint blockade.

By targeting both PD1 and TIM3 or LAG3 on dysfunctional tumor-specific T lymphocytes, the PD1-TIM3 and PD1-LAG3 bispecific antibodies aim to restore an effective anti-tumor immune-response and provide survival benefit to more patients with cancer than currently available agents do. PDL1 expression in ESCC ranges from 15% to 83% in tumor cells and from 13% to 31% in tumor-infiltrated immune cells. Studies with nivolumab, pembrolizumab, and other PD1 inhibitors demonstrated benefit over chemotherapy in the second-line (2L) ESCC population leading to market authorizations in that setting (e.g., in the U.S., EU, Japan, South Korea, and other jurisdictions). Both TIM3 and LAG3 have been shown to be expressed on tumor-infiltrating lymphocytes in patients with ESCC. RO7121661 and RO7247669 may therefore have the potential to be a therapeutic option for patients with ESCC.

The purpose of this study is to assess the efficacy of RO7121661 and RO7247669 compared with nivolumab to address a significant unmet medical need in patients with unresectable advanced or recurrent ESCC who are refractory or intolerant to one prior line of chemotherapy.

**OBJECTIVES AND ENDPOINTS**

| Objectives | Endpoints |
|---|---|
| **Primary** | |
| To evaluate the efficacy of RO7247669 compared with nivolumab. | • OS, defined as the time from randomization to death from any cause |
| **Secondary** | |
| To evaluate the safety and tolerability of RO7121661and RO7247669 compared with nivolumab. | • Nature, frequency, and severity of adverse events (AEs) graded according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) v5.0 |
| To evaluate the efficacy of RO7247669 compared with nivolumab. | • Objective response rate (ORR), defined as the proportion of participants with an objective response (i.e., complete response [CR] or partial response [PR]), according to RECIST v1.1<br>• Disease control rate (DCR), defined as ORR + stable disease rate (SDR)<br>• Duration of response (DoR) for participants with ORR, defined as the time from the first occurrence of a documented objective response to disease progression according to RECIST v1.1 or death from any cause, whichever occurs first<br>• Progression-free survival (PFS) defined as the time from randomization to the first occurrence of progression as determined by the Investigator according to RECIST v1.1 or death during the treatment period or within 60 days of the last tumor assessment after treatment discontinuation from any cause, whichever occurs first<br>• Proportion of participants reporting clinically meaningful improvement in global health status/quality of life, emotional functioning, social functioning and dysphagia as measured by the European Organisation for Research and Treatment of Cancer (EORTC) Quality-of-life questionnaire (QLQ)-C30, IL97, and OES-18, defined as an improvement of at least 10 points |
| To investigate the pharmacokinetics (PK) of RO7247669 and nivolumab. | • Serum concentrations, PK profiles and parameters for RO7121661, RO7247669, and nivolumab |
| To evaluate the immune response after administration RO7247669 and nivolumab. | • Incidence and titer of RO7121661, RO7247669 or nivolumab anti-drug antibodies (ADAs) during the study relative to the prevalence of ADA at baseline |
| To assess treatment-induced pharmacodynamic changes (PD Biomarkers) in peripheral blood and tumor microenvironment | • Changes from baseline in the phenotype and activation status (CD4/CD8 HLA-DR+Ki67+) of T-cell subsets in the peripheral blood<br>• Changes from baseline such as CD8 T-cell infiltration, proliferation (CD8+Ki67+) in the tumor microenvironment |
| To assess baseline characteristics in the tumor microenvironment as predictive biomarkers of response | • Baseline PDL1, CD8+PD1+, CD8+TIM3+, and CD8+LAG3+ expression in the tumor microenvironment |

## OVERALL DESIGN

### Study Design

This is a Phase II, randomized, blinded, active-controlled, global, multicenter study designed to evaluate the safety and efficacy of RO7121661 and RO7247669, compared with nivolumab in patients with advanced or metastatic ESCC refractory or intolerant to fluoropyrimidine- or taxane- and platinum-based regimen. The study *was planned to* enroll participants aged ≥ 18 years with Eastern Cooperative Oncology Group Performance Status of 0 or 1 *randomized in a* [redacted] *ratio to receive RO7121661, RO7247669, or nivolumab.*

*With version 3 of this protocol, recruitment into the RO7121661 is stopped and moving forward, participants will be randomized in a* [redacted] *ratio to receive either RO7247669 or nivolumab.* [redacted]

Participants will be stratified by [redacted]

Randomization should occur on Day -1 or Day 1after the patient's eligibility (i.e., inclusion/exclusion criteria) has been confirmed.

In the experimental arms, participants will receive RO7121661 or RO7247669 at a fixed dose of 2100 mg administered by IV infusion every 2 weeks (Q2W) on Day 1 of each 14-day cycle.

In the active comparator arm, participants will receive nivolumab at a fixed dose of 240 mg administered by IV infusion Q2W on Day 1 of each 14-day cycle.

Treatment may be continued as long as participants are experiencing clinical benefit, as assessed by the Investigator, in the absence of unacceptable toxicity or symptomatic deterioration attributed to disease progression after an integrated assessment of radiographic data, biopsy results (if available), and clinical status for a maximum of 24 months. Participants who meet the criteria for disease progression per RECIST v1.1 will be permitted to continue study treatment if they meet all criteria for treatment beyond progression.

[redacted]

regardless of treatment delays until radiographic disease progression per RECIST v1.1, initiation of a new anti-cancer therapy, withdrawal of consent, death, or study termination by the Sponsor, whichever occurs first. Thus, tumor assessments are to continue according to the schedule in participants who discontinue treatment for reasons other than disease progression or loss of clinical benefit. For participants who continue treatment after progressive disease, tumor assessments are to continue according to schedule until study treatment is discontinued. At the Investigator's discretion, tumor assessments may be repeated at any time if progressive disease is suspected.

Response will be assessed according to RECIST v1.1. Objective response at a single time-point will be determined by the Investigator according to RECIST v1.1. All primary imaging data used for tumor assessments may be collected by the Sponsor; centralized, blinded independent review of response endpoints by an independent review facility may be conducted.

The primary comparison of interest are the hazard ratio of OS of each experimental arm compared to nivolumab, assessing the superiority of the experimental arms over the active comparator treatment. The primary comparison of OS will be made regardless of whether participants withdraw from treatment or receive new anti-cancer therapy prior to disease progression. In order not to confound the OS endpoint, crossover from any of the treatment arms to another arm will not be allowed.

During the study, participants will be asked to complete patient-reported outcome (PRO) questionnaires at the beginning of the study, during study treatment, at treatment discontinuation, and during survival follow-up. These will assess disease and treatment-related symptoms, as well as functioning and overall health-related quality of life.

During the study, serum samples will be collected to monitor RO7121661, RO7247669, and nivolumab pharmacokinetics (PK) and to detect the presence of antibodies to RO7121661, RO7247669, or nivolumab. Blood samples for PK analysis may be collected at the participant's

home. This specifically applies to days where no other hospital assessments are required—i.e., C1D8 and C5D8.

Participant samples, including archival and fresh tumor tissue, serum, plasma, and blood samples, will also be collected for biomarker assessments.

Safety assessments will include the incidence, nature, and severity of AEs, and other protocol-specified tests such as laboratory abnormalities that are deemed critical to the safety evaluation of the study.

After study treatment discontinuation and disease progression per RECIST v1.1, survival follow-up information will be collected by means of telephone calls, participant medical records, and/or clinic visits approximately every 3 months until death, lost to follow-up, or study termination by the Sponsor, whichever occurs first. All participants will be periodically contacted for survival and new anti-cancer therapy information unless the participant requests to be withdrawn from follow-up (this request must be documented in the source documents and signed by the Investigator). If the participant withdraws from the study, study staff may use a public information source (e.g., county records) when permissible to obtain information about survival status.

The IMPs are: RO7121661 (2100 mg Q2W IV), RO7247669 (2100 mg Q2W IV), and nivolumab (240 mg Q2W IV).

**Length of Study**

The duration in each period of the study for each participant will be as follows:

- Screening: Days -28 to -1.
- Treatment Period: Cycle 1 Day 1 up to a maximum of 24 months.
- Survival follow-up: 90 (± 7) days after last treatment with study drug; then every 3 months (± 14 days) until death, loss to follow-up, or study termination by the Sponsor.

**End of Study**

The end of the study will occur when all of the following criteria have been met:

- The required number of deaths for the primary analysis of OS has been observed.
- The last participant, last visit has occurred.

**Data Monitoring Committee**

A Joint Monitoring Committee (JMC) will review available safety data periodically and make recommendations regarding study conduct to ensure the safety of patients enrolled in the study. The JMC will consist of designated Sponsor personnel and independent clinical expert(s) (i.e., expert[s] independent from the Sponsor). The JMC Chair will be a medical oncologist who is neither the Medical Monitor nor associated with the study. Other JMC members will include, but not be limited to, a drug-safety scientist and biostatistician. The responsibility, membership, and communication flow of the JMC is further described in the JMC Charter.

## PARTICIPANT POPULATION

The study population consists of male and female participants with advanced or metastatic ESCC who are not indicated for radical resection and who are refractory or intolerant to fluoropyrimidine- or taxane- and platinum-based regimen.

**Key Inclusion Criteria (for details, see Section 5.1 of the protocol)**

- Participants with advanced or metastatic, histologically confirmed ESCC.
- Patients who are not indicated for radical resection and have previously received 1 line of treatment in non-curative intention prior to randomization. The prior line must be either a fluoropyrimidine- and platinum- or a taxane- and platinum-based regimen, and patients must have experienced progressive disease after at least 3 cycles or be unable to tolerate potential side effects of this treatment.

  *Patients who did not receive treatment in the non-curative setting but received a fluoropyrimidine-/taxane and platinum-based drug regimen in curative intent may be allowed. This includes patients who had either radical resection in conjunction with chemotherapy including neo-adjuvant/adjuvant therapy (± radiotherapy) or patients who were treated with chemo-radiation (including patients who underwent chemo-radiation followed by salvage surgery).*

  - If recurrence *or progression* was confirmed by imaging or by pathological assessment of a biopsy within 24 weeks after the last dose of the treatment, patients are eligible and do not require an additional line of therapy in the non-curative setting.
  - If recurrence *or progression* occurred later than 24 weeks after the last dose of the treatment, patients need to be exposed to an additional line of fluoropyrimidine-/taxane- and platinum-based drugs in the non-curative setting to be eligible for the study—unless the Investigator considers the patient not eligible for the re-exposure with fluoropyrimidine/taxane and platinum-based drugs.
  - The last dose of chemotherapy or the last radiation treatment (whichever occurs later) should be considered for the determination of the time-point of recurrence *or progression* after chemo-radiation.
- Radiologically measurable disease according to RECIST v1.1. Previously irradiated lesions should not be counted as target lesions unless clearly progressed after the radiotherapy.
- Eastern Cooperative Oncology Group Performance Status 0-1.
- A life expectancy of ≥ 12 weeks.
- Tissue samples must be provided for analysis of PD-L1 tumor positivity using the PDL1 IHC 28-8 pharmDx assay. Testing will be done centrally and results must be obtained prior to stratification.
- Adequate visceral organ functions
- AEs from any prior radiotherapy, chemotherapy, or surgical procedure must have resolved to Grade ≤ 1, except alopecia (any grade), vitiligo, endocrinopathy managed with replacement therapy, and Grade 2 peripheral neuropathy.
- Adequate contraception

**Key Exclusion Criteria**

- Pregnancy, lactation, or breastfeeding.
- Known hypersensitivity to any of the components of RO7121661, RO7247669, or nivolumab, including but not limited to, hypersensitivity to Chinese hamster ovary cell products or other recombinant human or humanized antibodies.
- Patients with significant malnutrition. Patients whose nutrition has been well controlled for ≥ 28 days prior to randomization may be enrolled.
- Evidence of complete esophageal obstruction not amenable to treatment.
- Higher risk of bleeding or fistula caused by esophageal lesions invading adjacent organs (aorta or tracheobronchial tree). *Patients with manageable fistula may be included at the Investigator's discretion.*
- Symptomatic central nervous system (CNS) metastases.

- Spinal cord compression not definitively treated with surgery and/or radiation or without evidence that disease has been clinically stable for ≥ 14 days prior to randomization.
- Active or history of carcinomatous meningitis/leptomeningeal disease.
- Asymptomatic CNS primary tumors or metastases if they have requirement for steroids or enzyme-inducing anticonvulsants in the last 28 days prior to randomization.
- Uncontrolled tumor-related pain.
- Patients with an active second malignancy.
- Evidence of significant, uncontrolled concomitant diseases that could affect compliance with the protocol or interpretation of results.
- Encephalitis, meningitis, or uncontrolled seizures in the year prior to informed consent.
- Significant cardiovascular/cerebrovascular disease within 6 months prior to randomization.
- Known active or uncontrolled bacterial, viral, fungal, mycobacterial (including but not limited to tuberculosis [TB] and typical mycobacterial disease), parasitic, or other infection (excluding fungal infections of nail beds) or any major episode of infection requiring treatment with IV antibiotics or hospitalization (relating to the completion of the course of antibiotics, except if for tumor fever) within 28 days prior to randomization.
- Known clinically significant liver disease, including alcoholic hepatitis, cirrhosis, and inherited liver disease.
- Major surgical procedure or significant traumatic injury (excluding biopsies) within 28 days prior to randomization, or anticipation of the need for major surgery during the course of the study.
- Any other diseases, metabolic dysfunction, physical examination finding, or clinical laboratory finding giving reasonable suspicion of a disease or condition that contraindicates the use of an investigational drug or that may affect the interpretation of the results or render the participant at high risk from treatment complications.
- Dementia or altered mental status that would prohibit informed consent.
- Uncontrolled pleural effusion (with the exception of participants with indwelling catheters, e.g., PleurX®), pericardial effusion, or ascites requiring recurrent drainage procedures (expected to occur once monthly or more frequently).
- Active or history of autoimmune disease or immune deficiency.
- Positive HIV test at screening.
- Positive hepatitis B surface antigen (HBsAg) or positive total hepatitis B core antibody (HBcAb) test at screening. Participants with a positive HBsAg or total HBcAb test followed by a negative hepatitis B virus (HBV) DNA test at screening are eligible.
- Positive hepatitis C virus (HCV) antibody test at screening. Participants with a positive HCV antibody test followed by a negative HCV RNA test at screening are eligible.
- Prior cancer therapy with any immunomodulatory agents including CPIs (such as anti-PDL1/PD1, anti-CTLA-4, anti-LAG3, anti-TIM3).
- Vaccination with live vaccines within 28 days prior to randomization, or anticipation that a live attenuated vaccine will be required during the study.
- Treatment with therapeutic oral or IV antibiotics within 14 days prior to randomization.
- Concurrent therapy with any other investigational drug (defined as treatment for which there is currently no regulatory authority-approved indication) < 28 days or 5 half-lives of the drug, whichever is shorter, prior to randomization.
- Treatment with immune-modulating and immune suppressive agents/medication < 5 half-lives or 28 days (whichever is shorter) prior to randomization.
- Regular immunosuppressive therapy (i.e., for organ transplantation, chronic rheumatologic disease).

- Radiotherapy within the last 28 days before start of study drug treatment is not allowed, with the exception of limited palliative radiotherapy.
- Prior treatment with adoptive cell therapies, such as CAR-T therapies.

**NUMBER OF PARTICIPANTS**

[redacted]

*plus an estimated number of patients enrolled in the RO7121661 arm at the time of switching from 3 to 2 arms.*

**CONCOMITANT MEDICATIONS**

As a general rule, no concomitant medication will be permitted, with the exception of medications to treat AEs, unless the rationale for exception is discussed and clearly documented between the Investigator and the Sponsor.

Use of the following therapies is prohibited during the study and for at least 28 days or 5 half-lives of the drug, whichever is shorter, prior to randomization and during study treatment, unless otherwise specified below:

- Investigational or unlicensed/unapproved agents.
- Therapy intended for the treatment of cancer (including, but not limited to, chemotherapy, hormonal therapy, immunotherapy, and radiotherapy [with the exception of limited palliative radiotherapy], as well as herbal therapy or traditional Chinese medicines with anti-cancer activity in the label), whether Health Authority-approved or experimental.
- Chronic use of steroids (inhaled and topical steroids are permitted) at baseline of $>$ 10 mg of prednisone/day (or equivalent). Concurrent high doses of systemic corticosteroids.
- Administration of a live, attenuated vaccine or anticipation that such a live attenuated vaccine will be required during the study or within 4 months after the administration of the final dose of the study drug.
- Systemic immunostimulatory agents (including, but not limited to, interferons and IL-2) because these agents could potentially increase the risk for autoimmune conditions when given in combination with CPIs.
- Systemic immunosuppressive medications (including, but not limited to, cyclophosphamide, azathioprine, methotrexate, and thalidomide) because these agents could potentially alter the efficacy and safety of the study drug.
- Adoptive cell therapies, such as CAR-T therapies.

## 1.2 SCHEMATIC OF STUDY DESIGN

An overview of the study design is provided in Figure 1 *and Figure 2*.

**Figure 1 Overview of *Original* Study Design**

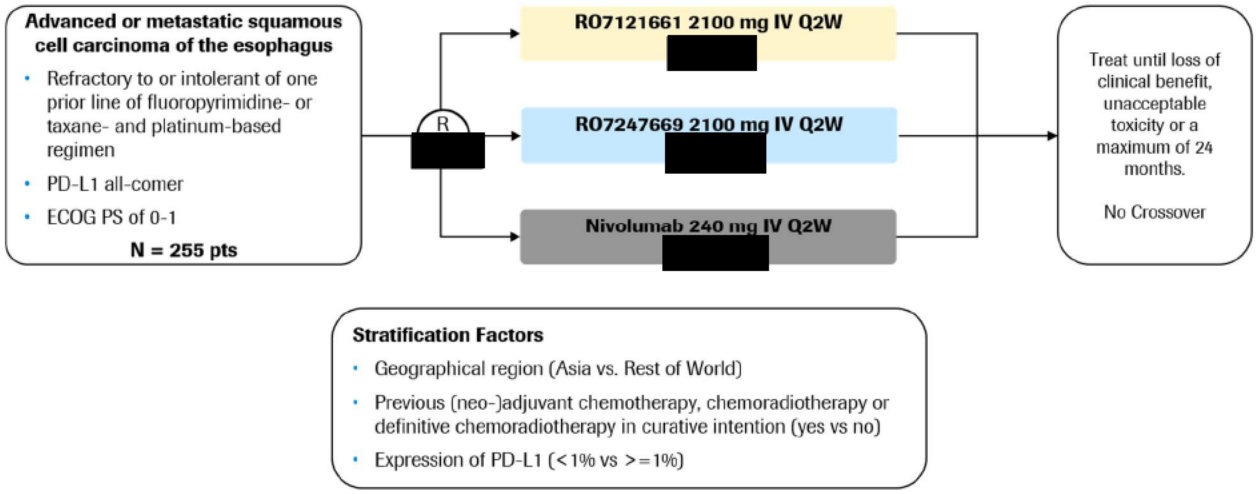
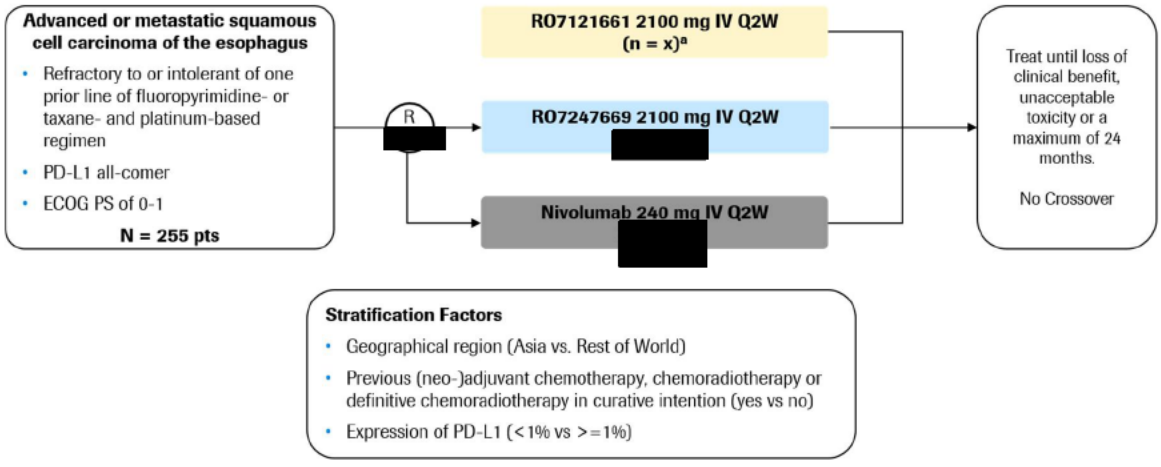



**Figure 2** ***Overview of Study Design After Stopping Recruitment into the RO7121661 Arm***




[a] *It is planned to stop enrollment when approximately* [redacted] *participants have been recruited in the RO7247669 and nivolumab arms. Patients already included in the RO7121661 arm will remain in the study. The estimated amount of participants enrolled in the RO7121661 arm at the time of recruitment stop will be added to the planned* [redacted] *The study will not be unblinded.*

## 1.3 SCHEDULE OF ACTIVITIES

The schedule of activities are provided in Table 1, Table 2, and Table 3.

# Table 1 Schedule of Activities

| Protocol Section | Cycle length 14 days | Screening | On dosing days of all treatment Cycles[a] | Cycle 1 - 5 Day 8 | Treatment Discontinuation | Follow-up | In case of Grade ≥2 IRR, suspected anaphylaxis, or Grade ≥ 2 suspected imAEs | |
|---|---|---|---|---|---|---|---|---|
| | Day (D) | D -28 to D -1 (unless otherwise indicated) | Every 14 Days (-1/+3 days) | (± 1 day) | ≤ 30 Days after Last Dose | 90 (±7 days) post last dose, then every 3 months (±2 weeks) | At the time of event | ≥48 hours after the onset of an IRR |
| | **Screening Assessments** | | | | | | | |
| | Informed consent (incl. RBR) | x | | | | | | |
| 8.2.8 | Medical history and demography | x | | | | | | |
| 8.2.5 | Royal Marsden Risk Score | x | | | | | | |
| | **IMP Administration** | | | | | | | |
| 6.1 | Study drug administration | | x | | | | | |
| | **Clinical Assessments** | | | | | | | |
| 6.5 | Previous and concomitant treatments | continuous | | | | | x | x |
| 8.3 | Adverse events | | | | | x | x | x |
| 8.2.1 | Physical examination | x | x | | x | | Weight only | |
| 8.2.1 | Height | x | | | | | | |
| 8.2.2 | Vital signs[b] | x | x | | x | | | |
| 8.2.3 | 12-lead ECG | x | x | | x | | x | |
| 8.2.4 | ECOG performance status | x | x | | x | | | |
| 8.2.6 | TTE or MUGA | x | | | | | | |
| 8.1.2 | PRO-assessments | | Refer to the PRO assessments table for specific Timepoint Details | | | | | |
| 8.8.2 | Nutritional assessment (optional) | | C1, C4 and upon occurrence of colitis | | | | | |
| 8.1.1 | Tumor assessment (CT scan of chest, abdomen, pelvis, brain, and other regions as clinically indicated) | [redacted] | | | | | | |
| 8.11.4 | Post-study survival and anti-cancer therapies | | | | | x | | |
| | **Local Laboratory Assessments** | | | | | | | |
| 8.2.7 and Appendix 4 | Viral serology | x | | | | | | |
| | Quantitative immunoglobulins | x | | | | | | |
| | Hematology | x | x | | x | | x | |
| | Blood chemistry | x | x | | x | | x | |
| | Coagulation | x | x | | x | | x | |
| | Lipid panel | x | C1 and then every 4 cycles | | x | | | |
| | Thyroid function | x | C3 and then every 3 cycles | | | | | |
| | Auto-antibody panel | x | In case of suspected Grade ≥ 2 imAEs | | | | In case of suspected imAEs | |
| | Urinalysis | x | x | | x | | | |
| | IgE/tryptase | | | | | | x[d] | x[d] |
| | Pregnancy test | x (blood test, D -7 to D -1) | C2 and then every 4 weeks (blood or urine) | | x (blood or urine) | x[e] (5 months after the last dose) | | |
| | **Central Laboratory Assessments** | | | | | | | |
| 8.5 | PK | Refer to Hourly Schedule of Assessments for specific sample collection timepoint details | | | | | x | |
| 8.6 | ADA | | | | | | | |
| 8.8.1 | PD plasma | | | | | | x | |
| | PD serum | | | | | | x | |
| | PD whole blood flow cytometry | | | | | | x | |
| | Whole Blood RNA | | | | | | | |
| | bTMB/ctDNA | | | | | | | |
| 8.7.1 | WGS | | | | | | | |
| 8.8.1 | Archival tumor sample | | | | | | | |
| 8.8.2 | Fresh tumor biopsy (optional) | | | | | | | |
| | Tongue scrape (optional) | | | | | | | |
| | Stool sample (optional) | | | | | | | |
| 8.9 | RBR sample (saliva DNA) | | | | | | | |

## Table 1 Schedule of Activities (cont.)

Abbreviations: ADA = Anti-drug antibody; AE = Adverse event; C = Cycle; D = Day; ECOG = Eastern Cooperative Oncology Group; imAE = Immune-mediated adverse event; IMP = Investigational medicinal product; IRR = Infusion-related reaction; MUGA = Multiple-Gated Acquisition Scans; PD = Pharmacodynamic; PK = Pharmacokinetic; PRO = Patient-reported outcome; RBR = Research biosample repository; TTE = Transthoracic echocardiogram; WGS = Whole genome sequencing.

a) During the study treatment period, assessments scheduled on the days of study treatment infusions should be performed before the start of infusion unless otherwise noted. Laboratory results have to be available prior the initiation of treatment.

b) Vital signs include pulse rate, respiratory rate, blood pressure, and temperature at every assessment and blood oxygen saturation pre-dose at visits where tumor assessments are performed. For the first infusion, vital signs should be determined within 60 minutes before and 30 (± 10) minutes after the end of infusion. Vital signs will also be collected during the first infusion (every 15 [± 5] minutes). During subsequent infusions, vital signs should be determined within 60 minutes before the infusion, during each infusion only as clinically indicated and within 15 (± 10) minutes after the end of each infusion. Additional vital signs should be collected during the infusion, if clinically indicated, or if symptoms occurred with the prior infusion. Blood oxygen saturation by pulse oximetry at baseline screening and pre-dose at every visit where tumor assessments are performed.

c) Participants who discontinue treatment for reasons other than radiographic disease progression per RECIST v1.1 (e.g., toxicity, symptomatic deterioration) will continue scheduled tumor assessments at the frequency described above until radiographic disease progression per RECIST v1.1, initiation of a new anti-cancer therapy, withdrawal of consent, death, or study termination by Sponsor, whichever occurs first. Thus, tumor assessments are to continue according to the schedule in participants who discontinue treatment for reasons other than disease progression or loss of clinical benefit.

d) Tryptase and total IgE should be analyzed for participants who experience a Grade ≥ 3 IRR during the first study treatment administration or for participants who experience a Grade ≥ 2 IRR for the first time with the second or subsequent study drug infusion or with clinical signs of hypersensitivity reaction at any time of the conduct of the study. A second sample for IgE/tryptase analysis should be collected at least 48 hours after the onset of the reaction to rule out the possibility of an anaphylactic reaction.

e) An at-home pregnancy test will be provided. The test has to be conducted 5 months after the final dose (for women of childbearing potential), and the site will inquire about the result during the second follow up.

## Table 2 Hourly Schedule of Assessments

| | Q2W regimen; Cycle length 14 days | Screening | Cycle 1 | | | | Cycle 2 | | | Cycle 3 | | Cycle 4 | | Cycle 5 | | | | Subsequent Cycles | | Treatment Discontinuation |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Day | | Day 1 | | | Day 8 | Day 1 | | | Day 1 | | Day 1 | | Day 1 | | | Day 8 | Day 1 | | |
| | Scheduled Time (h)[a] | | PreDose | EOI | 4 | 168 | PreDose | EOI | 4 | PreDose | EOI | PreDose | EOI | PreDose | EOI | 4 | 168 | PreDose | EOI | At Visit |
| Protocol Section | Time Window | | -4h | + 10 min | +/- 1 h | +/- 24 h | -4h | + 10 min | +/- 1 h | -4h | + 10 min | -4h | + 10 min | -4h | + 10 min | +/- 1 h | +/- 24 h | -4h | + 10 min | |
| 8.5 | PK Sample | | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x |
| 8.6 | ADA | | x | | | | x | | | x | | x | | x | | | | C7 and then every 3 cycles | | x |
| 8.8.1 | PD Serum | | x | | | | x | | | x | | | | x | | | | At the time of tumor assessment | | x |
| | PD Plasma | | x | | | | x | | | x | | | | x | | | | C9 and then every 3 cycles | | x |
| | Whole Blood Flow Cytometry | | x | | | x | x | | | x | | | | x | | | x | C9 and then every 3 cycles | | x |
| | Whole Blood RNA | | x | | | | | | | x | | | | | | | | | | |
| | bTMB/ctDNA | | x | | | | x | | | x | | | | | | | | | | |
| 8.7.1 | WGS | | x | | | | | | | | | | | | | | | | | |
| 8.8.1 | Archival Tumor Sample | x | | | | | | | | | | | | | | | | | | |
| 8.8.2 | Fresh Tumor Biopsy (Optional[b]) | x | | | | | | | | x (+2/ -1 day[s]) | | | | | | | | | | |
| | Tongue Scrape (Optional[c]) | | x (+0/ -5 day[s]) | | | | | | | | | x (+0/ -5 day[s]) | | | | | | | | |
| | Stool Sample (Optional[c]) | | x (+0/ -5 day[s]) | | | | | | | | | x (+0/ -5 day[s]) | | | | | | | | |
| 8.9 | RBR Sample (Saliva DNA) Optional[d] | | x | | | | | | | | | | | | | | | | | |

## Table 2 Hourly Schedule of Assessments (cont.)

Abbreviations: ADA = Anti-drug antibody; C = Cycle; EOI = End of infusion; h = Hour; PD = Pharmacodynamic; PK = Pharmacokinetic; Q2W = Every two weeks; RBR = Research biosample repository; WGS = Whole genome sequencing.

a) Assessments (e.g., pre-dose) should be performed relative to the start of the study drug infusion except for those at EOI time-points.
b) As exception, a mandatory baseline fresh biopsy is required to be collected in case no suitable archival tissue sample is available to assess the PD-L1 positivity of a participant's tumor (see Section 5.1)
c) An additional sample should be taken upon occurrence of colitis, as assessed and confirmed by the Investigator.
d) Samples for RBR DNA saliva will be collected on Day 1 from all participants who signed RBR ICF prior to study drug infusion. If the RBR DNA saliva sample is not collected during the scheduled visit, it may be collected at any time during the conduct of the clinical study.

## Table 3 Schedule of Assessment for Patient-Reported Outcomes

| Cycle length 14 days | Day (D) | QLQ-C30[a] | QLQ-IL97[a] | QLQ-OES18[a] | PGI-CI[a] | PGI-S[a] | PRO-CTCAE[a] |
|---|---|---|---|---|---|---|---|
| Cycle 1 | Day 1 | x | x | x | | x | x |
| | Day 8 (± 1 day) | | | | | | x[b] |
| Cycle 2 | Day 1 | | x | x | | | x |
| | Day 8 (± 1 day) | | | | | | x[b] |
| Cycle 3 | Day 1 | | x | x | x | x | x |
| | Day 8 (± 1 day) | | | | | | x[b] |
| Cycle 4 | Day 1 | x | | x | | | x |
| | Day 8 (± 1 day) | | | | | | x[b] |
| Cycle 5 | Day 1 | | x | x | | | x |
| | Day 8 ± 1 day) | | | | | | x[b] |
| Cycle 6 | Day 1 | | x | x | x | x | x |
| Cycle 7 | Day 1 | x | | x | | | x |
| Cycle 8 | Day 1 | | x | x | | | x |
| Cycle 9 | Day 1 | | x | x | x | x | x |
| Subsequent cycles | Day 1 | C10 and then every 6 cycles | | x | C12 and then every 6 cycles | C12 and then every 6 cycles | x |
| Treatment Discontinuation | ≤ 30 Days after Last Dose | x | | x | x | x | x |
| Follow-up | 90 (±7 days) post last dose, then every 3 months (±2 weeks) | Every 3 months during the 1st year post discontinuation[b] | | Every 3 months during the 1st year post discontinuation[b] | | | At 1st follow-up only[b] |

Abbreviations: C = Cycle. PRO = Patient-reported outcome.

a) All PRO instruments are required to be administered before the participant receives any information on disease status, prior to the performance of non-PRO assessments, and prior to the administration of study treatment, unless otherwise specified. In scenarios where assessments (e.g., blood draws) are done at a different location than the one providing treatment or when they are done on a different day than study treatment administration, laboratory assessments can be completed before the completion of PRO instruments as long as results have not been discussed with participants.

b) On days where no site visit is planned, remote completion of PROs is accepted.

# 2. INTRODUCTION

RO7121661, an anti-programmed death-1 (PD1)/T-cell immunoglobulin and mucin domain 3 (TIM3) bispecific antibody (BsAb) and RO7247669, an anti PD1/lymphocyte-activation gene 3 (LAG3) BsAb, were designed to target dysfunctional tumor antigen-specific T lymphocytes (expressing PD1 and TIM3 or LAG3 respectively) in order to establish or restore an effective anti-tumor immune response in patients with cancer with a high unmet medical need.

This Phase II study in patients with squamous cell carcinoma of the esophagus (ESCC) aims to evaluate the efficacy of RO7121661 and RO7247669 compared to nivolumab.

## 2.1 STUDY RATIONALE

Cancer remains a major cause of death worldwide despite several new agents providing survival benefits to patients. Many cancer indications have a poor prognosis and the management of most advanced solid tumors remains challenging because of the high rate of tumor recurrence or the development of distant metastases.

Despite the effectiveness of PD1/L1 checkpoint inhibition (CPI) therapy in various tumor types including ESCC (Kato et al. 2019; Kim et al. 2019), additional treatment options targeting immune checkpoints are needed, because the majority of patients eventually progress after an initial response or fail to respond to the PD1/L1 checkpoint blockade.

By targeting both PD1 and TIM3 or LAG3 on dysfunctional tumor-specific T lymphocytes, the PD1-TIM3 and PD1-LAG3 BsAbs aim to restore an effective anti-tumor immune-response and provide survival benefit to more patients with cancer than currently available agents do. PDL1 expression in ESCC ranges from 15% to 83% in tumor cells and from 13% to 31% in tumor-infiltrated immune cells (Jiang et al. 2017; Lam et al. 2017; Guo et al.2017; Qu et al. 2016). Studies with nivolumab, pembrolizumab, and other PD1 inhibitors demonstrated benefit over chemotherapy in the second-line (2L) ESCC population leading to market authorizations in that setting (e.g., in the U.S, EU, Japan, South Korea, and other jurisdictions). Both TIM3 and LAG3 have been shown to be expressed on tumor-infiltrating lymphocytes in patients with ESCC (Zhang et al. 2018; Wang et al 2019; Zhao et al. 2020). RO7121661 and RO7247669 may therefore have the potential to be a therapeutic option for patients with ESCC.

The purpose of this study is to assess the efficacy of RO7121661 and RO7247669 compared with nivolumab to address a significant unmet medical need in patients with unresectable advanced or recurrent ESCC who are refractory or intolerant to one prior line of chemotherapy.

The rationale for the study design is provided in Section 4.1.4.

## 2.2 BACKGROUND

### 2.2.1 Background on Esophageal Carcinoma

Esophageal cancer is the seventh most common cancer and the sixth most common cause of death from cancer worldwide (Bray et al. 2018). The incidence, prevalence, and histologic type of esophageal cancer varies between geographic regions. ESCC accounts for 70% of cases of esophageal cancer globally and is particularly common in a so-called “esophageal cancer belt,” which stretches from northern China through the central Asian republics to Northern Iran. Adenocarcinoma is the predominant histologic type in Western countries (United States and Europe). Adenocarcinoma and squamous cell carcinoma have differing biologic pathways and are therefore treated differently.

Advanced esophageal cancer is a rapidly fatal disease. More than two-thirds of patients diagnosed with esophageal cancer will have advanced or metastatic disease, with a median survival of 8 to11 months and an expected 5-year survival rate of $<$ 5% (Drahos et al 2013; Lin et al 2016; Kato et al. 2019; Kim et al. 2019). The impact of esophageal cancer on patients is multifaceted. Most affected individuals present with physical symptoms, primarily dysphagia (Daly et al. 2000), which can result in unintentional weight loss and loss of appetite; less common symptoms include chest pain, dyspnea, and gastrointestinal reflux. However, patients also frequently report poor emotional wellbeing, and in particular, high rates of anxiety and depression (Bergquist et al. 2007). Each of these patient-reportable issues has a significant impact on patients’ quality of life. These data, combined with the relative lack of highly effective treatments, are indicative of the large unmet medical need in patients diagnosed with advanced esophageal cancer.

### 2.2.2 TREATMENT FOR ADVANCED ESOPHAGEAL SQUAMOUS CELL CARCINOMA

#### 2.2.2.1 Chemotherapy

There is no consensus on the optimal regimen for first-line treatment of advanced esophageal cancer globally. For ESCC in particular, there are no data from recent randomized controlled studies. However, combination chemotherapy is typically given as first-line treatment. Treatment regimens for ESCC commonly consist of cisplatin in combination with paclitaxel or 5-fluorouracil (5-FU) (Lordick and Janjigian 2016; Kitagawa et al. 2019; NCCN 2019; NHCPRC 2019): These regimens are associated with objective response rates (ORRs) ranging from 20% to 48%, 5-year survival rates of less than 10%, and significant toxicity rates (Grünberger et al. 2007). There are regional preferences for the chemotherapy of choice, which may be based on the toxicity profile of each agent.

In the 2L setting, single-agent chemotherapy is an established option based on patient benefit-risk assessment (Lordick et al 2016; Muro et al 2019; NCCN 2019; Kitagawa et al. 2019). Although 2L treatments with docetaxel and paclitaxel are used for patients with advanced ESCC that has progressed after first-line chemotherapy, they are associated with hematological, gastrointestinal, and neurological toxicities (Jimenez et al. 2011); with poor long-term survival (Kato et al. 2011; Muro et al. 2004).

#### 2.2.2.2 Anti-PD1 Therapy

More recently, positive Phase 3 data have been shown with three anti-PD1 treatments in 2L ESCC.

Data from the ATTRACTION-3 study demonstrated the survival benefit of nivolumab versus Investigator-selected chemotherapy (paclitaxel or docetaxel) in patients with ESCC (Kato et al. 2019). In the intent-to-treat (ITT) population, overall survival (OS) was statistically significantly prolonged in the nivolumab arm compared with that in the chemotherapy arm. The survival benefit with nivolumab occurred regardless of patients' level of tumor PDL1 expression despite a numerically greater clinical benefit in patients with tumor PDL1 expression of at least 1% versus those with less than 1%.

Pembrolizumab showed positive data in ESCC in the Keynote-181 study compared to an Investigator's choice of paclitaxel, docetaxel or irinotecan (Kojima et al. 2019). While the OS benefit over chemotherapy was only statistically significant in patients with a combined positive score $\geq$ 10, the hazard ratio in the overall ESCC population was 0.78 (0.63-0.96) compared with chemotherapy, marginally missed statistical significance based on pre-specified statistical boundaries.

Likewise, camrelizumab provided positive data as 2L treatment of ESCC in the ESCORT study compared with Investigator's choice of either docetaxel or irinotecan (Huang et al. 2020). Camrelizumab significantly improved OS compared with chemotherapy. Subgroup analysis showed that clinical benefits of camrelizumab were observed in all PDL1 expression subgroups, and patients with higher PDL1 expression appeared to derive more benefit than those with low PDL1 expression.

Overall, these data indicate that CPIs (such as anti-PD1) demonstrate single-agent activity in 2L ESCC and treatment with anti-PD1 agents and is an approved treatment option in a variety of countries.

### 2.2.3 Background on RO7121661

RO7121661 is a novel, Fc-silent, IgG1-based BsAb in the 1 + 1 format that incorporates monovalent binding to the checkpoint receptors PD1 and TIM3. Use of a natural IgG-like monovalent heterodimeric IgG1 format allows avidity for simultaneous binding to PD1 and TIM3 when both receptors are co-expressed. RO7121661 binds with monovalent high affinity to a glycopeptide-epitope on PD1 and with low affinity to TIM3 to induce an avidity-driven selectivity effect for binding to T-cells in the tumor microenvironment that co-expresses both PD1 and TIM3 or to T-cells expressing PD1 alone. This preferential binding avoids the targeting of other TIM3 expressing cells such as myeloid or natural killer (NK) cells.

An additional feature of RO7121661 is the specifically engineered, IgG1-based, Fc-region that prevents binding to Fc-gamma receptors by introduction of PGLALA mutations (Kabat et al. 1991; Schlothauer et al. 2016). This avoids drug-shaving and thus tumor-associated macrophage resistance mechanisms, which have been observed with IgG4-based antibodies such as pembrolizumab and nivolumab (Arlauckas et al. 2017).

RO7121661 is currently being evaluated in the entry-into-human (EIH) Study NP40435.

The available nonclinical and clinical data provide a strong rationale for evaluating the potential clinical benefit of RO7121661 in patients with ESCC.

A detailed description of the chemistry, pharmacology, and safety of RO7121661 is provided in the RO7121661 Investigator's Brochure.

### 2.2.4 Background on RO7247669

RO7247669 is a novel, Fc-silent IgG1-based BsAb in 1 + 1 format that incorporates monovalent binding to the checkpoint receptors, PD1 and LAG3. Use of a natural IgG-like monovalent heterodimeric IgG1 format allows one to make use of avidity (e.g., simultaneous binding to PD1 and LAG3). RO7247669 BsAb is engineered to preferentially bind to T-cells in the tumor microenvironment that co-express both PD1 and LAG3, or to a lesser extent either PD1 or LAG3 alone. RO7247669 binds with monovalent high affinity to a PD1 glycoepitope and binds with monovalent high affinity to a novel epitope (E3) on LAG3 Domain 1. Although RO7247669 binds with high affinities to PD1 and LAG3, RO7247669 induces an avidity driven selectivity effect for binding to T-cells in the tumor microenvironment that co-express both PD1 and LAG3. Preferential binding to T-cells in the tumor microenvironment avoids the targeting of other LAG3 expressing cells such as regulatory T cells in the tumor and in the periphery (which do not express high levels of PD1). Monovalent binding to LAG3 reduces internalization of the antibody (Ab) upon binding to the T-cell surface. The retention time of monovalent RO7247669 on T-cell surface is higher when simultaneously bound to PD1 and LAG3.

As for RO7121661, PGLALA mutations have been introduced into the IgG1-based Fc-region RO7247669 to avoid drug-shaving and thus tumor-associated macrophage resistance mechanisms.

[redacted].

[redacted]

As of the cutoff date, 15 October 2020, the DCR in Part A of the study was 51.5% (17 out of 33 evaluable participants) and the ORR was 6.1 % (2 out of 33 participants). Responses were observed in one participant with breast cancer and one participant with non-small cell lung cancer. Amongst the participants dosed at the proposed dose of 2100 mg Q2W, 6 out of 11 participants had a best response of stable disease or better (DCR = 54.5%) including two participants (one participant with breast cancer and one participant with head and neck cancer) with an unconfirmed partial response at their first on treatment tumor assessment.

The available nonclinical and clinical data provide a strong rationale for evaluating the potential clinical benefit of RO7247669 in patients with ESCC.

A detailed description of the chemistry, pharmacology, and safety of RO7247669 is provided in the RO7247669 Investigator's Brochure.

### 2.2.5 Background on nivolumab

Nivolumab is a human monoclonal antibody that targets the human PD1 receptor. Nivolumab is approved for the treatment of several cancer types, including unresectable advanced, recurrent or metastatic ESCC after prior fluoropyrimidine- and platinum-based chemotherapy in the U.S., EU, Japan, South Korea, and other jurisdictions.

For detailed information, please refer to the nivolumab EU SmPC.

## 2.3 BENEFIT/RISK ASSESSMENT

Clinical data emerging in the field of tumor immunotherapy have demonstrated that therapies focused on enhancing T-cell responses against cancer can result in a significant survival benefit in patients with metastatic cancer, including ESCC. Recent Heath Authority approvals in 2L ESCC of the PD1 inhibitors nivolumab, pembrolizumab, and camrelizumab validate the inhibition of the immune checkpoint pathways for achieving clinical benefit in ESCC. Nevertheless, a significant unmet medical need remains in patients in the 2L setting with advanced or metastatic ESCC. Despite recent advancements, the median OS for patients treated with PD1 inhibitors in the 2L is reported to be between 8.3 and 10.9 months (Kato et al. 2019; Kim et al. 2019; Huang et al. 2020).

It is hypothesized that dual checkpoint inhibition may result in enhanced and/or more durable responses than either therapy modality alone. Thus, compared to monospecific PD1/PDL1 directed antibodies, one might expect a better efficacy primarily coming from targeting both PD1 and TIM3- or LAG3-mediated immune-resistance mechanisms. PDL1 expression in ESCC ranges from 15% to 83% in tumor cells and from 13% to 31% in tumor-infiltrated immune cells (Jiang et al. 2017; Lam et al. 2017; Guo et al. 2017; Qu et al. 2016) and PD1 inhibition resulted in benefit in the ESCC population (Section 2.2.2.2). Both TIM3 and LAG3 have been shown to be expressed on tumor-infiltrating lymphocytes in patients with ESCC (Zhang et al. 2018; Wang et al. 2019; Zhao et al. 2020). As the TIM3 and LAG3 pathways are associated with immune dysfunction, these findings suggest that TIM3 and LAG3 blockade to restore T-cell function could potentially improve clinical outcomes for patients. Both molecules have demonstrated single-agent activity in the respective EIH studies (Sections 2.2.3 and 2.2.4). RO7121661 and RO7247669 may therefore have the potential to be a therapeutic option for patients with ESCC.

Overall, both RO7121661 and RO7247669 have been well tolerated at the proposed dose/schedule of 2100 mg Q2W; AEs have been manageable, and the safety profile is observed to be consistent across different solid tumor indications as well as with approved PD1 directed antibodies (Sections 2.2.3 and 2.2.4). Precaution against general risks for patients have been taken into account in the safety measures for this study, which include the definition of the inclusion/exclusion criteria (Section 5), and rules for treatment interruption and withdrawal from study (Section 7). Recommendations for the prophylaxis and the management of specific and known PD1/PDL1-mediated AEs can be found in Section 8.3.7 and Appendix 7.

Advanced or metastatic ESCC is an incurable disease with a high unmet need for improved medical intervention. Taking into account the preliminary efficacy and manageable safety profiles, as well as the potential for improved outcomes due to their mechanisms of action of dual checkpoint inhibition, treatment with RO7121661 and RO7247669 has therapeutic potential in solid tumors such as ESCC. Based on the considerations above, currently available data and the planned safety monitoring and management guidance, the proposed study treatments are considered to have an appropriate benefit/risk profile for the population included in this study.

More detailed information about the known and expected benefits in the context of potential risks and reasonably expected AEs of RO7121661 and RO7247669 is provided in the respective Investigator's Brochures.

Nivolumab has demonstrated efficacy in ESCC and is an approved 2L treatment option. More detailed information about the known and expected benefits in the context of potential risks and reasonably expected AEs of nivolumab is provided in the EU SmPC.

**COVID-19 Benefit-Risk Assessment**

In the setting of the coronavirus disease (COVID-19) pandemic, patients with comorbidities (including those with ESCC) are a more vulnerable population. Infection with sudden acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has been associated with higher morbidity and mortality in patients with cancer in some retrospective analyses. It is unclear how immunotherapy affects the incidence or severity of COVID-19. It is not anticipated that treatment with RO7121661 or RO7247669 will increase the risk of infection with SARS-CoV-2. Severe COVID-19 is associated with a cytokine release syndrome (CRS) involving the inflammatory cytokines IL-6, IL-10, IL-2, and interferon-gamma. RO7121661 and RO7247669 have a low risk of CRS and, while it is not known, there may be a potential for an increased risk of an enhanced inflammatory response if a participant develops SARS-CoV-2 infection while receiving RO7121661 or RO7247669. Clinical studies with RO7121661 and RO7247669 are ongoing during this pandemic and, although the study numbers are small, neither has shown any increased risk of developing COVID-19 or of having a worse outcome in participants receiving treatment with RO7121661 or RO7247669.

There are limited data concerning the possible interactions between cancer immunotherapy treatment and SARS-CoV-2 vaccination. It is recognized that human immune responses are highly regulated and that immune-modifying therapies may positively or negatively affect the efficacy and safety of SARS-CoV-2 vaccination (Society for Immunotherapy for Cancer [SITC] 2020).

Per recommendations of the National Comprehensive Cancer Network® (NCCN 2021) COVID-19 Vaccination Advisory Committee, SARS-CoV-2 vaccination is recommended for all patients with cancer receiving active therapy (including immune checkpoint inhibitors), with the understanding that there are limited safety and efficacy data in such patients (NCCN 2021). Given the lack of clinical data, currently no recommendations can be made regarding the optimal sequence of SARS-CoV-2 vaccination in patients who are receiving cancer immunotherapy (SITC 2020). For patients enrolling in this study and receiving study treatment, a decision to administer the vaccine to a patient should be made on an individual basis by the Investigator in consultation with the patient.

In alignment with clinical practice procedures, factors to consider when making the individualized decision for a given patient receiving study treatment to receive SARS-CoV-2 vaccination include the following: the risk of SARS-CoV-2 infection and potential benefit from the vaccine, the general condition of the patient and potential complications associated with SARS-CoV-2 infection, underlying disease, and the severity of COVID-19 outbreak in a given area or region.

SITC and NCCN recommendations (SITC 2020; NCCN 2021), along with institutional guidelines, should be used by the Investigator when deciding on administering SARS-CoV-2 vaccines. When administered, SARS-CoV-2 vaccines must be given in accordance with the approved or authorized vaccine label. Receipt of the SARS-CoV-2 vaccine is considered a concomitant medication and should be documented as such (see Section 6.5).

# 3. OBJECTIVES AND ENDPOINTS

The primary objective is expressed in the estimand framework through the 5 attributes as described in Table 4.

## Table 4 Estimands

| Attribute | Study Definitions |
|---|---|
| Population | Patients with unresectable advanced or recurrent ESCC who are refractory or intolerant to one prior line of chemotherapy |
| Primary endpoint (variable) | Overall survival |
| Treatments | • Experimental: 2100 mg Q2W RO7121661<br>• Experimental: 2100 mg Q2W RO7247669<br>• Active comparator: 240 mg Q2W nivolumab |
| Intercurrent events and their handling | New anti-cancer therapy and treatment discontinuation, handled via treatment policy (intercurrent event is ignored) |
| Summary measure | Hazard ratios |

The objectives and corresponding endpoints are provided in Table 5.

## Table 5 Objectives and Endpoints

| Objectives | Endpoints |
|---|---|
| **Primary** | |
| To evaluate the efficacy of RO7247669 compared with nivolumab. | • OS, defined as the time from randomization to death from any cause |
| **Secondary** | |
| To evaluate the safety and tolerability of RO7121661 and RO7247669 compared with nivolumab. | • Nature, frequency, and severity of adverse events (AEs) graded according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) v5.0 |
| To evaluate the efficacy of RO7247669 compared with nivolumab. | • Objective response rate (ORR), defined as the proportion of participants with an objective response (i.e., complete response [CR] or partial response [PR]), according to RECIST v1.1<br>• Disease control rate (DCR), defined as ORR + stable disease rate (SDR)<br>• Duration of response (DoR) for participants with ORR, defined as the time from the first occurrence of a documented objective response to disease progression according to RECIST v1.1 or death from any cause, whichever occurs first<br>• Progression-free survival (PFS) defined as the time from randomization to the first occurrence of progression as determined by the Investigator according to RECIST v1.1 or death during the treatment period or within 60 days of the last tumor assessment after treatment discontinuation from any cause, whichever occurs first<br>• Proportion of participants reporting clinically meaningful improvement in global health status/quality of life, emotional functioning, social functioning and dysphagia |

| | |
|---|---|
| | as measured by the European Organisation for Research and Treatment of Cancer (EORTC) Quality-of-life questionnaire (QLQ)-C30, IL97, and OES-18, defined as an improvement of at least 10 points |
| To investigate the pharmacokinetics (PK) of RO7247669 and nivolumab. | • Serum concentrations, PK profiles and parameters for RO7121661, RO7247669, and nivolumab |
| To evaluate the immune response after administration of RO7247669 and nivolumab. | • Incidence and titer of RO7121661, RO7247669 or nivolumab anti-drug antibodies (ADAs) during the study relative to the prevalence of ADA at baseline |
| To assess treatment-induced pharmacodynamic changes (PD Biomarkers) in peripheral blood and tumor microenvironment | • Changes from baseline in the phenotype and activation status (CD4/CD8 HLA-DR+Ki67+) of T-cell subsets in the peripheral blood<br>• Changes from baseline such as CD8 T-cell infiltration, proliferation (CD8+Ki67+) in the tumor microenvironment |
| To assess baseline characteristics in the tumor microenvironment as predictive biomarkers of response | • Baseline PDL1, CD8+PD1+, CD8+TIM3+, and CD8+LAG3+ expression in the tumor microenvironment |
| **Exploratory** | |
| To evaluate the efficacy of RO7121661 and RO7247669 compared with nivolumab. | • Changes in disease-related symptoms, function, and health-related quality of life as measured by the EORTC QLQ-C30, IL-97, and OES-18<br>• Proportion of responses on the PGI-CI and PGI-S |
| *To evaluate the efficacy of RO7121661 compared with nivolumab.* | • *OS, defined as the time from randomization to death from any cause*<br>• *ORR, DCR, DoR, PFS as defined above according to RECIST v1.1*<br>• *Proportion of participants reporting clinically meaningful improvement in global health status/quality of life, emotional functioning, social functioning and dysphagia as measured by the EORTC QLQ-C30, IL97, and OES-18, defined as an improvement of at least 10 points* |
| *To investigate the PK of RO7121661* | • *Serum concentrations, PK profiles and parameters for RO7121661.* |
| *To evaluate the immune response after administration of RO7121661* | • *Incidence and titer of RO7121661 ADAs during the study relative to the prevalence of ADA at baseline* |
| To correlate anti-tumor activity of RO7121661, RO7247669, and nivolumab with PK and exploratory safety biomarkers. | • Compare anti-tumor activity by RECIST with PK parameters, safety events, and exploratory safety biomarkers (including genetic and genomic analyses). |
| To explore potential pharmacodynamics and predictive biomarkers associated with the anti-tumor activity of RO7121661, RO7247669, and nivolumab | • PD Biomarkers: Changes from baseline such as Treg profile, cytotoxic T cells in the tumor microenvironment, and immune cell subsets such as Tregs and central/effector memory subsets |

| | |
|---|---|
| | • Predictive Biomarkers: Baseline profiles such as (p)TMB, tumor gene expression, ctDNA, peripheral blood immune-cell subsets, oral and gut microbiome |
| To evaluate the safety and tolerability of RO7121661and RO7247669 compared with nivolumab. | • Compare participant-reported tolerability with treatment-related symptoms through the PRO-CTCAE and EORTC treatment bother item |
| To explore potential effects of anti-drug antibodies (ADAs). | • Relationship between ADA status and PK, safety, PD, and efficacy. |

# 4. STUDY DESIGN

## 4.1 OVERALL DESIGN

This is a Phase II, randomized, blinded, active-controlled, global, multicenter study designed to evaluate the safety and efficacy of RO7121661 and RO7247669, compared with nivolumab in patients with advanced or metastatic ESCC refractory or intolerant to fluoropyrimidine- or taxane- and platinum-based regimen.

The study *was planned to* enroll participants aged ≥ 18 years with Eastern Cooperative Oncology Group (ECOG) Performance Status of 0 or 1 *randomized in a* [redacted] *ratio to receive RO7121661, RO7247669, or nivolumab.*

*With version 3 of this protocol, recruitment into the RO7121661 is stopped and moving forward, participants will be randomized in a* [redacted] *ratio to receive either RO7247669 or nivolumab. Recruitment will continue until approximately* [redacted].

An overview of the study design is provided in Section 1.2 and the schedules of assessments (SoAs) are provided in Section 1.3.

Participants will be stratified by previous [redacted]. Randomization should occur on Day -1 or Day 1 after the patient's eligibility (i.e., inclusion/exclusion criteria) has been confirmed (Section 6.3).

In the experimental arms, participants will receive RO7121661 or RO7247669 at a fixed dose of 2100 mg administered by IV infusion Q2W on Day 1 of each 14-day cycle (Section 6.1).

In the active comparator arm, participants will receive nivolumab at a fixed dose of 240 mg administered by IV infusion Q2W on Day 1 of each 14-day cycle (Section 6.1).

Treatment may be continued as long as participants are experiencing clinical benefit, as assessed by the Investigator, in the absence of unacceptable toxicity or symptomatic deterioration attributed to disease progression after an integrated assessment of radiographic data, biopsy results (if available), and clinical status for a maximum of

24 months. Participants who meet the criteria for disease progression per RECIST v1.1 will be permitted to continue study treatment if they meet all criteria for treatment beyond progression (Section 7.1.1).

[redacted]regardless of treatment delays until radiographic disease progression per RECIST v1.1, initiation of a new anti-cancer therapy, withdrawal of consent, death, or study termination by the Sponsor, whichever occurs first (Section 8.1.1). Thus, tumor assessments are to continue according to the schedule in participants who discontinue treatment for reasons other than disease progression or loss of clinical benefit. For participants who continue treatment after progressive disease, tumor assessments are to continue according to schedule until study treatment is discontinued. At the Investigator's discretion, tumor assessments may be repeated at any time if progressive disease is suspected.

Response will be assessed according to RECIST v1.1 (Appendix 6). Objective response at a single time-point will be determined by the Investigator according to RECIST v1.1. All primary imaging data used for tumor assessments may be collected by the Sponsor; centralized, blinded independent review of response endpoints by an independent review facility may be conducted.

The primary comparison of interest are the hazard ratio of OS of each experimental arm compared to nivolumab, assessing the superiority of the experimental arms over the active comparator treatment. The primary comparison of OS will be made regardless of whether participants withdraw from treatment or receive new anti-cancer therapy prior to disease progression. In order not to confound the OS endpoint, crossover from any of the treatment arms to another arm will not be allowed.

During the study, participants will be asked to complete patient-reported outcome (PRO) questionnaires at the beginning of the study, during study treatment, at treatment discontinuation, and during survival follow-up (Section 8.1.2). These will assess disease and treatment-related symptoms, as well as functioning and overall health-related quality of life.

During the study, serum samples will be collected to monitor RO7121661, RO7247669, and nivolumab pharmacokinetics (PK) and to detect the presence of antibodies to RO7121661, RO7247669, or nivolumab (Section 8.5 and Section 8.6). Blood samples for PK analysis may be collected at the participant's home. This specifically applies to days where no other hospital assessments are required—i.e., C1D8 and C5D8.

Participant samples, including archival and fresh tumor tissue, serum, plasma, and blood samples, will also be collected for biomarker assessments (Section 8.7 and Section 8.8).

Safety assessments will include the incidence, nature, and severity of AEs, and other protocol-specified tests such as laboratory abnormalities that are deemed critical to the safety evaluation of the study (Section 8.2).

After study treatment discontinuation and disease progression per RECIST v1.1, survival follow-up information will be collected by means of telephone calls, participant medical records, and/or clinic visits approximately every 3 months until death, lost to follow-up, or study termination by the Sponsor, whichever occurs first (Section 8.11.4). All participants will be periodically contacted for survival and new anti-cancer therapy information unless the participant requests to be withdrawn from follow-up (this request must be documented in the source documents and signed by the Investigator). If the participant withdraws from the study, study staff may use a public information source (e.g., county records) when permissible to obtain information about survival status (Section 7.2).

### 4.1.1 Length of the Study

The duration in each period of the study for each participant will be as follows:

- Screening: Days -28 to -1.
- Treatment Period: Cycle 1 Day 1 up to a maximum of 24 months.
- Survival follow-up: 90 (± 7) days after last treatment with study drug; then every 3 months (± 14 days) until death, loss to follow-up, or study termination by the Sponsor.

### 4.1.2 Communication Strategy

The Sponsor and Investigators will be in regular contact throughout the study by email/telephone/fax, as per normal interactions during the conduct of a clinical study, and the Sponsor will arrange teleconferences and meetings to discuss study status.

The Sponsor will be available 24 hours a day to discuss any medical or study-related issues that may arise during the conduct of this study.

### 4.1.3 Joint Monitoring Committee

A Joint Monitoring Committee (JMC) will review available safety data periodically and make recommendations regarding study conduct to ensure the safety of patients enrolled in the study. The JMC will consist of designated Sponsor personnel and independent clinical expert(s) (i.e., expert[s] independent from the Sponsor). The JMC Chair will be a medical oncologist who is neither the Medical Monitor nor associated with the study. Other JMC members will include, but not be limited to, a drug-safety scientist and biostatistician. The responsibility, membership, and communication flow of the JMC is further described in the JMC Charter.

### 4.1.4 Scientific Rationale for Study Design

The study rationale is provided in Section 2.1.

In this study, the primary efficacy endpoints will be OS. This study will test the hypothesis that treatment with RO7247669 will prolong OS compared to treatment with nivolumab. Improvement in OS is generally accepted as the best measure of clinical benefit for patients with solid tumors. Prior studies with anti-PD1 treatments in 2L CPI-naïve ESCC showed inconsistent results for other commonly used endpoints such as ORR and PFS, which do not necessarily correlate with the observed OS benefits.

This study is blinded. Investigators, site staff, and participants will be unaware of the treatment allocation. Rationale for the blinded design is reducing potential bias in the assessment of disease recurrence/progression, PROs, and safety.

Nivolumab was chosen as active comparator for this study (Section 2.2.5). Given the positive data and approval of nivolumab for patients with ESCC after prior fluoropyrimidine- and platinum-based chemotherapy, independent of PDL1 expression, nivolumab was considered the best comparator for the anticipated patient population in this study.

### 4.1.5 Rationale for Study Population

This study will enroll patients with advanced or metastatic ESCC who are not indicated for radical resection and who are refractory or intolerant to one prior line of fluoropyrimidine- or taxane- and platinum-based regimen regardless of tumor PDL1 expression.

As described in Section 2.2, combination chemotherapy consisting of cisplatin together with paclitaxel or 5-FU is typically given as first-line treatment for ESCC. Chemotherapy options in the 2L setting for patients with ESCC are associated with considerable toxicity and poor long-term survival. At the same time, anti-PD1 treatments have demonstrated a clinically meaningful improvement in OS over chemotherapy for 2L ESCC. In Keynote-181, patients with both adenocarcinoma and squamous histology were included. However, OS was only positive for patients in the subgroup with a combined positive score $\geq 10$. The clinical benefits observed in the 2L ESCC population with nivolumab as well as camrelizumab occurred regardless of patients' level of tumor PDL1 expression. Despite the results for pembrolizumab in 2L esophageal cancer not reaching statistical significance in the ITT patient population, the data show a clear trend towards a clinical benefit over chemotherapy in accordance to the studies with nivolumab and camrelizumab. These data suggest that CPI treatment provides clinical benefit in the 2L setting for patients with esophageal cancer with squamous histology, but independent of tumor PDL1 expression.

Based on these data, 2L patients with ESCC not indicated for radical resection and who are refractory or intolerant to fluoropyrimidine/taxane- and platinum-based treatment, independent of their tumor PDL1 expression will be eligible to enroll in the current study.

### 4.1.6 Rationale for Biomarker Assessments

The main hypothesis is that additional checkpoint blockade via PD1-TIM3 or PD1-LAG3 will re-invigorate exhausted T cells and lead to an increase in CD8 T-cell infiltration and proliferation in the tumor microenvironment. As such, treatment-induced biomarker exploration will focus on changes from baseline associated with anti-PD1-LAG3, anti-PD1-TIM3, and anti-PD1 therapy in both the tumor microenvironment and peripheral blood. In peripheral blood, serial blood sampling will also be done to assess kinetic changes in immune cellular profiles and selected cytokines, and examined for association with treatment with RO7121661, RO7247669, and nivolumab. Samples for pharmacodynamics (PD) and biomarker research will be collected as described in the SoAs (Section 1.3), and with respect to analyses and samples detailed in Section 8.7 and Section 8.8.

To explore predictive markers of response for RO7247669 or RO7121661, the initial hypothesis focuses on association of response with baseline PDL1, CD8+TIM3+, CD8+LAG3+, and PD1 expression. Other exploratory biomarkers considered to identify potential predictive markers also include assessing baseline immune-cell subsets/effector gene signatures in the peripheral blood and tumor microenvironment, oral, and gut microbiomes, or other soluble markers (such as bTMB, ctDNA, etc.).

Additional biomarkers may be measured if initial data lead to a strong scientific rationale for these measurements.

### 4.1.7 Rationale for Non-Standard Clinical Outcome Assessments

Cancer treatments, particularly combination therapies, can produce significant symptomatic AEs. Recent research has shown that clinicians may underreport the incidence and severity of symptoms experienced by patients receiving treatment for cancer (Fromme et al. 2004; Trotti et al. 2007; Pakhomov et al. 2008; Basch et al. 2010; Quinten et al. 2011; Atkinson et al. 2012; Basch et al. 2014). Collecting side effect tolerability information directly from patients can provide a complementary understanding of treatment characteristics and their effects.

In order to evaluate the tolerability of RO7121661 and RO7247669, and the experience with nivolumab, participants will be asked to report on their experience with 6 treatment-related symptoms selected from the validated PRO-CTCAE item bank (Appendix 13). These symptoms were identified as being salient to patients' experience with RO7121661, RO7247669, and nivolumab, based on available safety data from the nivolumab label or initial studies of RO7121661 and RO7247669.

Additional items related to the safety profile of these drugs (e.g., diarrhea, fatigue, nausea, decreased appetite) are included in the other measures (European Organisation for Research and Treatment of Cancer [EORTC] QLQ_C30, OES-18, Item library 97 (IL97), Patient Global Impression of Change and its Importance (PGI-CI) and Patient Global Impression of Severity (PGI-S); Appendix 8, Appendix 9, Appendix 10, Appendix 11, and Appendix 12) included in the study. These other measures (EORTC QLQ_C30, OES-18, IL97, PGI-CI and PGI-S) are included to understand the impact of the disease on patients, support the use of more targeted assessments, and determine meaningful change thresholds.

## 4.2 JUSTIFICATION FOR RO7121661 DOSE AND SCHEDULE

A fixed dosing regimen of 2100 mg Q2W was selected as the dose for this study for RO7121661. [redacted] During the dose-escalation in Part A of the study, no specific safety concern associated with RO7121661 was identified. In total, one single DLT (Grade 3 TnT increased) was reported and observed at the highest 1200-mg dose group, and no MTD was reached. Anti-tumor activity, as measured by radiographic PRs, was observed at the selected dose for this study. A two compartmental PK linear model predicts the exposure data well, particularly at the higher dose range. A dose regimen of 2100 mg Q2W is predicted to result in a trough concentration of $>$ 320 µg/mL, the predicted EC95 from an ex vivo SEB cytokine assay, in 62% of participants.

In addition, RO7121661 was well tolerated in both the dose-range finding and GLP monkey toxicology studies up to the highest dose evaluated (150 mg/kg). Toxicology findings were consistent with reported findings in cynomolgus monkey studies with marketed CPIs.

Supporting data for the selected dose can be found in the RO7121661 Investigator's Brochure.

[redacted]

[redacted]

[redacted]

### 4.2.2 Justification for Nivolumab Dose and Schedule

The approved dose and schedule for ESCC of 240 mg Q2W was selected for this study for nivolumab. This dose and schedule was used in the ATTRACTION-3 study (Kato et al. 2019).

For detailed information, please refer to the nivolumab EU SmPC.

## 4.3 END OF STUDY DEFINITION

The end of the study will occur when all of the following criteria have been met:

- The required number of deaths for the primary analysis of OS has been observed.
- The last participant, last visit has occurred.

The Sponsor has the right to terminate this study at any time. Reasons for terminating the study may include, but are not limited to, the following:

- The incidence or severity of AEs in this or other studies indicates a potential health hazard to patients.
- Unsatisfactory patient enrollment.
- Inaccurate or incomplete data recording.

The Sponsor will notify the Investigator if the Sponsor decides to discontinue the study.

If the Sponsor decides to terminate the study, participants who are still receiving study treatment or are undergoing survival follow-up may be enrolled in an extension study, if available.

# 5. STUDY POPULATION

The study population rationale is provided in Section 4.1.5.

This study will enroll male and female participants with advanced or metastatic ESCC who are not indicated for radical resection and who are refractory or intolerant to fluoropyrimidine- or taxane- and platinum-based regimen.

Prospective approval of protocol deviations, also known as protocol waivers or exemptions, is not permitted.

## 5.1 INCLUSION CRITERIA

Participants are eligible to be included in the study only if all of the following criteria apply:

**General Criteria**

1. Able and willing to provide written informed consent and to comply with the study protocol according to ICH and local regulations.
2. Age ≥ 18 years.

**Disease-Specific Criteria**

3. Participants with advanced or metastatic, histologically confirmed ESCC.
4. Patients who are not indicated for radical resection and have previously received 1 line of treatment in non-curative intention prior to randomization. The prior line must be either a fluoropyrimidine- and platinum- or a taxane- and platinum-based regimen, and patients must have experienced progressive disease after at least 3 cycles or be unable to tolerate potential side effects of this treatment.

   *Patients who did not receive treatment in the non-curative setting but received a fluoropyrimidine-/taxane and platinum-based drug regimen in curative intent may be allowed. This includes patients who had either radical resection in conjunction with chemotherapy including neo-adjuvant/adjuvant therapy (± radiotherapy) or patients who were treated with chemo-radiation (including patients who underwent chemo-radiation followed by salvage surgery).*

   - If recurrence *or progression* was confirmed by imaging or by pathological assessment of a biopsy within 24 weeks after the last dose of the treatment, patients are eligible and do not require an additional line of therapy in the non-curative setting.
   - If recurrence *or progression* occurred later than 24 weeks after the last dose of the treatment, patients need to be exposed to an additional line of fluoropyrimidine-/taxane- and platinum-based drugs in the non-curative setting to be eligible for the study—unless the Investigator considers the patient not eligible for the re-exposure with fluoropyrimidine/taxane and platinum-based drugs.
   - The last dose of chemotherapy or the last radiation treatment (whichever occurs later) should be considered for the determination of the time-point of recurrence *or progression* after chemo-radiation.
5. Radiologically measurable disease according to RECIST v1.1. Previously irradiated lesions should not be counted as target lesions unless clearly progressed after the radiotherapy.
6. ECOG Performance Status 0-1.
7. A life expectancy of ≥ 12 weeks.

8. Tissue samples must be provided for analysis of PD-L1 tumor positivity using the PDL1 IHC 28-8 pharmDx assay. Testing will be done centrally and results must be obtained prior to stratification.
    - Expression will be determined in a fresh tumor biopsy collected during study screening or a possibly available archival sample, provided that the latter is not older than 12 months.
    - Tumor tissue should be of good quality based on total and viable tumor content and must be evaluated for PDL1 expression.
    - Patients whose tumor tissue is not evaluable for PDL1 expression are not eligible.

**Medical Conditions**

9. Adequate cardiovascular function:
    - New York Heart Association (NYHA) Heart Failure Stage $\leq 2$.
    - Baseline-corrected QT (QTcF) interval $\leq 470$ ms.
    - Resting systolic blood pressure (BP) $\leq 150$ mmHg and diastolic BP $\leq 100$ mmHg (average of $\geq 3$ readings on $\geq 2$ sessions with short break between sessions; no clinically significant hypertension).
    - Resting heart rate between 45-100 bpm (no clinically significant tachycardia).
    - LVEF $\geq 50\%$ assessed by either transthoracic echocardiogram (TTE) or MUGA (TTE preferred test) within 6 months prior to randomization.
    - TnT or I (TnI) $\leq$ institutional upper limit of normal (ULN). Patients with TnT or TnI levels between $> 1$ and $< 2 \times$ ULN will be permitted to enter the study if repeat levels are $\leq 1 \times$ ULN. If repeat levels are between $> 1$ and $< 2 \times$ ULN, the patients need to undergo a cardiac evaluation and can be considered for treatment in case of no clinically significant findings.
10. AEs from any prior radiotherapy, chemotherapy, or surgical procedure must have resolved to Grade $\leq 1$, except alopecia (any grade), vitiligo, endocrinopathy managed with replacement therapy, and Grade 2 peripheral neuropathy.
11. Adequate hematological function:
    - Neutrophil count of $\geq 1.5 \times 10^9$ cells/L (1500/$\mu$L).
    - Platelet count of $\geq 100 \times 10^9$/L (100,000/$\mu$L) without transfusion.
    - Hemoglobin $\geq 9$ g/dL (90 g/L).
    - Lymphocyte count of $\geq 0.5 \times 10^9$ cells/L (500/$\mu$L).
12. Adequate liver function: total bilirubin $\leq 1.5 \times$ ULN; aspartate aminotransferase (AST), alanine aminotransferase (ALT), and alkaline phosphatase (ALP) $\leq 2.5 \times$ ULN; with the following exceptions:
    - Participants with known Gilbert disease: serum total bilirubin level $\leq 3 \times$ ULN.
    - Participants with documented liver metastases: AST and ALT $\leq 5 \times$ ULN.
    - Participants with documented liver or bone metastases: ALP $\leq 5 \times$ ULN.

13. Adequate renal function: serum creatinine ≤ 1.5 × ULN or creatinine clearance by eGFR by MDRD formula ≥ 50 mL/min for participants in whom, in the Investigator's judgment, serum creatinine levels do not adequately reflect renal function.
14. Additional adequate laboratory parameters obtained:
    - Serum albumin ≥ 25 g/L (2.5 g/dL).
    - For participants not receiving therapeutic anticoagulation: Prothrombin time (PT) and activated partial thromboplastin time ≤ 1.5 × ULN.
    - For participants receiving therapeutic anticoagulation: stable anticoagulant regimen.

**Contraception**

15. Male and/or female participants:

    The contraception and abstinence requirements are intended to prevent exposure of an embryo to the study treatment. The reliability of sexual abstinence for male and/or female enrollment eligibility needs to be evaluated in relation to the duration of the clinical study and the preferred and usual lifestyle of the participant. Periodic abstinence (e.g., calendar, ovulation, symptom-thermal, or post-ovulation methods) and withdrawal are not acceptable methods of contraception.

    Female Participants: A female participant is eligible to participate if she is not pregnant, not breastfeeding, and at least one of the following conditions applies:

    - Not a woman of childbearing potential (WOCBP).
    - WOCBP, who:
        - Agree to remain abstinent (refrain from heterosexual intercourse) or use contraceptive methods that result in a failure rate of < 1% per year during the treatment period and for at least 5 months after the final dose of study drug.

          Examples of contraceptive methods with a failure rate of < 1% per year include bilateral tubal occlusion, male sterilization, established proper use of hormonal contraceptives that inhibit ovulation, hormone-releasing intrauterine devices and copper intrauterine devices.
        - Have a negative pregnancy test (blood) within the 7 days prior to randomization.

    Male Participants: During the treatment period and for at least 5 months after the final dose of study drug, agreement to:

    - Remain abstinent (refrain from heterosexual intercourse) or use contraceptive measures such as a condom plus an additional contraceptive method that together result in a failure rate of < 1% per year, with partners who are women of childbearing potential.
    - With pregnant female partners, remain abstinent (refrain from heterosexual intercourse) or use contraceptive measures such as a condom to avoid exposing the embryo.
    - Refrain from donating sperm during this period.

## 5.2 EXCLUSION CRITERIA

Participants are excluded from the study if any of the following criteria apply:

**General Exclusion Criteria**

1. Pregnancy, lactation, or breastfeeding.
2. Known hypersensitivity to any of the components of RO7121661, RO7247669, or nivolumab, including but not limited to, hypersensitivity to Chinese hamster ovary cell products or other recombinant human or humanized antibodies.

**Medical Conditions**

3. Patients with significant malnutrition. Patients whose nutrition has been well controlled for ≥ 28 days prior to randomization may be enrolled.
4. Evidence of complete esophageal obstruction not amenable to treatment.
5. Higher risk of bleeding or fistula caused by esophageal lesions invading adjacent organs (aorta or tracheobronchial tree). *Patients with manageable fistula may be included at the Investigator's discretion.*
6. Symptomatic central nervous system (CNS) metastases. Patients with previously treated brain metastases may participate provided they:
    - Are stable (without evidence of progression by computed tomography (CT) or magnetic resonance imaging (MRI) for at least 28 days prior to randomization).
    - Have no evidence of new or enlarging brain metastases for at least 28 days prior to randomization.
    - Are off systemic steroids for at least 28 days prior to randomization.
7. Spinal cord compression not definitively treated with surgery and/or radiation or without evidence that disease has been clinically stable for ≥ 14 days prior to randomization.
8. Active or history of carcinomatous meningitis/leptomeningeal disease.
9. Asymptomatic CNS primary tumors or metastases if they have requirement for steroids or enzyme-inducing anticonvulsants in the last 28 days prior to randomization.
10. Uncontrolled tumor-related pain. Participants requiring pain medication must be on a stable regimen at study entry.
11. Patients with an active second malignancy. Concurrent malignancy exceptions include: curatively treated carcinoma in situ of the cervix, good-prognosis ductal carcinoma in situ of the breast, basal- or squamous-cell skin cancer, Stage I melanoma, or low-grade, early-stage localized prostate cancer and any previously treated early stage non-hematological malignancy that has been in remission for at least two years.
12. Evidence of significant, uncontrolled concomitant diseases that could affect compliance with the protocol or interpretation of results, including diabetes mellitus, history of relevant pulmonary disorders, known autoimmune diseases or immune

deficiency, or other diseases with ongoing fibrosis (such as scleroderma, pulmonary fibrosis, emphysema, neurofibromatosis, palmar/plantar fibromatosis, etc.).

13. Encephalitis, meningitis, or uncontrolled seizures in the year prior to informed consent.
14. Significant cardiovascular/cerebrovascular disease within 6 months prior to randomization, including any of the following:
    - Hypertensive crisis/encephalopathy.
    - Unstable angina.
    - Transient ischemic attack/stroke.
    - Congestive heart failure (for NYHA classification, refer to inclusion criteria).
    - Serious cardiac arrhythmia requiring treatment (exceptions are atrial fibrillation, paroxysmal supraventricular tachycardia).
    - History of thromboembolic events (such as myocardial infarction, stroke or pulmonary embolism).
15. Known active or uncontrolled bacterial, viral, fungal, mycobacterial (including but not limited to tuberculosis [TB] and typical mycobacterial disease), parasitic, or other infection (excluding fungal infections of nail beds) or any major episode of infection requiring treatment with IV antibiotics or hospitalization (relating to the completion of the course of antibiotics, except if for tumor fever) within 28 days prior to randomization.
16. Known clinically significant liver disease, including alcoholic hepatitis, cirrhosis, and inherited liver disease.
17. Major surgical procedure or significant traumatic injury (excluding biopsies) within 28 days prior to randomization, or anticipation of the need for major surgery during the course of the study.
18. Any other diseases, metabolic dysfunction, physical examination finding, or clinical laboratory finding giving reasonable suspicion of a disease or condition that contraindicates the use of an investigational drug or that may affect the interpretation of the results or render the participant at high risk from treatment complications.
19. Dementia or altered mental status that would prohibit informed consent.
20. Uncontrolled pleural effusion (with the exception of participants with indwelling catheters, e.g., PleurX®), pericardial effusion, or ascites requiring recurrent drainage procedures (expected to occur once monthly or more frequently).
21. Active or history of autoimmune disease or immune deficiency with the following exceptions:
    - Participants with a history of autoimmune-mediated hypothyroidism or endocrinopathy who are stable on thyroid-replacement hormone or appropriate replacement therapy are eligible for the study.

- Participants with controlled Type 1 diabetes mellitus who are on an insulin regimen are eligible for the study.
- Participants with eczema, psoriasis, lichen simplex chronicus, or vitiligo with dermatologic manifestations only (e.g., participants with psoriatic arthritis are excluded) are eligible for the study provided all of following conditions are met:
  - Rash must cover < 10% of body surface area.
  - Disease is well controlled at baseline and requires only low-potency topical corticosteroids.
  - No occurrence of acute exacerbations of the underlying condition requiring psoralen plus ultraviolet A radiation, methotrexate, retinoids, biologic agents, oral calcineurin inhibitors, or high-potency or oral corticosteroids within the previous 12 months.

22. Positive HIV test at screening.
23. Positive hepatitis B surface antigen (HBsAg) or positive total hepatitis B core antibody (HBcAb) test at screening. Participants with a positive HBsAg or total HBcAb test followed by a negative hepatitis B virus (HBV) DNA test at screening are eligible.
    - The HBV DNA test will only be performed for participants who have a positive HBsAg or total HBcAb test.
24. Positive hepatitis C virus (HCV) antibody test at screening. Participants with a positive HCV antibody test followed by a negative HCV RNA test at screening are eligible.
    - The HCV RNA test will be performed only for participants who have a positive HCV antibody test.

**Prior/Concomitant Therapy**

25. Prior cancer therapy with any immunomodulatory agents including CPIs (such as anti-PDL1/PD1, anti-CTLA-4, anti-LAG3, anti-TIM3).
26. Vaccination with live vaccines within 28 days prior to randomization, or anticipation that a live attenuated vaccine will be required during the study
27. Treatment with therapeutic oral or IV antibiotics within 14 days prior to randomization.
28. Concurrent therapy with any other investigational drug (defined as treatment for which there is currently no regulatory authority-approved indication) < 28 days or 5 half-lives of the drug (whichever is shorter) prior to randomization.
29. Treatment with immune-modulating and immune suppressive agents/medication < 5 half-lives or 28 days (whichever is shorter) prior to randomization, with the following exceptions:
    - The use of inhaled corticosteroids and mineralocorticoids (e.g., fludrocortisone) is allowed.

- Participants who have received acute and/or low-dose systemic immunosuppressive medications (e.g., a one-time dose of dexamethasone for nausea or chronic use of ≤ 10 mg/day of prednisone or dose-equivalent corticosteroid) are allowed.

30. Regular immunosuppressive therapy (i.e., for organ transplantation, chronic rheumatologic disease).
31. Radiotherapy within the last 28 days before start of study drug treatment is not allowed, with the exception of limited palliative radiotherapy.
32. Prior treatment with adoptive cell therapies, such as CAR-T therapies.

## 5.3 LIFESTYLE CONSIDERATIONS

Participants will be expected to follow protocol requirements for contraception (Appendix 5) and study center rules during visits, but there are no other lifestyle restrictions during the study. There are no study-specific restrictions to meals and dietary requirements.

## 5.4 SCREEN FAILURES

Screen failures are defined as participants who consent to participate in the study but are not subsequently randomized to study treatment.

All screening evaluations must be completed and reviewed to confirm that participants meet all eligibility criteria before entering the study. The Investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure. In case of uncertain or questionable results, any of the tests performed during screening may be repeated prior to randomization to confirm eligibility.

One re-screening is allowed for participants who were screened in the study and met study inclusion/exclusion criteria but failed to be randomized within 28 days after the start of screening period because of an administrative reason. Participants who do not initially meet all eligibility criteria for participation in the study may also qualify for one re-screening at the Investigator's discretion. Patients are not required to re-sign the consent form if they are re-screened within 60 days after previously signing the consent form. In order to re-screen such participants, all inclusion and exclusion criteria should be re-evaluated and all applicable screening assessments repeated if done more than 28 days prior to randomization unless a longer period is specified for certain assessments elsewhere.

Biopsy samples will only be entered in the eCRF and analyzed for enrolled participants.

In the event that a fresh biopsy is taken during the screening period and the participant is not enrolled into the study, the formaldehyde-fixed paraffin-embedded (FFPE) biopsy block can be returned to the site upon site request.

## 5.5 RECRUITMENT PROCEDURES

Participants will be identified for potential recruitment using pre-screening enrollment logs and Institutional Review Board (IRB)/Ethics Committee (EC) approved recruitment strategies prior to consenting to take place on this study.

# 6. TREATMENTS

Study intervention is defined as any investigational product (including placebo) or marketed product intended to be administered to a study participant according to the study protocol.

The investigational medicinal products (IMPs) for this study are RO7121661, RO7247669, and nivolumab. All IMPs required for completion of this study will be provided by the Sponsor. All study drug administration will be done at the study center under supervision of site staff.

Cases of accidental overdose or medication error, along with any associated AEs, should be reported as described in Section 5.2 of Appendix 2.

## 6.1 TREATMENTS ADMINISTERED

The administered treatments are summarized in Table 6. Guidelines for dosage modification and treatment interruption or discontinuation are provided in Section 6.6 and Section 7.1.2, respectively.

All study drugs will be administered IV. A 0.2 µm or 0.22 µm inline filter must be mandatorily used with the infusion set during administration.

The initial dose of study drug will be delivered over 60 ± 10 minutes (the infusion may be slowed or interrupted for participants who experience infusion-associated symptoms; Section 8.3.7.1), followed by a 60-minute observation period. If the 60-minute infusion is tolerated without infusion-associated AEs, all subsequent infusions may be delivered over 30 ± 10 minutes, followed by a 30-minute observation period.

For additional details, refer to the Pharmacy Manual.

**Table 6 Summary of Treatments Administered**

| **Study Treatment Name:** | RO7121661 | RO7247669 | Nivolumab |
|---|---|---|---|
| **IMP and NIMP** | IMP | IMP | IMP |
| **Dose Formulation:** | Liquid | Liquid | Liquid |
| **Unit Dose Strength(s)/Dosage Level(s):** | 300mg/6mL | 300 mg/6mL | 240 mg/24mL |
| **Dose:** | 2100 mg | 2100 mg | 240 mg |
| **Route of Administration:** | IV infusion | IV infusion | IV infusion |
| **Sourcing:** | Provided centrally by the Sponsor | Provided centrally by the Sponsor | Provided centrally by the Sponsor |
| **Packaging and Labeling:** | Study treatment will be provided in vials. Each vial will be labeled as required per country requirement. | Study treatment will be provided in vials. Each vial will be labeled as required per country requirement. | Study treatment will be provided in vials. Each vial will be labeled as required per country requirement. |

### 6.1.1 Pre-medication

No pre-medication is foreseen prior to the first administration of study drug.

However, if administered, all pre-medications should be captured as concomitant medications in the participant's electronic Case Report Form (eCRF). Please refer to Section 8.3.7.1 for details on pre-medications in case of Grade 2 IRRs.

Participants who experienced a Grade 2 infusion-related reaction (IRR) on a previous infusion should be pre-medicated for subsequent infusions. Pre-medication regimens for future cycles may be reduced or if the participants do not experience Grade 2 or higher IRR events with the current infusion (Section 8.3.7.1).

## 6.2 PREPARATION/HANDLING/STORAGE/ACCOUNTABILITY

Study drug packaging will be overseen by the Sponsor's clinical study supplies department and bear a label with the identification required by local law, the protocol number, drug identification and dosage.

The packaging and labeling of the study medication will be in accordance with the Sponsor's standard and local regulations.

The study site should follow all instructions included with each shipment of IMP. The investigational site will acknowledge receipt of IMPs and confirm the shipment condition and content. Any damaged shipments will be replaced. The unblinded pharmacist or designee must confirm that appropriate temperature conditions have been maintained during transit for all IMPs received and that any discrepancies have been reported and resolved before use of the IMPs. All IMPs must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions, with access limited to the unblinded pharmacist and authorized staff.

Only patients enrolled in the study may receive IMPs, and only authorized staff may supply or administer IMPs.

The study site (i.e., unblinded pharmacist or other authorized personnel) is responsible for maintaining records of IMP delivery to the site, IMP inventory at the site, IMP use by each patient, and disposition or return of unused IMP, thus enabling reconciliation of all IMP received, and for ensuring that patients are provided with doses specified by the protocol. Upon arrival of the IMPs at the site, site personnel will complete the following:

- Check the IMPs for damage.
- Verify proper identity, quantity, integrity of seals and temperature conditions.
- Report any deviations or product complaints to the Study Monitor upon discovery.

The qualified individual responsible for dispensing the study treatment will prepare the correct dose according to the Pharmacy Manual.

Only participants enrolled in the study may receive study treatment and only authorized site staff may supply or administer study treatment. All study treatments must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to authorized site staff.

The investigational site is responsible for study treatment accountability, reconciliation, and record maintenance (i.e., receipt, reconciliation and final disposition records).

For information on IMP handling (including preparation, storage, and accountability), refer to the Pharmacy Manual and/or the Investigator's Brochure.

IMPs will either be disposed of at the study site according to the study site's institutional standard operating procedure (SOP) or returned to the Sponsor with the appropriate documentation. The site's method of IMP destruction must be agreed upon by the Sponsor. Local or institutional regulations may require immediate destruction of used IMP for safety reasons. The site must obtain written authorization from the Sponsor before any IMP is destroyed, and IMP destruction must be documented on the appropriate form. Accurate records of all IMPs received at, dispensed from, returned to, and disposed of by the study site should be recorded on the drug accountability log.

Refer to the Pharmacy Manual and/or the applicable Investigator's Brochure for information on IMP formulation, IMP handling, including preparation and storage, and accountability.

## 6.3 MEASURES TO MINIMIZE BIAS: RANDOMIZATION AND BLINDING

### 6.3.1 Method of Treatment Assignment

This is a Phase II, randomized, blinded, active-controlled study. After written informed consent has been obtained and eligibility has been established (including determination of tumor PD-L1 status by central testing), the study site will obtain the participant's identification number and blinded treatment assignment from the interactive response system (IxRS). An IxRS User Guide will be provided to each site.

*Using a permuted-block randomization method, p*articipants will be randomized to receive either RO7121661, RO7247669, or nivolumab in a [redacted] randomization ratio *or – after the decision to stop enrollment into the RO7121661 arm – to receive either RO7247669 or nivolumab in a* [redacted] *randomization ratio.*

Eligible participants will be stratified by the following criteria:

- [redacted]
- 
- 

These stratification factors were chosen because of their known or suspected potential to affect prognosis of treatment outcome with anti-PD1 treatment in ESCC. Prospective stratification by these factors will minimize differences in the three treatment arms due to sources other than the study drug.

Participants should receive their first dose of study drug on the day of randomization or at the latest on the day after randomization.

### 6.3.2 Blinding

Investigators and participants will remain blinded to each participant's assigned study treatment throughout the course of the study. In order to maintain this blind, an otherwise uninvolved, unblinded pharmacist will be responsible for the reconstitution and dispensation of all study treatment and will endeavor to ensure that there are no differences in time taken to dispense following randomization. Because of the size of the study, use of IxRS, randomization, blinding, and expected lack of substantial emergency unblinding, collected data will be protected from any biases that would arise from subjectivity in the reporting of the outcome measures. To further protect the integrity of the study, the results of interim safety and efficacy analyses will not be made known to the Investigators.

Treatment codes should not be broken except in emergency situations. *This includes the decision to stop recruitment into the RO7121661 arm of the study. The study will not be unblinded and patients already randomized to the RO7121661 arm prior to this decision will continue to receive treatment with RO7121661.* If the Investigator wishes to know the identity of the study drug for any other reason, the Investigator should contact the Medical Monitor directly.

If emergency unblinding is necessary for participant management (e.g., in the case of a serious AE (SAE) for which participant management might be affected by knowledge of treatment assignment), the Investigator will be able to break the treatment code by contacting the IxRS. This emergency unblinding may occur without prior authorization from the Sponsor. However, the Investigator should document and provide an explanation to the Sponsor for any premature unblinding (e.g., unblinding due to an SAE or accidental unblinding).

As per Health Authority reporting requirements, the Sponsor's drug safety representative will break the treatment code for all serious, unexpected suspected adverse reactions that are considered by the Investigator or Sponsor to be related to study drug. The participant may continue to receive treatment, and the Investigator and participant will remain blinded to treatment assignment.

## 6.4 TREATMENT COMPLIANCE

The unblinded pharmacist will prepare the correct treatment according to the randomization schedule. This individual will write the date dispensed and participant number on the study-treatment-vial label and on the Drug Accountability Record. This individual will also record the study treatment number received by each participant during the study. The Drug Accountability Record should be kept in a restricted area, not accessible to blinded study site personnel or the blinded site monitor. For details, please refer to the Pharmacy Manual.

## 6.5 CONCOMITANT THERAPY

Any medication or vaccine (including over-the-counter [OTC] or prescription medicines, approved dietary and herbal supplements, nutritional supplements) used by a participant within 7 days of study screening must be recorded along with reason for use, dates of administration (including start and end dates) and dosage information (including dose and frequency).

The Medical Monitor should be contacted if there are any questions regarding concomitant or prior therapy.

All concomitant medications should be reported to the Investigator and recorded on the Concomitant Medications eCRF.

All medication administered to manage AEs should be recorded on the Adverse Event eCRF.

### 6.5.1 Permitted Therapy

Participants are permitted to use the following therapies during the study:

- Oral contraceptives with a failure rate of $<$ 1% per year.
- Hormone-replacement therapy.
- Prophylactic or therapeutic anticoagulation therapy (such as warfarin at a stable dose or low-molecular-weight heparin).
- Inactivated influenza vaccinations.
- Megestrol acetate administered as an appetite stimulant.
- Inhaled corticosteroids and mineralocorticoids (e.g., fludrocortisone).
- Acute and/or low-dose systemic immunosuppressive medications (e.g., a one-time dose of dexamethasone for nausea or chronic use of $\leq$ 10 mg/day of prednisone or dose-equivalent corticosteroid).
- Limited field palliative radiotherapy is allowed at any time during the study, except for days where study drug is administered.

Concomitant use of herbal therapies is not recommended because their PK, safety profiles, and potential drug-drug interactions are generally unknown. However, herbal therapies not intended for the treatment of cancer may be used during the study at the discretion of the Investigator.

### 6.5.2 Prohibited Therapy

As a general rule, no concomitant medication will be permitted, with the exception of medications to treat AEs, unless the rationale for exception is discussed and clearly documented between the Investigator and the Sponsor.

Use of the following therapies is prohibited during the study and for at least 28 days or 5 half-lives of the drug, whichever is shorter, prior to randomization and during study treatment, unless otherwise specified below:

- Investigational or unlicensed/unapproved agents.
- Therapy intended for the treatment of cancer (including, but not limited to, chemotherapy, hormonal therapy, immunotherapy, and radiotherapy [with the exception of limited palliative radiotherapy as described in Section 6.5.1], as well as herbal therapy or traditional Chinese medicines with anti-cancer activity in the label), whether Health Authority-approved or experimental.
- Chronic use of steroids (inhaled and topical steroids are permitted) at baseline of $>$ 10 mg of prednisone/day (or equivalent). Concurrent high doses of systemic corticosteroids.
- Administration of a live, attenuated vaccine or anticipation that such a live attenuated vaccine will be required during the study or within 4 months after the administration of the final dose of the study drug.
- Systemic immunostimulatory agents (including, but not limited to, interferons and IL-2) because these agents could potentially increase the risk for autoimmune conditions when given in combination with CPIs.
- Systemic immunosuppressive medications (including, but not limited to, cyclophosphamide, azathioprine, methotrexate, and thalidomide) because these agents could potentially alter the efficacy and safety of the study drug.
- Adoptive cell therapies, such as CAR-T therapies.

## 6.6 DOSE MODIFICATION

Dose modifications, including dose reductions, will not be allowed in this study.

## 6.7 TREATMENT AFTER THE END OF THE STUDY

Currently, the Sponsor does not have any plans to provide RO7121661, RO7247669, nivolumab, or any other study treatments or interventions to the participants after the end of the study or when participants discontinue or have been withdrawn from the study. The Sponsor will evaluate whether to continue providing RO7121661 and/or RO7247669 to participants after the main study is over, in accordance with the Roche Global Policy on Continued Access to Investigational Medicinal Product, available at the following website:

http://www.roche.com/policy_continued_access_to_investigational_medicines.pdf

# 7. DISCONTINUATION OF STUDY, STUDY TREATMENT AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

An excessive rate of withdrawals (either participants discontinuing study treatment or withdrawing from the study) can render the study non-interpretable. Therefore, unnecessary withdrawal of participants should be avoided and efforts should be taken to motivate participants to comply with all the study-specific procedures as outlined in this protocol.

Details on study and site closures are provided in Section 4 of Appendix 1 Study Governance Considerations Study.

## 7.1 DISCONTINUATION OF STUDY TREATMENT

For data to be collected at the time of treatment discontinuation and follow-up and for any further evaluations that need to be completed see the SoAs in Section 1.3.Participants have the right to voluntarily withdraw from the study treatment at any time for any reason.

In addition, the Investigator has the right to discontinue a participant from study treatment for medical conditions that the Investigator or Sponsor determines, may jeopardize the participant's safety if he/she continues with the study treatment.

Participants must permanently discontinue study treatment if they experience any of the following:

- Intolerable toxicity related to study treatment, including development of an immune-mediated AE (imAE) determined by the Investigator to be unacceptable given the individual participant's potential response to therapy and severity of the event.
- Any medical condition that may jeopardize the participant's safety if he or she continues study treatment.
- Investigator or Sponsor determination that treatment discontinuation is in the best interest of the participant.
- Use of another non-protocol anti-cancer therapy.
- Pregnancy.
- Loss of clinical benefit as determined by the Investigator after an integrated assessment of radiographic and biochemical data, local biopsy results (if available), and clinical status (e.g., symptomatic deterioration such as pain secondary to disease).

The primary reason for study treatment discontinuation should be documented on the appropriate eCRF. Participants who discontinue study treatment prematurely will not be replaced.

Participants who discontinue study treatment will be asked to return to the clinic for treatment discontinuation visit (Section 8.11.3) ≤ 30 days after the final dose of study treatment and will undergo follow-up assessments (Section 8.11.4). The visit at which response assessment shows progressive disease may be used as the treatment discontinuation visit. Participants who discontinue study treatment for any reason other than progressive disease or loss of clinical benefit will continue to undergo tumor response assessments as outlined in the SoAs (Section 1.3) until they start a new anti-cancer therapy.

After treatment discontinuation, information on survival status, new anti-cancer therapy and other assessments as applicable will be collected via telephone calls, participant medical records, and/or clinic visits approximately every 3 months until death (unless the participant withdraws consent or the Sponsor terminates the study, Section 7.2). In particular, every effort should be made to obtain survival information on participants who withdraw from study treatment but have not withdrawn consent.

### 7.1.1 Treatment after Disease Progression

Because of the possibility of an initial increase in tumor burden caused by immune-cell infiltration in the setting of a T-cell response (termed “pseudoprogression”) with cancer immunotherapy, radiographic progression per RECIST v1.1 may not be indicative of true disease progression. During the study, participants who meet criteria for disease progression per RECIST v1.1 and show evidence of clinical benefit may continue study treatment at the Investigator’s discretion provided that the participants meet all of the following criteria:

- Absence of clinically important symptoms and signs (including worsening of laboratory values) indicative of disease progression
- Investigator-assessed potential clinical benefit for the participant
- The participant is tolerating study drugs.
- No decline in ECOG Performance Status.
- Absence of rapid progression of disease or of progressive tumor at critical anatomical sites (e.g., cord compression) requiring urgent alternative medical intervention.

### 7.1.2 Temporary Interruption

Before permanently discontinuing study treatment (regardless of whether initiated by the participant, the Investigator, or Sponsor), an interruption should be considered. Participants who have temporarily interrupted study treatment should be considered to restart as soon as medically justified in the opinion of the Investigator.

Study treatment may be temporarily suspended for up to 12 weeks to allow for resolution of toxicity to NCI CTCAE Grade $\leq$ 2 for hematological toxicities or Grade $\leq$ 1 for non-hematological toxicities (with the exception of a toxicity considered as non-study treatment related). If study treatment is withheld for $>$ 12 weeks, the participant will be discontinued from study treatment.

Dose interruptions for reason(s) other than toxicity, such as surgical procedures, may be allowed, and the acceptable length of interruption should be discussed between the Investigator and the Medical Monitor. Minor elective surgery will generally be permitted during the study with resumption of treatment as soon as possible post-procedure, assuming normal recovery. This can be done to avoid the discontinuation of participants who could potentially benefit from study treatment.

It should be noted that infusions/cycles not occurring at the anticipated schedule, are considered as delayed, not missed.

If a participant has a complete response (CR) or achieves maximum clinical benefit as determined by the Investigator and the Sponsor after an integrated assessment of radiographic data, biopsy results (if available), and clinical status, the study treatment may be paused at the discretion of the Investigator after discussion with the Medical Monitor. While the treatment is paused, assessments per SoA (Section 1.3) will be suspended, except for tumor assessments. The length of the treatment pause is to be included in the calculation of the maximum treatment period duration (24 months from C1D1 to discontinuation visit), as per Section 4.1.

## 7.2 PARTICIPANT DISCONTINUATION/WITHDRAWAL FROM THE STUDY

Participants have the right to voluntarily withdraw from the study at any time for any reason.

If possible, information on reason for withdrawal from the study should be obtained. The primary reason for withdrawal from the study should be documented on the appropriate eCRF. If a participant requests to be withdrawn from the study, this request must be documented in the source documents and signed by the Investigator. Participants will not be followed for any reason after consent has been withdrawn. However, the study staff may use a public information source (e.g., county records) to obtain information about survival status.

When a participant voluntarily withdraws from the study samples collected until the date of withdrawal will be analyzed, unless the participant specifically requests for these to be discarded or local laws require their immediate destruction. However, if samples have been tested prior to withdrawal, results from those tests will be used as part of the overall research data. A participant's withdrawal from this study does not, by itself, constitute withdrawal of samples donated to the Research Biosample Repository (RBR).

Participants who withdraw from the study for any reasons will not be replaced.

For data to be collected at the time of study discontinuation, at follow-up visits, and for any further evaluations that need to be completed, refer to the SoAs (Section 1.3).

## 7.3 LOST TO FOLLOW-UP

A participant will be considered lost to follow-up if he/she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible, counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether or not the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the Investigator or designee must make every effort to regain contact with the participant. These contact attempts should be documented in the participant's medical record.
- Should the participant continue to be unreachable, he/she will be considered to have withdrawn from the study. Attempts to obtain survival information should continue.

Discontinuation of sites or of study as a whole are handled as part of Appendix 1.

# 8. STUDY ASSESSMENTS AND PROCEDURES

Study procedures and their time-points are summarized in the SoAs (Section 1.3). Accepted time windows are indicated, where applicable. In addition, any efficacy or safety assessments may be repeated as clinically indicated, at the Investigator's discretion. Protocol waivers or exemptions are not allowed.

Immediate safety concerns should be discussed with the Sponsor immediately upon occurrence or awareness to determine whether the participant should continue or discontinue study treatment.

Procedures conducted as part of the participant's routine clinical management (e.g., blood count, tumor assessments) and obtained before signing of the Informed Consent Form (ICF) may be utilized for screening or baseline purposes provided that the procedure met the protocol-specified criteria and was performed within the time-frame defined in the SoAs (Section 1.3).

Exceptional measures during the COVID-19 pandemic, such as adjustments in study visits, may be considered if in the overall best interest of the participant.

Adjustments may include:

- Use of alternative facility for assessments (e.g., local laboratory or imaging centers).
- Replacement of a study visit with alternative methods for assessments (such as phone contacts or virtual visits to assess safety).
- Postponement of a study visit or of individual assessments.

A robust benefit-risk assessment should be performed by the Investigator and discussed with the Medical Monitor. This assessment will be fully documented and any deviations to the protocol will be recorded in accordance with the Sponsor standard procedure.

## 8.1 EFFICACY ASSESSMENTS

### 8.1.1 Tumor and Response Evaluations

[redacted] Tumor assessments should be performed at the described interval regardless of treatment delays until radiographic disease progression per RECIST v1.1 (Appendix 6), initiation of a new anti-cancer therapy, withdrawal of consent, death, or study termination by the Sponsor, whichever occurs first. Thus, tumor assessments are to continue according to schedule in participants who discontinue treatment for reasons other than disease progression or loss of clinical benefit. For participants who continue treatment after progressive disease, tumor assessments are to continue according to schedule until study treatment is discontinued.

At the Investigator's discretion, tumor assessments may be repeated at any time if progressive disease is suspected. [redacted] Exceptions may apply at the discretion of the Investigator (e.g., in case of suspected rapid tumor growth).

Participants who are treated beyond disease progression per RECIST v1.1 will undergo tumor assessments at the frequency described above until study treatment is discontinued.

Screening assessments must include CT scans (with oral or IV contrast) or MRI scans of the chest, abdomen, pelvis, and head. A spiral CT scan of the chest may be obtained but is not a requirement. If a CT scan with contrast is contraindicated (e.g., in patients with impaired renal clearance), a non-contrast CT scan of the chest may be performed and MRI scans of the abdomen, pelvis, and head should be performed. A CT scan with contrast or MRI scan of the head must be done at screening to evaluate CNS metastasis in all patients (MRI scan must be performed if CT scan is contraindicated). An MRI scan of the head is required to confirm or refute the diagnosis of CNS metastases at baseline in the event of an equivocal CT scan. Bone scans and CT scans of the neck should also be performed if clinically indicated. If a CT scan for tumor assessment is performed in a positron emission tomography-CT scanner, the CT acquisition must be of full diagnostic quality and include CT contrast. Ultrasound and x-rays are not acceptable for monitoring target lesions. At the Investigator's discretion, other methods of assessment of measurable disease as per RECIST v1.1 may be used.

All measurable and evaluable lesions identified at screening should be re-assessed at each subsequent tumor evaluation. If the participant presents with a CNS metastasis at screening, on treatment tumor assessments must also contain a CT or MRI scan of the head. If the participant has no brain metastasis at screening, then CT/MRI scan of the head is only indicated if symptoms suggest potential brain disease. Objective response at a single time-point will be determined by the Investigator according to RECIST v1.1. Tumor measurements should be made by the same Investigator/radiologist for each participant to the extent that this is feasible and using the assessment technique or procedure throughout the study (e.g., the same contrast protocol for CT scans).

All primary imaging data used for tumor assessments may be collected by the Sponsor; centralized, blinded independent review of response endpoints by an independent review facility per RECIST v1.1 may be conducted.

### 8.1.2 Clinical Outcome Assessment

PRO instruments will be completed to more fully characterize the clinical profile of RO7121661 and RO7247669 compared with nivolumab. PRO data will be collected through use of the following instruments:

European Organisation for Research and Treatment of Cancer (EORTC) quality-of-life questionnaire (QLQ-C30).

- EORTC quality-of-life questionnaire for esophageal cancer (QLQ-OES18).
- Selected items from the EORTC Item Library (IL97).
- Patient Global Impression of Change and its Importance (PGI-CI).
- Patient Global Impression of Severity (PGI-S).
- Patient-Reported Outcomes Common Terminology Criteria for Adverse Events (PRO-CTCAE).

#### 8.1.2.1 Data Collection Methods for Clinical Outcome Assessments

PRO questionnaires will be completed at the clinic at specified time-points during the study (SoAs in Section 1.3). The PRO questionnaires will be completed by the participants at the investigational site or remotely on an electronic device or via telephone at time-points where no site visit is planned, as well as during the follow-up period. If the participant is unable to complete the questionnaire on his or her own, interview assessment is allowed but can only be conducted by site staff. Unless otherwise specified, the PRO questionnaires will be completed before the participant receives any information on disease status, prior to the performance of non-PRO assessments, and prior to the administration of study treatment. The PRO questionnaires will be collected via a web-based solution.

The PRO questionnaires, translated into the local language as appropriate, will be completed through use of an electronic device provided by the Sponsor when possible. The device will be pre-programmed to enable the appropriate questionnaires to be administered in the correct order at each specified time-point. The electronic device and instructions for completing the questionnaires electronically will be provided by the site staff. The data will be transmitted to a centralized database maintained by the electronic device vendor. The data will be available for access by appropriate study personnel. In circumstances when the electronic device is not available (e.g., device failure or due to supply issues), a backup data collection method will be used.

During clinic visits, the PRO questionnaires should be administered as follows:

- Participants' health status should not be discussed prior to completing the PRO questionnaires.
- Sites must administer the official version of each questionnaire, as provided by the Sponsor. Questionnaires must not be copied from the protocol.
- Sites should allow sufficient time for participants to complete the questionnaires, estimated to be 20 minutes at each specified visit.
- Sites should administer the questionnaires in a quiet area with minimal distractions and disruptions.
- Participants should be instructed to answer questions to the best of their ability; there are no right or wrong answers.
- Site staff should not interpret or explain questions but may read questions verbatim upon request.
- Participants should not obtain advice or help from others (e.g., family members or friends) when completing the questionnaires.

Reasons for non-completion of PROs by participants should be recorded in the electronic device by site staff. Reasons for non-completion will be pre-populated on the

device, and may include if the questionnaire is not available in the participants' language.

#### 8.1.2.2 Description of Clinical Outcome Assessment Instruments

**EORTC QLQ-C30**

The QLQ-C30 is a validated and reliable self-reported measure (Aaronson et al. 1993; Fitzsimmons et al. 1999; Appendix 8.

It consists of 30 questions that assess five aspects of patient functioning (physical, emotional, role, cognitive, and social), global health status and quality of life (GHS/QoL), and nine symptoms (fatigue, nausea and vomiting, pain, dyspnea, insomnia, appetite loss, constipation, diarrhea, and financial difficulties) with a recall period of the previous week. The functioning and symptoms items are scored on a 4-point scale that ranges from "not at all" to "very much," and the GHS/QoL items are scored on a 7-point scale that ranges from "very poor" to "excellent."

**EORTC QLQ-OES18**

The QLQ-OES18 is a validated and reliable self-reported measure that serves as a modular supplement to the QLQ-C30 for use in patients with esophageal cancer (Blazeby et al. 2003; Appendix 9). It consists of 18 questions that assess four scales and six single items with a recall period of the previous week. The scoring for the QLQ-OES18 follows that of the QLQ-C30.

**EORTC IL97**

The IL97 is a reduced version of the QLQ-C30 that was created specifically for this study from the EORTC Quality of Life Group Item Library. It consists of 17 questions that assess two aspects of patient functioning (emotional and social), GHS/QoL, and six symptoms (fatigue, nausea, vomiting, pain, appetite loss, and diarrhea) with a recall period of the previous week (Appendix 10). The scoring for the IL97 follows that of the QLQ-C30.

**PGI-CI**

The PGI-CI is a two-item, self-reported measure used to assess patients' impression about changes to their overall health because of their cancer and the associated importance compared with when they began the study (Appendix 11). In the first item, the PGI-CI uses a 7-point response scale that ranges from "very much worse" to "very much improved" (adapted from Guy et al. 1976). In the second item, the PGI-CI uses a 3-point response scale ("yes," "no," and "not applicable") for patients to indicate if the change they experienced (and reported in the first item) was important to them.

**PGI-S**

The PGI-S is a one-item, self-reported measure used to assess patients' impression about how severely their overall health has been impacted because of their cancer during the preceding week (Appendix 12). The PGI-S utilizes a 5-point response scale that ranges from "very severe" to "none" (adapted from Guy et al. 1976).

**PRO-CTCAE**

The PRO-CTCAE is a validated item bank that is used to characterize the presence, frequency of occurrence, severity, and/or degree of interference with daily function of 78 patient-reportable symptomatic treatment toxicities (Basch et al. 2014; Dueck et al. 2015). The PRO-CTCAE contains 124 questions that are rated either dichotomously (for determination of presence versus absence) or on a 5-point Likert scale (for determination of frequency of occurrence, severity, and interference with daily function). Treatment toxicities can occur with observable signs (e.g., vomiting) or non-observable symptoms (e.g., nausea). The standard PRO-CTCAE recall period is the previous 7 days.

A subset of four symptoms deemed most applicable to the current treatments has been selected for this study (Appendix 13). Symptoms have been selected based on known adverse drug reactions, mechanism of action of the treatments under investigation, and recent work to identify common AEs associated with immunotherapies (King-Kallimanis et al. 2019; Hansen et al. 2020).

## 8.2 SAFETY ASSESSMENTS

Planned time-points for all safety assessments are provided in the SoAs (Section 1.3). On dosing days, the safety assessments are to be performed prior to the study treatment administration. If the assessments have been performed within maximum 72 hours prior to dosing, they do not need to be repeated on the scheduled dosing day.

Safety assessments will consist of monitoring and recording AEs, including SAEs and non-serious AEs of special interest (NSAESI); measurement of protocol-specified safety laboratory assessments; and measurement of protocol-specified vital signs, electrocardiograms (ECGs), and other protocol-specified tests that are deemed critical to the safety evaluation of the study.

### 8.2.1 Physical Examinations

A complete physical examination, performed at screening and all scheduled visits as indicated in the SoAs, will include, at a minimum, assessments of the cardiovascular, respiratory, gastrointestinal, dermatological and neurological, musculoskeletal systems in addition to the head, eyes, ears, nose, throat, neck, and lymph node systems. Weight will also be measured and recorded. Height will only be collected at screening. Further examination of other body systems may be performed in case of evocative symptoms at the Investigator's discretion.

Limited, symptom-directed physical examinations should be performed at unscheduled visits as clinically indicated.

Changes from baseline abnormalities should be recorded in participant notes. New or worsened clinically significant abnormalities should be recorded as AEs on the Adverse Event eCRF.

### 8.2.2 Vital Signs

Vital signs will be recorded at the time-points specified in the SoAs. For vital sign assessments on infusion days it is not required to capture vital signs collected during the infusion in the eCRF unless abnormalities are observed.

Vital signs will include measurements of systolic and diastolic BP, respiratory rate, pulse rate, and body temperature while the participant is in a sitting or semi-supine position at every assessment.

Additionally, blood oxygen saturation will be measured by pulse oximetry at screening and pre-dose at every visit where tumor assessments are performed.

### 8.2.3 Electrocardiograms

Single 12-lead ECG will be obtained as outlined in the SoAs using an ECG machine that automatically calculates the heart rate and measures PR interval, QRS complex, QT interval, and QT corrected for heart rate (QTc) interval.

Additional unscheduled ECG assessments should be performed in case of abnormalities and if clinical symptoms occur. ECGs for each participant should be obtained from the same machine whenever possible.

To minimize variability, it is important that participants be in a resting position for at least 10 minutes prior to each ECG evaluation. Body position should be consistently maintained for each ECG evaluation to prevent changes in heart rate. Environmental distractions (e.g., television, radio, conversation) should be avoided during the pre-ECG resting period and during ECG recording. ECGs should be performed prior to meals and any scheduled vital sign measurements and blood draws, whenever logistically possible. To minimize variability between visits, it is also recommended that for a given patient, assessments should be conducted in the same order throughout the trial. In some cases, it may be appropriate to repeat abnormal ECGs to rule out improper lead placement as contributing to the ECG abnormality.

For safety monitoring purposes, the Investigator or designee must review, sign, and date all ECG tracings. Paper or electronic copies will be kept as part of the participant's permanent study file at the site. If considered appropriate by the Sponsor, ECGs may be analyzed retrospectively at a central laboratory.

ECG characteristics, including heart rate, QRS duration, and PR and QT intervals, will be recorded on the eCRF. QTcB (Bazett's correction, Appendix 14), QTcF (Fridericia's correction, Appendix 14), and RR will be calculated by the Sponsor and recorded on the eCRF. Changes in T-wave and U-wave morphology and overall ECG interpretation will be documented on the eCRF. T-wave information will be captured as normal or abnormal, U-wave information will be captured in two categories: absent/normal or abnormal.

### 8.2.4 Eastern Cooperative Oncology Group Performance Status

ECOG Performance Status will be assessed at screening, before each study treatment administration, and at the discontinuation visit as specified in the SoAs (Section 1.3). It is recommended, where possible, that a participant's performance status will be assessed by the same person throughout the study.

### 8.2.5 Royal Marsden Hospital Risk Score

The Royal Marsden hospital risk score will be derived at screening for each participant (Arkenau et al. 2008). This risk-based score is derived from:

- Lactate dehydrogenase (LDH) $\leq ULN$ = 0 versus LDH > ULN = 1
- $A$lbumin $\geq$ 35 g/L = 0 versus < 35 g/L = 1
- $S$ite of metastasis $\leq$ 2 = 0 versus > 2 = 1.

### 8.2.6 Transthoracic Echocardiogram or MUGA

TTE or MUGA scans will be performed at screening as specified in the SoAs (Section 1.3) if no scan is available within 6 months prior to randomization. This may be further repeated at the Investigator's discretion if there are signs or symptoms of cardiotoxicity.

### 8.2.7 Clinical Safety Laboratory Assessments

Normal ranges for the study laboratory parameters must be supplied to the Sponsor before the study starts.

A list of clinical laboratory tests to be performed is provided in Appendix 4 and these assessments must be conducted in accordance with the separate laboratory manual and the SoAs (Section 1.3).

The Investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the CRF. The laboratory reports must be filed with the source documents. Clinically significant abnormal laboratory findings are those, which are not associated with the underlying disease, unless judged by the Investigator to be more severe than expected for the participant's condition.

- In the event of unexplained abnormal clinically significant laboratory test values, the tests should be repeated immediately and followed up until they have returned to the normal range and/or an adequate explanation of the abnormality is found.
- If such values do not return to normal/baseline within a period judged reasonable by the Investigator, the etiology should be identified and the Sponsor notified.
- If laboratory values from non-protocol-specified laboratory assessments performed at the local laboratory require a change in participant management or are considered clinically significant by the Investigator (e.g., SAE, AE, or dose-modification), then the results must be recorded in the CRF.

Results of clinical laboratory testing will be recorded on the eCRF or be received as electronically produced laboratory reports submitted directly from the local or central laboratory.

Additional blood or urine samples may be taken at the discretion of the Investigator if the results of any test fall outside the reference ranges or clinical symptoms necessitate additional testing to monitor participant safety.

Where the clinical significance of abnormal laboratory results at screening is considered uncertain, screening laboratory tests may be repeated prior to randomization to confirm eligibility.

Based on continuous analysis of the data in this study and other studies, any sample type not considered to be critical for safety may be stopped at any time if the data from the samples collected do not produce useful information.

### 8.2.8 Medical History and Demographic Data

Medical history includes clinically significant diseases, surgeries, cancer history (including prior cancer therapies and procedures), reproductive status, smoking history, use of alcohol and drugs of abuse and all medications (e.g., prescription drugs, OTC drugs, herbal or homeopathic remedies, nutritional supplements) used by the participant within 7 days prior to the screening visit.

Demographic data will include age, sex, and self‑reported race/ethnicity.

## 8.3 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

The definitions of an AE or SAE can be found in Appendix 2. The NSAESI and disease-related events and/or disease-related outcomes not qualifying as AEs or SAEs are discussed in Section 8.3.6 and Section 8.3.7.

The Investigator and any qualified designees are responsible for ensuring that all AEs (including assessment of seriousness, severity and causality; see Appendix 2) are

recorded on the Adverse Event eCRF and reported to the Sponsor in accordance with instructions provided in this section and in Appendix 2.

Procedures used for recording AEs are provided in Appendix 3:

### 8.3.1 Time Period and Frequency for Collecting Adverse Event and Serious Adverse Event Information

The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Appendix 2.

Investigators will seek information on AEs at each participant's contact. All AEs, whether reported by the participant or noted by study personnel, will be recorded in the participant's medical record and on the Adverse Event eCRF as follows:

**After informed consent** has been obtained **but prior to initiation of study treatment**, only SAEs caused by a protocol-mandated intervention should be reported (e.g., SAEs related to invasive procedures such as biopsies). Any other AE should not be reported.

**After initiation of study treatment**, all AEs, regardless of relationship to study treatment, will be reported until 30 days after the final dose of study treatment or until initiation of new systemic anti-cancer therapy, whichever occurs first. SAEs will continue to be reported until 90 days after the final dose of study treatment or until initiation of new systemic anti-cancer therapy, whichever occurs first. In addition, AEs of special interest will continue to be reported until 90 days after the final dose of study treatment, regardless of initiation of new systemic anti-cancer therapy.

**Post-study AEs and SAEs:** The Investigator is not required to actively monitor participants for AEs after the end of the AE reporting period.

However, if the Investigator learns of any SAE (including a death) or other AEs of concern that are believed to be related to prior treatment with study treatment, at any time after a participant has been discharged from the study, and the Investigator considers the event to be reasonably related to the study treatment or study participation, the Investigator must promptly notify the Sponsor. For the procedure of reporting, see Appendix 2.

### 8.3.2 Method of Detecting Adverse Events and Serious Adverse Events

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and non-leading verbal questioning of the participant is the preferred method to inquire about AE occurrence.

A consistent methodology of non-directive questioning should be adopted for eliciting AE information at all participant evaluation time-points.

### 8.3.3 Follow-Up of Adverse Events and Serious Adverse Events

#### 8.3.3.1 Investigator Follow-Up

The Investigator should follow each AE until the event has resolved to baseline grade or better, the event is assessed as stable by the Investigator, the event is otherwise explained, the participant is lost to follow-up (Section 7.3), or the participant withdraws consent. Every effort should be made to follow all SAEs considered to be related to study treatment or study-related procedures until a final outcome can be reported.

During the study period, resolution of AEs (with dates) should be documented on the Adverse Event eCRF and in the participant's medical record to facilitate source data verification. If, after follow-up, return to baseline status or stabilization cannot be established, an explanation should be recorded on the Adverse Event eCRF.

All pregnancies reported during the study should be followed until pregnancy outcome and reported according to the instructions provided in Section 8.3.5.

#### 8.3.3.2 Sponsor Follow-Up

For SAEs, NSAESIs, and pregnancies, the Sponsor or a designee may follow up by telephone, fax, electronic mail, and/or a monitoring visit to obtain additional event details and outcome information (e.g., from hospital discharge summaries, consultant reports, autopsy reports) in order to perform an independent medical assessment of the reported event.

### 8.3.4 Regulatory Reporting Requirements for Serious Adverse Events

Prompt notification by the Investigator to the Sponsor of a SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study treatment under clinical investigation are met.

The Sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study treatment under clinical investigation. The Sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRB/Independent Ethics Committees (IEC), and Investigators.

Investigator safety reports must be prepared for suspected unexpected serious adverse reactions according to local regulatory requirements and Sponsor policy and forwarded to investigators as necessary.

An Investigator who receives an Investigator safety report describing an SAE or other specific safety information (e.g., summary or listing of SAEs) from the Sponsor will review and then, file it along with the Investigator's Brochure and will notify the IRB/IEC, if appropriate according to local requirements.

For immediate and expedited reporting requirements from Investigator to Sponsor and from Sponsor to Health Authority, Investigators, IRB and EC, see Appendix 2.

#### 8.3.4.1 Emergency Medical Contacts

To ensure the safety of study participants, access to the Medical Monitors is available 24 hours a day, 7 days a week. Details will be available separately.

### 8.3.5 Pregnancy

Female participants of childbearing potential will be instructed to immediately inform the Investigator if they become pregnant during the study or within 5 months after the final dose of study treatment.

Male participants will be instructed through the ICF to immediately inform the Investigator if their partner becomes pregnant during the study or within 5 months after the final dose of study drug. Male participants should refrain from donating sperm during the treatment period and for at least 5 months after the final dose of study.

If a pregnancy is reported, the Investigator should inform the Sponsor within 24 hours of learning of the pregnancy and should follow the pregnancy reporting process as detailed in Appendix 5.

Abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs (Appendix 5).

### 8.3.6 Non-Serious Adverse Events of Special Interest

NSAESI are required to be reported by the Investigator to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Appendix 2 for reporting instructions).

NSAESI for this study include the following:

- Cases of an elevated ALT or AST in combination with either an elevated bilirubin or clinical jaundice, as defined in Appendix 3.
- Suspected transmission of an infectious agent by the study treatment, as defined below:

  Any organism, virus, or infectious particle (e.g., 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 participant exposed to a medicinal product. This term applies only when a contamination of the study treatment is suspected.

### 8.3.7 Management of Specific Adverse Events

Based on the mode of action, RO7121661and RO7247669are expected to show a safety profile that is similar to that of other CPIs including nivolumab. Toxicities from CPIs can include infusion-related reactions and imAEs. Toxicities associated or possibly associated with study treatment should be managed according to standard medical practice. Additional tests, such as autoimmune serology or biopsies, should be used to determine a possible immunogenic etiology as clinically indicated.

Measures will be taken to ensure the safety of participants in this study, including the use of stringent inclusion and exclusion criteria and close monitoring of participants during the study. Administration of study drug will be performed in a monitored setting in which there is immediate access to trained personnel and adequate equipment and medicine to manage potentially serious reactions.

For events in which management guidelines are not covered in this protocol, participants should be managed as deemed appropriate by the Investigator according to best medical judgment and local medical guidelines. Clinical judgment may be applied, and risk/benefit consideration may suggest deviating from these guidelines. In this specific case, decisions on study treatments will be taken by the Investigator upon consultation with the Medical Monitor.

#### 8.3.7.1 Infusion-Related Reactions

Administration of therapeutic antibodies may cause IRRs characterized by symptoms such as fever, chills, dizziness, hypertension, hypotension, dyspnea, restlessness, sweating, flushing, rash, tachycardia, tachypnea, headache, tumor pain, nausea, and/or vomiting. Respiratory and cardiac symptoms such as, bronchospasm, larynx, and throat irritation, wheezing, laryngeal edema and atrial fibrillation may also occur. Such reactions typically occur during or shortly after an infusion or within 24 hours after study treatment infusion, predominantly at the first infusion. The incidence and severity typically decrease with subsequent infusions.

Participants may also develop immunoglobulin (Ig)E-mediated hypersensitivity reactions. IRRs may be indistinguishable from an anaphylactic reaction; however, in case of IgE-mediated hypersensitivity, symptoms typically occur after previous exposure and very rarely with the first infusion. In case of confirmed IgE-mediated hypersensitivity reaction, treatment should be permanently discontinued.

No pre-medication is indicated for the administration of Cycle 1. However, participants who experience a Grade 2 should receive pre-medication for subsequent infusions. In case of Grade 3 or 4 IRRs related to study treatment, the participant should be permanently discontinued from the study treatment. If an IRR occurs during the infusion of study drug, refer to Table 7.

**Table 7 Recommendations for Infusion-related Reaction Prevention and Management**

| Infusion-Related Reactions[a] | Guidance |
|---|---|
| Grades 1−2 | • Slow infusion to ≤ 50% or interrupt infusion.<br>• Give supportive treatment.[b]<br>• Upon symptom resolution may resume infusion (if interrupted) at 50% starting rate. The infusion must remain at the lower rate resulting in symptom resolution for the remainder of the infusion.<br>• For Grade 2 IRRs, subsequent cycles of study drug should be administered with pre-medication including acetaminophen/paracetamol and an antihistamine, such as diphenhydramine.<br><br>Notes:<br>• For Grade 2 wheezing or urticaria, the participant must also be pre-medicated prior to subsequent doses (as described above).<br>• If symptoms recur with the same or greater severity following the slower or interrupted infusion, the infusion must be stopped immediately. No further study drug will be administered for the cycle. |
| Grades 3-4 | • Discontinue infusion.<br>• Give supportive treatment. [b]<br>• Permanently discontinue study treatment. |

NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events.

[a] Refer to the NCI-CTCAE, v5.0 scale for the grading of symptoms.

[b] Supportive treatment: Participants should be treated with acetaminophen/paracetamol and an antihistamine, such as diphenhydramine, if they have not been administered in the last 4 hours. Intravenous fluids (e.g., normal saline) may be administered as clinically indicated. For bronchospasm, urticaria, or dyspnea, antihistamines, oxygen, corticosteroids (e.g., 100 mg IV prednisolone or equivalent), and/or bronchodilators may be administered per institutional practice.

### 8.3.7.2 Immune-mediated Adverse Events

Most imAEs observed with CPIs have been mild and self-limiting, however, such events should be recognized early and treated promptly to avoid potentially major complications. Any organ or tissue can be involved, although some imAEs occur much more commonly than do others. The most frequently occurring imAEs affect the skin, colon, endocrine organs, liver, and lungs. Others are very infrequent but may be very serious, even lethal, such as neurological disorders and myocarditis.

Discontinuation of study treatment may not have an immediate therapeutic effect, and in severe cases, immune-mediated toxicities may require acute management with topical corticosteroids, systemic corticosteroids, mycophenolate, or TNF-α inhibitors. Study treatment may be suspended for most Grade 2 toxicities, with consideration of resuming when symptoms revert to Grade 1 or less. Corticosteroids may be administered. Grade 3 toxicities generally warrant suspension of study treatment and the initiation of high-dose corticosteroids (prednisone, 1-2 mg/kg/day, or methylprednisolone, 1-2 mg/kg/day). Corticosteroids should be tapered over the course of at least 4 to 6 weeks. Some

refractory cases may require infliximab or other immunosuppressive therapy. In general, permanent discontinuation of study treatment is recommended with Grade 4 toxicities, with the exception of endocrinopathies that have been controlled by hormone replacement. The management guidelines for imAEs associated with study treatment are provided in Appendix 7.

## 8.4 TREATMENT OF OVERDOSE

Study treatment overdose is the accidental administration of a drug in a quantity that is higher than the assigned dose. An overdose or incorrect administration of study treatment is not an AE unless it results in untoward medical effects (see Sections 5 and 5.2 of Appendix 2 for further details).

Decisions regarding dose-interruptions will be made by the Investigator/treating physician in consultation with the Medical Monitor based on the clinical evaluation of the participant.

In the event of an overdose, the Investigator should:

- Contact the Sponsor's Medical Monitor immediately.
- Closely monitor the participant for AEs/SAEs and laboratory abnormalities until resolved.
- Obtain a blood sample for PK analysis as soon as possible.
- Document the quantity of the excess dose.

Any dose of study treatment greater than the planned dose will be considered an overdose.

The Sponsor does not recommend specific treatment for an overdose.

## 8.5 PHARMACOKINETICS

Mandatory blood samples to evaluate concentrations of study treatment will be collected from an IV line from the arm opposite to that used for study treatment administration. The date and time of each sample collection will be recorded in the eCRF.

RO7121661, RO7247669, and nivolumab levels will be analyzed by using validated assays. The PK samples will be taken as outlined in the SoAs (Section 1.3). Additional PK samples should be taken, if the participant experiences an infusion-related AE (such as an IRR) or if the participant experiences an AE leading to a delay in study drug administration. Blood samples for PK analysis may be collected at the participant's home. This specifically applies to days where no other hospital assessments are required—i.e. C1D8 and C5D8.

Remaining volumes of PK samples may be used for additional PK/anti-drug antibodies (ADA) analyses or assay development or validation, for treatment-related exploratory

analyses, or to help develop further blood tests for exploratory analysis (e.g., further characterization of immune responses), after they are used for the mentioned intended use and as deemed appropriate.

The PK blood samples will be destroyed within 2 years after the date of final clinical study report or earlier depending on local regulations, unless participants give optional consent for further use of remaining samples as part of RBR after the end of the study. Details on sampling procedures, sample storage, and shipment are given in the sample documentation.

Drug concentration information that would unblind the study will not be reported to investigative sites or other blinded personnel until the study has been unblinded.

## 8.6 IMMUNOGENICITY ASSESSMENTS

As the study drugs are human antibodies, there is a risk that ADAs against the study drugs could develop, potentially reducing their efficacy and/or potentially resulting in symptomatic hypersensitivity reaction, including immune-complex reactions.

Antibodies to the study drugs will be evaluated in blood samples collected from all participants according to the SoAs (Section 1.3). For each collected ADA sample, a corresponding PK sample will be collected at the same time-point for the determination of the study drug concentration. During the course of the study, ADA sampling time-points may be modified based on emerging data to ensure the immunogenicity of RO7121661 and RO7247669 can be adequately characterized.

Validated screening, confirmatory, and titer assays will be employed to detect ADAs. The date and time of each sample will be recorded in the eCRF.

If required, remaining volumes of ADA samples may also be used for assay development/validation experiments, ADA characterization, for compound-related exploratory analyses, or to help develop further blood tests, after they are used for the mentioned intended uses.

The blood samples will be destroyed within 2 years after the date of final clinical study report, or earlier, depending on local regulations unless participants give optional consent for further use of remaining samples as part of RBR after the end of the study.

Details on sampling procedures, sample storage, and shipment are documented in the sample documentation.

## 8.7 PHARMACODYNAMICS AND BIOMARKERS ANALYSES

Blood, tissue, tongue scrape, and stool samples will be collected as specified in the SoAs (Section 1.3). Details on processes for collection and shipment of these samples can be found in the Laboratory Flow Chart.

Collected samples will be tested for protein, nucleic acid, or other tissue and/or blood derived biomarkers relating to the proposed mechanism of actions of RO7247669, RO7121661, and nivolumab. These may include, but are not limited to, cellular profiling, determination of the activation status of immune cells in blood and in the tumor, assessment of the oral and gut microbiome, as well as cytokines and/or other soluble markers of inflammation. Additional markers may be measured in case a strong scientific rationale for these analyses develops.

The specimens will also be used for research purposes to identify biomarkers useful for predicting and monitoring response to the respective treatments, identifying biomarkers useful for predicting and monitoring safety, assessing PD effects, and investigating mechanisms of therapy resistance.

Planned analyses include, but are not limited to:

- Blood samples:
    - Blood samples for flow cytometry will be analyzed for changes in the numbers and activation status of lymphocyte subsets including but not limited to CD4+, CD8+, and/ or NK cells.
    - Blood samples for measurement of select cytokines/chemokines (e.g., IL-2Ra, IL-6, IL-8, and IP-10), and/or soluble markers (such as, but not limited to, sPD1, sLAG3, and/or sTIM3).
    - Blood for whole genome sequencing (WGS; Section 8.7.1.1).
    - Blood for RNA extraction will be collected for gene expression analysis.
    - Blood for blood tumor mutation burden and ctDNA determination.
- Tongue scrape and stool samples:
    - Examining the role of the gut and oral microbiome as a determinant of treatment response and safety for cancer immunotherapy via whole metagenomic sequencing (WMS) of microbial communities and calprotectin detection in stool samples.
- Tumor tissue samples (archival samples and/or fresh biopsies):
    - Tumor tissue samples will be used for immunohistochemistry (IHC) and/or immunofluorescence (IF) analyses (such as, but not limited to, CD8, Ki67, PD1, LAG3, TIM3, and PDL1), as well as the assessment of tumor mutational burden (TMB), and tumor gene expression.

Analysis techniques may include, but are not limited to, flow cytometry, immunohistochemistry, gene expression, and gene sequencing. DNA and/or RNA will be extracted for exploratory biomarker research on genetic biomarkers (including, but not limited to, cancer-related genes and biomarkers associated with common molecular pathways or immune-related markers, and TMB.

Residual plasma/serum samples (e.g., from PK and/or PD assessments) may be used for retrospective and longitudinal testing of bacterial or viral infection by serological methods (such as but not limited to SARS-CoV-2). This testing may be performed for each participant. In addition to serving as an important safety measure, these analyses will inform as to any association of bacterial or viral infection and response to treatment.

Based on continuous analysis of data any sample type, time-point, and/ or analysis not considered critical may be stopped at any time if the data do not produce useful information.

When a participant withdraws from the study, samples collected prior to the date of withdrawal may still be analyzed, unless the participant specifically requests that the samples be destroyed or local laws require destruction of the samples. However, if samples have been tested prior to withdrawal, results from those tests will remain as part of the overall research data.

Archival tumor blocks will be returned, unless notified by the site that they do not want them returned. Blood, tissue, and other residual material (slides, extracts, on-study blocks, etc.) will be destroyed within 2 years after the final closure of the clinical database unless the participant gives specific consent for the remainder of the material to be stored for optional exploratory research (RBR, Section 8.9).

Data arising from all biosamples including samples for analyses of inherited DNA will be subject to the local confidentiality standards.

### 8.7.1 Genetic and Genomic Analyses

Whole blood, tissue, tongue scrape, and stool samples for genetic analyses will be taken at the time-points mentioned in SoA (Section 1.3), with respect to the analyses described in Section 8.7. These samples will be destroyed no later than 2 years after the date of final clinical study report, unless the participant gives specific consent for the remainder of the residual material to be stored for optional potential exploratory research within the RBR (see Section 8.9).

#### 8.7.1.1 Whole Genome/Exome/Targeted DNA Analysis

Blood, tissue samples (archival and/or fresh biopsies), tongue scrape, and stool samples will be collected for DNA extraction (Section 1.3). These samples may be sent to one or more laboratories for analysis of germline or somatic mutations via WGS, whole WMS of microbial communities, whole exome sequencing (WES), next-generation sequencing (NGS), or other targeted genomic analysis methods including (but not limited to) TMB and ctDNA determination.

Genomics is increasingly informing researchers' understanding of disease pathobiology. WGS, WES, WMS, and NGS provide a comprehensive characterization of the genome and, along with clinical data collected in this study, may increase the opportunity for developing new therapeutic approaches, and understanding genetic predisposition to greater response or certain AEs after treatment. Data will be analyzed in the context of this study but may also be explored in aggregate with data from other studies. The availability of a larger dataset will assist in identification of important pathways, guiding the development of new, targeted agents.

Given the complexity and exploratory nature of these analyses, data and analyses will not be shared with Investigators or study participants unless required by law. Participants will not be identified by name or any other personally identifying information. Data arising from all biosamples, including samples for analyses of inherited DNA, will be subject to the confidentiality standards described in the sample documentation.

#### 8.7.1.2 Transcriptome Analysis

Archival and/or fresh tissue biopsies and blood samples (other matrices possible) will be collected as outlined in the SoAs (Section 1.3) for RNA extraction and subsequent gene expression profiling to enable the identification of PD biomarkers and markers predictive of treatment response.

### 8.8 PHARMACODYNAMICS AND BIOMARKER SAMPLES

All samples for PD and biomarker research should be collected as specified in the SoAs (Section 1.3), with respect to the analyses described in Section 8.7. Details on processes for collection and shipment of these samples can be found in separate sample documentation.

Any remaining samples after the specified analyses may also be used for additional (assay) validation experiments. Samples may be used for research to develop methods, assays, prognostics, and/or companion diagnostics related to RO7247669 and/or RO7121661, disease process, pathways associated with disease state, and/or mechanism of action of the study treatments. Note that as science and research is evolving, the list of biomarkers that will be evaluated cannot be fully defined.

Based on continuous analysis of the data in this study and other studies, any sample type and/or analysis not considered critical for safety may be stopped at any time if the data from the samples collected does not produce useful information.

Unless otherwise specified below, samples (including blood, slides, extracts, etc.) will be destroyed no later than 5 years after the date of final clinical study report. For participants who consent to RBR, leftover samples will be transferred to RBR (Section 8.9).

For sampling procedures, storage conditions, and shipment instructions, see the sample flowchart and additional instruction documents.

### 8.8.1 Mandatory Samples

The following samples for PD and biomarker research are required and will be collected from all participants with respect to the analyses described in Section 8.7:

- All PD blood samples as outlined in the SoAs (Section 1.3) for:
  - Flow cytometry analyses.
  - Measurement of select cytokines/chemokines and/or soluble markers.
  - Whole genome sequencing (Section 8.7.1.1). If this sample is missing on C1D1, it should be collected at the next scheduled visit, where possible. Collection of this sample is contingent on approval by relevant institutions in the respective countries/sites.
  - RNA extraction for gene expression analysis.
  - Blood tumor mutation burden and ctDNA determination.
- FFPE archival tumor tissue is to be provided for all participants, if available.
  - In case no suitable archival tissue is available for central assessment of tumor PD-L1 positivity using the IHC 28-8 pharmDx assay, a mandatory fresh baseline biopsy will be required (Section 5.1 and Section 8.8.2).
  - The primary and the most recent metastasis (if both are available) should be submitted for analysis, and the tissue sample should not be older than 12 months. Ideally, these samples should include the invasive margin.
  - Tumor blocks are preferred but unstained slides containing freshly cut, serial sections will be accepted.
  - Acceptable samples include core needle biopsies for deep tumor tissue or excisional, incisional, punch, or forceps biopsies for cutaneous, subcutaneous, or mucosal lesions.
  - Fine-needle aspiration, brushing, cell pellet from effusions, bone metastases, and lavage samples are not acceptable.
  - Archival tumor blocks will be returned to the sites when requested by the Investigator or at the end of the study, unless notified by the site that they do not want them returned.

### 8.8.2 Optional Samples

Upon consent, the following optional samples for biomarker research should be collected from participants as outlined in the SoAs (Section 1.3), with respect to the analyses described in Section 8.7).

- Tongue scrape and stool samples for the assessment of the participant's oral and gut microbiome as well as calprotectin detection
    - Dietary intake is a central determinant of changes in the microbiota. A nutritional assessment will therefore be performed as indicated in the SoAs to better correlate the profiles of the microbiota for participants who consent to provide these optional samples.
    - Screening samples of participants who are not enrolled in the study will be destroyed.
- Fresh tumor biopsies at baseline and as indicated in the SoAs:
    - Collection of tumor biopsies should be guided by ultrasound, CT scan, or other methods according to the location of the selected lesion using a 16-gauge needle (preferred) to provide cores, ideally, of at least 20 mm in length or equivalent size. Ideally, 4 (minimum 2) core biopsies should be obtained at each time-point (at the physician's discretion). In order to mitigate the potential risk associated with tumor biopsies, all participants required to have a biopsy must have tumor lesions from which biopsies can be safely obtained, as per clinical judgment of the treating physician.
    - Fresh screening samples should generally be collected after eligibility is confirmed. Post-dose samples can be collected + 2/– 1 day(s) from scheduled time-point. If the participant progresses and discontinues treatment prior to the on-treatment biopsy day, the tumor biopsy should be taken at the time of treatment discontinuation. An additional biopsy at the time of PR, stable disease, progression, or at any other time-point of interest based on participants' course of disease may be taken after discussion between the Investigator and the Sponsor. A minimum interval of 4 weeks is necessary between the collections of optional tumor biopsies.
    - Baseline and on-treatment biopsies should be preferably taken from the same tumor lesion (metastasis) to ensure comparability. If the sample cannot be collected from the same lesion (e.g., lesion disappears after treatment) then preferably the biopsy should be collected from the same organ, if possible.
    - Fine-needle aspiration is not acceptable. The biopsies will be taken from accessible tumor locations, including, but not limited to, skin, lymph nodes, rectum, liver, etc. Bone biopsies and trans-bronchial biopsies are not acceptable.

- Use of available existing biopsies at the sites prior to the participant's entry in the study should be discussed with the Sponsor (i.e., biopsy should have recently been obtained as part of diagnosis biopsy and participants should have not received any tumor treatment after this collection).
- In the event that a fresh biopsy is taken during the screening period and the participant is not enrolled into the study, the fixed and embedded biopsy (FFPE block) can be returned to the site upon site request. The site must confirm that a written consent is obtained from the participant before return request submission to the Sponsor. If the participant does enroll in the study, fresh biopsies will not be returned to the site.
- The Sponsor will continuously assess the need for making the biopsies mandatory, and additional participants may be enrolled to ensure that sufficient paired fresh biopsy samples are evaluable to conclude the intended PD analyses.

The ICF will contain a separate section that addresses the use of remaining samples for optional exploratory research. A separate signature will be required to document a participant's agreement to allow any remaining samples to be used for optional exploratory research.

## 8.9 SAMPLES FOR RESEARCH BIOSAMPLE REPOSITORY

### 8.9.1 Overview of the Research Biosample Repository

The Roche RBR is a centrally administered group of facilities for the long-term storage of human biologic samples, including body fluids, solid tissues, and derivatives thereof (e.g., DNA, RNA, proteins, peptides). The collection, storage, and analysis of the RBR samples will facilitate the rational design of new pharmaceutical agents and the development of diagnostic tests, which may allow for individualized drug therapy for patients in the future.

Samples for the RBR will be collected from participants who give specific consent to participate in this optional RBR. Collected RBR samples will be used to achieve the following objectives:

- To study the association of biomarkers with efficacy or progressive disease.
- To identify safety biomarkers that are associated with susceptibility to developing AEs or can lead to improved AE monitoring or investigation.
- To increase knowledge and understanding of disease biology and drug safety.
- To study treatment response, including drug effects and the processes of drug absorption and disposition.
- To develop biomarker or diagnostic assays and establish the performance characteristics of these assays.

### 8.9.2 Sample Collection

The following samples will be collected for identification of genetic (inherited) biomarkers:

- Saliva for DNA extraction

The following samples will be stored in the RBR and used for research purposes, including, but not limited to, research on biomarkers related to RO7121661, RO7247669, diseases or drug safety:

- Leftover plasma samples
- Leftover serum samples
- Leftover blood samples
- Leftover fresh or archival tumor tissue samples and unstained slides
- Leftover blood samples for DNA extraction
- Leftover genetic material such as DNA and RNA

The samples collected for DNA extraction include, but is not limited to, genomic analysis and may be sent to one or more laboratories for analysis of germline or somatic mutations via WGS, WES, NGS, or other genomic analysis methods.

Genomics is increasingly informing researcher's understanding of disease pathobiology. WGS provides a comprehensive characterization of the genome and, along with clinical data collected in this study, may increase the opportunity for developing new therapeutic approaches. Data will be analyzed in the context of this study but may also be explored in aggregate with data from other studies. The availability of a larger dataset will assist in identification of important pathways, guiding the development of new targeted agents.

Upon RBR consent, samples may be used for DNA extraction to enable whole genome/exome sequencing WGS/WES and other genomic analysis.

Samples may be sent to one or more laboratories for analysis of germline or somatic mutations via WGS/WES, or other genomic analysis methods. WGS and WES provide a comprehensive characterization of the genome and exome, respectively, and, along with clinical data collected in this study, may increase the opportunity for developing new therapeutic approaches or new methods for monitoring efficacy and safety or predicting which patients are more likely to respond to a drug or develop AEs.

Participants will not be identified by name or any other personally identifying information. Data generated from RBR samples will be analyzed in the context of this study but may also be explored in aggregate with data from other studies. The availability of a larger dataset will assist in identification and characterization of important biomarkers and pathways to support future drug development.

For all samples, dates of consent, and sample collection should be recorded on the associated RBR page of the eCRF. Details on processes for collection and shipment of these samples can be found in separate sample documentation.

RBR samples will be stored and used until they are depleted or come to end of their retention period and are thus destroyed. The RBR storage period will be in accordance with the IRB/EC‑approved ICF and applicable laws (e.g., Health Authority requirements).

The repository samples will be subject to the confidentiality standards (as described under Confidentiality in Appendix 1).

## 8.10 HEALTH ECONOMICS/MEDICAL RESOURCE UTILIZATION AND HEALTH ECONOMICS

Health economics/medical resource utilization and health economics parameters are not evaluated in this study.

## 8.11 TIMING OF STUDY ASSESSMENTS

### 8.11.1 Screening and Pre-treatment Assessments

Written informed consent for participation in the study must be obtained before performing any study-specific screening tests or evaluations. ICFs for enrolled participant and for participants who are not subsequently enrolled will be maintained at the study site.

All screening, and all pre-treatment assessments (related to entry criteria), must be completed and reviewed to confirm that participants meet all eligibility criteria. The Investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure.

An Eligibility Screening Form documenting the Investigator's assessment of each screened participant with regard to the protocol's inclusion and exclusion criteria is to be completed by the Investigator and kept at the investigational site.

Screening and pre-treatment assessments will be performed within 28 days prior to randomization, unless otherwise specified. Results of standard-of-care tests or examinations performed prior to obtaining informed consent and within 28 days prior to randomization may be used (and do not need to be repeated for screening).

### 8.11.2 Assessments during Treatment

Under no circumstances will participants who enroll in this study and have completed treatment as specified be permitted to be allocated a new randomization number and re-enroll in the study.

All assessments must be performed as per SoAs (Section 1.3). Assessments scheduled on the day of study treatment administration should be performed prior to administration of study treatment, unless otherwise noted in the SoAs. PRO questionnaires will be completed before the participant receives any information on disease status, prior to the performance of non-PRO assessments, and prior to the administration of study treatment.

### 8.11.3 Assessments at Treatment Discontinuation Visit

Participants who discontinue study treatment early will be asked to return to the clinic ≤ 30 days after the final dose of study drug for a follow‑up visit. The visit at which response assessment shows progressive disease may be used as the treatment discontinuation visit.

### 8.11.4 Follow-Up Assessments

As part of the post-treatment follow-up, the sites will provide to the Sponsor every 3 months with an update on survival status and new anti-cancer therapies of each participant who has completed or discontinued from the study. The survival follow-up will be performed for the first time 90 days (± 7 days) post last dose of study treatment and then every 3 months (± 2 weeks). The sites will use a designated section of the eCRF for this purpose. Post-treatment follow-up visits can be done at site, over the phone, or participant medical records. In addition, all participants will be asked to complete PROs every 3 months during the first year post discontinuation.

For participants who discontinue treatment for reasons other than disease progression or loss of clinical benefit tumor assessments are to continue according to schedule until they start new anti-cancer therapy.

After the treatment discontinuation visit, AEs should be followed as outlined in Section 8.3.1 and Section 8.3.3.

### 8.11.5 Assessments at Unscheduled Visits

If clinically indicated, any sample or assessment specified in the SoAs can be performed any time as unscheduled sample or assessment at the discretion of the Investigator.

In case of Grade 2 IRRs or Grade ≥ 3 IRRs, suspected anaphylaxis, or Grade ≥ 3 suspected imAEs, the assessments as per SoAs (Section 1.3) are to be performed.

# 9. STATISTICAL CONSIDERATIONS

The data will be analyzed by the Sponsor and/or designated contract research organization. Any data analysis carried out independently by the Investigator should be submitted to the Sponsor before publication or presentation. The data will be summarized with respect to demographic and baseline characteristics, efficacy, safety, PK, and biomarkers observations and measurements. The core analysis will *focus on the OS comparison of RO7247669 against nivolumab and take place* when approximately [redacted] OS events have been observed in the*se two arms of the* study. The additional data for any participant continuing to receive study treatment or being followed for survival past this time (as allowed by the protocol) will be further summarized in a subsequent extension report once the study is terminated.

## 9.1 SAMPLE SIZE DETERMINATION

This study was designed to provide an assessment of the efficacy and safety of RO7121661 and RO7247669. The primary purpose is the estimation of the OS hazard ratios (HR) *of RO7247669* against nivolumab.

The planned number of enrolled participants *was* 255, randomized [redacted] into 3 arms. *With the decision to stop enrollment into the RO7121661 arm, the study sample size has been re-estimated to reflect the new randomization scheme (new participants will be randomized [redacted] to either RO7247669 or nivolumab).* [redacted]

## 9.2 POPULATIONS FOR ANALYSES

For purposes of analysis, the following populations are defined in Table 8.

### Table 8 Analysis Populations

| Population | Description |
|---|---|
| Intent-to-treat | All randomized participants will be included in the intent-to-treat population. |
| Safety | All participants randomized to study treatment and who received any amount of the study treatment, whether prematurely withdrawn from the study or not, will be included in the safety analysis. |
| Pharmacokinetic | All participants who have received at least one dose of study treatment and who have data from at least one post-dose sample will be included in the PK analysis population. Participants will be excluded from the PK analysis population if they significantly violate the inclusion or exclusion criteria, deviate significantly from the protocol, or if data are unavailable or incomplete which may influence the PK analysis. Excluded cases will be documented together with the reason for exclusion. All decisions on exclusions from the analysis will be made prior to database closure. |
| Immunogenicity | Participants who had at least one pre-dose or at least one post-dose ADA assessment will be included and analyzed according to the treatment they actually received or were allocated to receive. The relationship between ADA status and safety, efficacy, PK, and biomarker endpoints will be analyzed and reported descriptively via subgroup analyses. |
| PRO-evaluable population | All randomized participants with a non-missing baseline assessment and at least one post-baseline assessment for the respective PRO will be included in the PRO-evaluable population. |

ADA = Anti-drug antibody; PK = Pharmacokinetic; PRO = Patient-reported outcome.

## 9.3 STATISTICAL ANALYSES

*A technical document describing the statistical analyses plan will provide more details on the* statistical analyses.

### 9.3.1 Demographics and Baseline Characteristics

Study enrollment, study drug administration, reasons for study drug discontinuation, and reasons for discontinuation from the study will be summarized by treatment arm. Major protocol deviations, including major deviations with regard to the inclusion and exclusion criteria, will be summarized by treatment arm.

Demographic (including age, sex, and self-reported race/ethnicity) and baseline disease characteristics (e.g., ECOG Performance Status) will be summarized overall and by treatment arm.

Descriptive statistics (mean, median, standard deviation, and range) will be presented for continuous data, and frequencies and percentages will be presented for categorical data, as appropriate.

Baseline measurements are the last available data obtained prior to the participant receiving the study treatment.

### 9.3.2 Efficacy Analyses

The efficacy analyses will include all participants in the ITT population, with participants grouped according to the treatment assigned at randomization (Table 9).

*Descriptive statistics for the various endpoints will be provided for all 3 arms. However, since the primary aim has shifted from comparing the 2 experimental arms to nivolumab to only compare the RO7247669 arm to nivolumab, the statistical models will only include participants assigned to RO7247669 and nivolumab.*

**Table 9 Efficacy Statistical Analysis Methods**

| Endpoint | Statistical Analysis Methods |
|---|---|
| Primary | **OS**<br>OS is defined as the time from randomization to death from any cause. Data for participants who are alive at the time of the data cutoff will be censored at the last date they were known to be alive. Data from participants without post-baseline information will be censored at the date of randomization.<br>Kaplan-Meier methods will be used to estimate median OS for each treatment arm and the 95% CIs for median OS will be computed using the Brookmeyer and Crowley method. The stratified Cox proportional hazard model will be used to estimate the hazard ratio *for RO7247669 versus nivolumab* (i.e., the magnitude of the treatment effect) and the corresponding 95% confidence interval, stratified by the protocol-defined stratification factors. |
| Secondary | **ORR and DCR based on RECIST**<br>ORR is defined as the proportion of participants who have achieved an objective response, characterized by a CR or PR according to RECIST v1.1.<br>Objective response will be evaluated by treatment arm, and participants without post-baseline overall response assessments will be counted as non-responders.<br>DCR is defined as ORR + stable disease rate (SDR).<br>An estimate of ORR for each treatment group as well as of the difference between the ORR of each experimental arm compared with the active comparator will be computed along with its 95% CI. The Mantel-Haenszel test will be used to compare the ORR *of RO7247669* and the active comparator at the two-sided significance level of 20%, stratified by the protocol-defined stratification factors.<br><br>**PFS based on RECIST**<br>PFS defined as the time from randomization to the first occurrence of progression as determined by the Investigator according to RECIST v1.1 or death during the treatment period or within on study (i.e., within 60 days of the last study treatment tumor assessment) after treatment discontinuation, whichever occurs first.<br>Participants who have not experienced disease progression at the time of analysis and who have not died during the treatment period or within 60 days of the last tumor assessment after treatment discontinuation will be censored at the time of the last tumor assessment. Participants with no post-baseline tumor assessment will be censored at the date of randomization.<br>The requirement that participants without a radiographic disease progression per RECIST v1.1 are still followed for the tumor assessments until progression or when the participant starts a new anti-cancer therapy (whatever occurs first), means that: |

| Endpoint | Statistical Analysis Methods |
|---|---|
| | - intercurrent events of treatment discontinuations in absence of disease progression per RECIST 1.1 do not per se censor the PFS observation, since the participant will still undergo tumor assessments (treatment policy strategy)<br>- intercurrent events of new anticancer therapy imply instead that the PFS observation is censored at the last available tumor assessment before the new anticancer treatment starts, therefore assuming that participants who experience this intercurrent event have the same risk as those who did not (hypothetical strategy).<br>PFS will be compared between treatment arms with use of the stratified log-rank test.<br>The HR and its 95% CI for PFS will be estimated using a stratified Cox proportional-hazards model. Kaplan-Meier methodology will be used to estimate the median PFS for each treatment arm, and Kaplan-Meier curve will be constructed to provide a visual description of the difference between treatment arms.<br><br>**DoR based on RECIST**<br>DoR is defined as the time from the first occurrence of a documented objective response to disease progression according to RECIST v1.1 or death from any cause, whichever occurs first.<br>The analysis of DoR will include only participants who achieved an objective response to study treatment. DoR will be estimated using the Kaplan-Meier methodology. As the determination of DoR is based on a non-randomized subset of participants, no formal hypothesis testing will be performed.<br><br>**Proportion of participants reporting clinically meaningful improvements in PRO measures**<br>The proportion of participants in each treatment group reporting clinically meaningful improvement (defined as $\geq$ 10 points) in global health status/quality of life, emotional functioning, social functioning and dysphagia as measured by the EORTC QLQ-C30, IL-97, and OES-18 will be computed.<br>An estimate of this proportion for each treatment group as well as of the difference between proportions of each experimental arm compared to the active comparator will be computed along with its 95% CI. |

CI = Confidence interval; CR = Complete response; DCR = Disease control rate; DoR = Duration of response; EORTC = European Organisation for Research and Treatment of Cancer; HR = Hazard ratio; IL97 = Item Library 97; OS = Overall survival; PFS = Progression-free survival; PR = Partial response; PRO = Patient-reported outcomes; RECIST = Response evaluation criteria in solid tumors.

### 9.3.3 Safety Analyses

All safety analyses will be based on the safety analysis population grouped according to the treatment assigned at randomization (Table 10).

Safety analyses will include all participants randomized to study treatment and who received any amount of the study treatment, whether prematurely withdrawn from the study or not. Safety analyses will be performed by treatment arm and will be based on actual treatment received. Drug exposure will be summarized, including duration.

Verbatim description of AEs will be mapped to the MedDRA terms. Severity for all AEs will be graded by the Investigator according to the NCI CTCAE v5.0. All AEs will be

summarized by treatment arm and NCI CTCAE grade. In addition, SAEs and AEs leading to study treatment discontinuation or interruption will be summarized accordingly. Multiple occurrences of the same event will be counted once at the maximum severity. Laboratory data with values outside of the normal ranges will be identified. In addition, selected laboratory data, including ADA results, will be summarized by treatment arm. Deaths and causes of deaths will be summarized.

### Table 10 Safety Statistical Analysis Methods

| Endpoint | Statistical Analysis Methods |
|---|---|
| Adverse events | The original terms recorded on the eCRF by the Investigator for AEs will be coded by the Sponsor.<br>Adverse events will be summarized by mapped term and appropriate thesaurus level. |
| Clinical laboratory tests | All clinical laboratory data will be stored on the database in the units in which they were reported. Laboratory test values will be presented in International System of Units (SI units; Système International d'Unités) by individual listings with flagging of abnormal results.<br>Shifts in NCI CTCAE v5.0 grades from baseline to the worst grade observed during treatment and summary tables of change from baseline over time based on SI units will be presented for selected laboratory parameters. Individual participant listings (abnormal values or out of range) will be produced. For details on standard reference ranges and data transformation and the definition of laboratory abnormalities, see Appendix 4. Additional figures/tables/listings will be produced as deemed appropriate. |
| Vital signs | Vital signs data will be presented by individual listings with flagging of values outside the normal ranges and flagging of abnormalities. In addition, tabular summaries will be used, as appropriate. |
| ECG data analysis | ECG data will be presented by individual listings. In addition, tabular summaries will be used, as appropriate. |
| Concomitant medications | The original terms recorded on the participants' eCRF by the Investigator for concomitant medications will be standardized by the Sponsor by utilizing a mapped term and appropriate drug dictionary level.<br>Concomitant medications will be presented in summary tables and listings. |

AE = Adverse event; ECG = Electrocardiogram; eCRF = Electronic case report form; NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events; SI units = Système International d'Unités.

### 9.3.4 Pharmacokinetic Analyses

Analyses will be carried out on the PK analysis population. All PK parameters will be presented by listings and descriptive summary statistics (mean, standard deviation, coefficient of variation, median, minimum, and maximum) separately by treatment group.

Individual and mean serum RO7121661, RO7247669, and nivolumab versus time data will be tabulated and plotted by treatment group. Graphical displays of PK data may also be provided. The serum pharmacokinetics of RO7121661, RO7247669 and nivolumab will be summarized by estimating total exposure (area under the curve), maximum concentration, total clearance, volume of distribution at steady-state, and terminal half-life, as appropriate for the data collected. Estimates for these parameters will be tabulated and summarized. Inter-participant variability and drug accumulation will be evaluated.

### 9.3.5 Immunogenicity Analyses

The immunogenicity analyses will include all participants with at least one ADA assessment, irrespective of whether or not the participant receives any treatment (Shankar et al., 2014).

The numbers and proportions of ADA-positive participants and ADA-negative participants at baseline (baseline prevalence) and after study drug administration (post-baseline incidence during both the treatment and follow-up periods) will be summarized.

- Participants are considered to be ADA positive if they are ADA negative at baseline but develop an ADA response following study drug administration (treatment-induced ADA response), or if they are ADA positive at baseline and the titer of one or more post-baseline samples is greater than the titer of the baseline sample by a scientifically reasonable margin such as at least 4-fold (treatment-enhanced ADA response).
- Participants are considered to be ADA negative if they are ADA negative at baseline and all post-baseline samples are negative, or if they are ADA positive at baseline but do not have any post-baseline samples with a titer that is greater than the titer of the baseline sample by a scientifically reasonable margin such as at least 4-fold (treatment unaffected).

The relationship between ADA status and safety, efficacy, PK, and biomarker endpoints may be analyzed and reported descriptively via subgroup analyses.

### 9.3.6 Pharmacodynamic Analyses

All PD parameters will be presented by listings and descriptive summary statistics separately by treatment group.

All analyses of PD and exploratory biomarkers will be based on the safety analysis population (Section 9.2).

For the analysis of PD biomarkers, the primary evaluation will be based on the observed change from baseline. Both actual values and estimated parameters will be presented in summary tables and graphically as deemed appropriate.

To assess predictability of a biomarker, the association between clinical outcome and the biomarker level or changes thereof will be explored.

### 9.3.7 Pharmacokinetic/Pharmacodynamic Relationships

Exploratory graphical analyses of exposure-effect relationships may be produced for selected efficacy, PD, and/or safety measurements if appropriate. A PK/PD modelling approach may be considered in order to further explore the exposure-response relationship of selected response variables. Data will be explored using linear and/or exponential models, as appropriate, in non-linear mixed effect modelling software. Additional PK analyses will be conducted as appropriate.

### 9.3.8 Other Analyses

Completion rates and reasons for missing data will be summarized for the QLQ-C30, QLQ-OES18, IL97, PGI-CI, and PGI-S at each treatment cycle by treatment arm and within the ITT population.

Visit mean summary and change from baseline analyses will be performed for all scales of the QLQ-C30, QLQ-OES18, and IL97. Summary statistics (e.g., number of participants, mean, standard deviation, median, minimum, maximum, 95% CI) of linearly transformed scores (per the EORTC scoring manual) will be calculated at all assessment time-points for each treatment arm. These analyses will be performed in the PRO-evaluable population.

Summary statistics (e.g., number of participants, proportions) will be calculated for the PGI-CI and PGI-S in the PRO-evaluable population.

#### 9.3.8.1 Exploratory Analyses of PRO-CTCAE

PRO-CTCAE analyses will be primarily descriptive, with a focus on characterizing the pattern of symptomatic treatment toxicities over the course of the study. Results from these exploratory analyses will be presented separately from the other safety analyses. PRO-CTCAE data will be analyzed at the item level in line with current NCI recommendations for data handling (Basch et al. 2014).

PRO-CTCAE data will be summarized over time. The proportion of missing data at each assessment time-point will also be summarized to facilitate interpretation of data.

The number and percentage of participants reporting each symptom and the change from baseline by category (frequency of occurrence, severity, interference) will be summarized at each assessment time-point by treatment arm. For items that are rated on a 5-point Likert scale, the maximum post-baseline score and change from baseline will be summarized by treatment arm.

Graphical representation of PRO-CTCAE data over time will also be provided.

## 9.4 INTERIM ANALYSES

For this study, blinded periodic analyses of cumulative safety data will be conducted by the JMC.

In addition, given the hypothesis-generating nature of this study, [redacted]

The interim analysis will be performed and interpreted by Sponsor study team personnel who will have full access to unblinded data. Access to treatment assignment information will follow the Sponsor's standard procedures.

*A technical document describing the statistical analyses plan will provide more details on the* planned interim analyses.

## 9.5 SUMMARIES OF CONDUCT OF STUDY

Enrollment, duration of survival follow-up, study drug administration, reasons for study drug discontinuation, and reasons for discontinuation from the study will be summarized by treatment arm for the ITT population. Major protocol deviations, including major deviations with regard to the inclusion and exclusion criteria, will be summarized by treatment arm for the ITT population.

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## 11. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

The following appendices are included in this section:

Appendix 1: Regulatory, ethical, and study oversight considerations

Appendix 2: Adverse events definitions and procedures for evaluating, follow-up, and reporting

Appendix 3: Procedures for recording adverse events

Appendix 4: Clinical laboratory tests

Appendix 5. Contraceptive guidance and collection of pregnancy information

Appendix 6: New Response Evaluation Criteria in Solid Tumors Version 1.1

Appendix 7: Risks and guidelines for adverse events associated with study drugs

Appendix 8: EORTC QLQ-C30

Appendix 9: QLQ-OES18

Appendix 10: EORTC IL97

Appendix 11: PGI-CI

Appendix 12: PGI-S

Appendix 13: PRO-CTCAE

Appendix 14: Correction formulas for QTc intervals

# Appendix 1
# Regulatory, Ethical, and Study Oversight Considerations

## 1. REGULATORY AND ETHICAL CONSIDERATIONS

### 1.1. COMPLIANCE WITH LAWS AND REGULATIONS

This study will be conducted in full conformance with the ICH E6 guideline for Good Clinical Practice and the principles of the Declaration of Helsinki, or the laws and regulations of the country in which the research is conducted, whichever affords the greater protection to the individual. The study will comply with the requirements of the ICH E2A guideline (Clinical Safety Data Management: Definitions and Standards for Expedited Reporting). Studies conducted in the United States or under a U.S. Investigational New Drug (IND) application will comply with U.S. Food and Drug Administration (FDA) regulations and applicable local, state, and federal laws. Studies conducted in the EU/EEA will comply with the EU Clinical Trial Directive (2001/20/EC).

### 1.2. INSTITUTIONAL REVIEW BOARD OR ETHICS COMMITTEE

This protocol, the Informed Consent Forms (ICFs), any information to be given to the participant (e.g., advertisements, diaries etc.), and relevant supporting information must be submitted to the IRB/EC by the Principal Investigator and reviewed and approved by the IRB/EC before the study is initiated. In addition, any participant recruitment materials must be approved by the IRB/EC.

The Principal Investigator is responsible for providing written summaries of the status of the study to the IRB/EC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/EC. Investigators are also responsible for promptly informing the IRB/EC of any protocol amendments (Section 2.3.1 of this Appendix).

The Investigator should follow the requirements for reporting all adverse events to the Sponsor. Investigators may receive written IND safety reports or other safety-related communications from the Sponsor. Investigators are responsible for ensuring that such reports are reviewed and processed in accordance with Health Authority requirements and the policies and procedures established by their IRB/EC, and archived in the site's study file.

## 1.3. INFORMED CONSENT

The Sponsor's Master Informed Consent Form (and ancillary sample ICFs such as a Child's Assent or Caregiver's Informed Consent Form, if applicable) will be provided to each site. If applicable, it will be provided in a certified translation of the local language. Participants must be informed that their participation is voluntary. Participants or their legally authorized representative will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act of 1996 (HIPAA) requirements, where applicable, and the IRB/IEC or study center. The Sponsor or its designee must review and approve any proposed deviations from the Sponsor's sample ICFs or any alternate Consent Forms proposed by the site (collectively, the "Consent Forms") before IRB/EC submission. The final IRB/EC‑approved Consent Forms must be provided to the Sponsor for Health Authority submission purposes according to local requirements. Participants must be re-consented to the most current version of the ICF(s) during their participation in the study. A copy of the ICF(s) signed by all parties must be provided to the participant or the participant's legally authorized representative.

The ICFs must be signed and dated by the participant or the participant's legally authorized representative before his or her participation in the study. The case history or clinical records for each participant shall document the informed consent process and that written informed consent was obtained prior to participation in the study.

The ICFs should be revised whenever there are changes to study procedures or when new information becomes available that may affect the willingness of the participant to take part. The final revised IRB/EC-approved ICFs must be provided to the Sponsor for Health Authority submission purposes if required as per local regulations.

If the ICFs are revised (through an amendment or an addendum) while a participant is participating in the study, the participant or a legally authorized representative may be re-consented by signing the most current version of the ICFs or the addendum, in accordance with applicable laws and IRB/EC policy. For any updated or revised ICFs, the case history or clinical records for each participant shall document the informed consent process and that written informed consent was obtained using the updated/revised ICFs for continued participation in the study. The study team will provide guidance for which participants need to re-consent in the event of an update to the ICF.

A copy of each signed ICF must be provided to the participant or the participant's legally authorized representative. All signed and dated ICFs must remain in each participant's study file or in the site file and must be available for verification by study monitors at any time.

A participant who is re-screened is not required to sign another ICF if the re-screening occurs within 60 days from the previous ICF signature date.

### Consent to Participate in the Research Biosample Repository

The ICF will contain a separate section that addresses participation in the RBR. The Investigator or authorized designee will explain to each participant the objectives, methods, and potential hazards of participation in the RBR. Participants will be told that they are free to refuse to participate and may withdraw their samples at any time and for any reason during the storage period. A separate, specific signature will be required to document a participant's agreement to provide optional RBR samples. Participants who decline to participate will not provide a separate signature.

The Investigator should document whether or not the participant has given consent to participate by completing the RBR Sample Informed Consent eCRF.

In the event of death or loss of competence of a participant who is participating in the research, the participant's samples and data will continue to be used as part of the RBR.

For sites in the United States, each ICF may also include participant authorization to allow use and disclosure of personal health information in compliance with the U.S. HIPAA. If the site utilizes a separate Authorization Form for participant authorization for use and disclosure of personal health information under the HIPAA regulations, the review, approval, and other processes outlined above apply except that IRB review and approval may not be required per study site policies.

### Approval by the Institutional Review Board or Ethics Committee

Collection, storage, and analysis of RBR samples is contingent upon the review and approval of the exploratory research and the RBR portion of the ICF by each site's IRB/EC and, if applicable, an appropriate regulatory body. If a site has not been granted approval for RBR sampling, this section of the protocol will not be applicable at that site

### Withdrawal from the Research Biosample Repository

Participants who give consent to provide samples for the RBR have the right to withdraw their samples at any time for any reason. If a participant wishes to withdraw consent to the testing of his or her samples, the Investigator must inform the Medical Monitor and Site Monitor in writing of the participant's wishes using the RBR Withdrawal Form and, if the study is ongoing, must enter the date of withdrawal on the RBR Withdrawal of Informed Consent eCRF. The participant will be provided with instructions on how to withdraw consent after the study is closed. A participant's withdrawal from Study BP42772 does not, by itself, constitute withdrawal of samples from the RBR. Likewise, a participant's withdrawal from the RBR does not constitute withdrawal from Study BP42772. Data already generated before time of withdrawal of consent to RBR will still be used.

## 1.4. CONFIDENTIALITY

Participants will be assigned a unique identifier by the Sponsor. Any participant records or datasets that are transferred to the Sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.

The participant must be informed that his/her personal study-related data will be used by the Sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant.

Medical information may be given to a participant's personal physician or other appropriate medical personnel responsible for the participant's welfare, for treatment purposes.

The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the Sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

Study data, which may include data on germline mutations, may be submitted to government or other health research databases or shared with researchers, government agencies, companies, or other groups that are not participating in this study. These data may be combined with or linked to other data and used for research purposes, to advance science and public health, or for analysis, development, and commercialization of products to treat and diagnose disease. In addition, redacted clinical study reports and other summary reports will be provided upon request.

### Confidentiality for Research Biosample Repository

Data generated from RBR samples must be available for inspection upon request by representatives of national and local Health Authorities, and Roche monitors, representatives, and collaborators, as appropriate.

Participant medical information associated with RBR samples is confidential and may only be disclosed to third parties as permitted by the ICF (or separate authorization for use and disclosure of personal health information) signed by the participant, unless permitted or required by law.

Data derived from RBR sample analysis on individual participants will generally not be provided to study Investigators unless a request for research use is granted. The aggregate results of any conducted research will be available in accordance with the effective Roche policy on study-data publication.

Genetic research data and associated clinical data may be shared with researchers who are not participating in the study or submitted to government or other health research databases for broad sharing with other researchers. Participants will not be identified by name or any other personally identifying information. Given the complexity and exploratory nature of these analyses, genetic data and analyses will not be shared with Investigators or participants unless required by law.

Any inventions and resulting patents, improvements, and/or know-how originating from the use of the RBR sample data will become and remain the exclusive and unburdened property of the Sponsor, except where agreed otherwise.

### Monitoring and Oversight Research Biosample Repository

Samples collected for the RBR will be tracked in a manner consistent with Good Clinical Practice by a quality-controlled, auditable, and appropriately validated laboratory information management system, to ensure compliance with data confidentiality as well as adherence to authorized use of samples as specified in this protocol and in the ICF. The Sponsor's monitors and auditors will have direct access to appropriate parts of records relating to participant participation in RBR for the purposes of verifying the data provided to the Sponsor. The site will permit monitoring, audits, IRB/EC review, and Health Authority inspections by providing direct access to source data and documents related to the samples.

## 1.5. FINANCIAL DISCLOSURE

Investigators will provide the Sponsor with sufficient, accurate financial information in accordance with local regulations to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate Health Authorities. Investigators are responsible for providing information on financial interests during the course of the study and for one year after completion of the study.

# 2. DATA HANDLING AND RECORD

## 2.1. DATA COLLECTION AND MANAGEMENT RESPONSIBILITIES

### 2.1.1. Data Quality Assurance

All participant data relating to the study will be recorded on printed or electronic CRF unless transmitted to the Sponsor or designee electronically (e.g., laboratory data). The Investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.

The Investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.

The Investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.

The Sponsor or designee is responsible for the data management of this study including quality checking of the data.

Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

### 2.1.2. Clinical Outcome Assessment Data

#### 2.1.2.1 Electronic Clinical Outcome Assessment Data

An electronic clinical outcome assessment (eCOA) device will be used to capture clinical outcome assessment data. The data will be transmitted automatically to a centralized database at the eCOA vendor via web or wireless transmission after data entry. The data may be reviewed by site staff via secure access to a web portal provided by the eCOA vendor.

The eCOA data will be collected using an electronic device provided by an eCOA vendor. The device is designed for entry of data in a way that is attributable, secure, and accurate, in compliance with U.S. FDA regulations for electronic records (21 CFR Part 11). In situations where there is no on-site visit required, remote options for eCOA completion (e.g., URL or phone) will be provided. System backups for data stored by the Sponsor and records retention for the study data will be consistent with the Sponsor's standard procedures.

### 2.1.3. Source Data Records

Source documents (paper or electronic) are those in which participant data are recorded and documented for the first time. They include, but are not limited to, hospital records, clinical and office charts, laboratory notes, memoranda, clinical outcome assessments (paper or eCOA), evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies of transcriptions that are certified after verification as being accurate and complete, microfiche, photographic negatives, microfilm or magnetic media, X-rays, participant files, and records kept at pharmacies, laboratories, and medico-technical departments involved in a clinical study.

Before study initiation, data to be entered directly into the eCRFs (i.e., no prior written or electronic record of the data) and considered source data must be defined in the Trial Monitoring Plan.

Source documents that are required to verify the validity and completeness of data entered into the eCRFs must not be obliterated or destroyed and must be retained per the policy for retention of records described below.

To facilitate source data verification, the Investigators and institutions must provide the Sponsor direct access to applicable source documents and reports for trial-related monitoring, Sponsor audits, and IRB/EC review. The investigational site must also allow inspection by applicable Health Authorities.

### 2.1.4. Use of Computerized Systems

When clinical observations are entered directly into an investigational site's computerized medical record system (i.e., in lieu of original hardcopy records), the electronic record can serve as the source document if the system has been validated in accordance with Health Authority requirements pertaining to computerized systems used in clinical research. An acceptable computerized data collection system allows preservation of the original entry of data. If original data are modified, the system should maintain a viewable audit trail that shows the original data as well as the reason for the change, name of the person making the change, and date of the change.

### 2.1.5. Safety Biomarker Data

Adverse event reports will not be derived from safety biomarker data by the Sponsor, and safety biomarker data will not be included in the formal safety analyses for this study. In addition, safety biomarker data will not inform decisions on participant management.

## 2.2. RETENTION OF RECORDS

Records and documents, including signed ICF, pertaining to the conduct of this study must be retained by the Investigator for at least 15 years after study completion or discontinuation of the study, or for the length of time required by relevant national or local Health Authorities, whichever is longer. After that period, the documents may be destroyed, subject to local regulations. No records may be destroyed during the retention period without the written approval of the Sponsor. No records may be transferred to another location or party without written notification to the Sponsor.

The Sponsor will retain study data for 25 years after the final study results have been reported or for the length of time required by relevant national or local Health Authorities.

## 2.3. STUDY RECORDS

The Investigator must maintain adequate and accurate records to enable the conduct of the study to be fully reconstructed, including but not limited to the protocol, protocol amendments, ICFs, and documentation of IRB/EC and governmental approval.

Roche shall also submit an Annual Safety Report once a year to the IEC and Competent Authorities according to local regulatory requirements and timelines of each country participating in the study.

### 2.3.1. Protocol Amendments

Any substantial protocol amendments will be prepared by the Sponsor. Substantial protocol amendments will be submitted to the IRB/EC and to regulatory authorities in accordance with local regulatory requirements.

Approval must be obtained from the IRB/EC and regulatory authorities (as locally required) before implementation of any changes, except for changes necessary to eliminate an immediate hazard to participants or any non-substantial changes, as defined by regulatory requirements.

### 2.3.2. Publication Policy

The results of this study may be published or presented at scientific meetings. If this is foreseen, the Investigator agrees to submit all manuscripts or abstracts to the Sponsor for approval prior to submission. This allows the Sponsor to protect proprietary information and to provide comments based on information from other studies that may not yet be available to the Investigator.

The Sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the Sponsor will generally support publication of multicenter trials only in their entirety and not as individual center data. In this case, a coordinating Investigator will be designated by mutual agreement.

Any formal publication of the study in which contribution of Sponsor personnel exceeded that of conventional monitoring will be considered as a joint publication by the Investigator and the appropriate Sponsor personnel.

Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

Any inventions and resulting patents, improvements, and/or know-how originating from the use of data from this study will become and remain the exclusive and unburdened property of the Sponsor, except where agreed otherwise.

### 2.3.3. Dissemination of Clinical Study Data

Regardless of the outcome of a study, the Sponsor is dedicated to openly providing information on the study to healthcare professionals and to the public, at scientific congresses, in clinical trial registries, and in peer-reviewed journals. The Sponsor will comply with all requirements for publication of study results. Study data may be shared with others who are not participating in this study (for more details, see Section 2.3.5), and redacted clinical study reports and other summary reports will be made available upon request, provided the requirements of Roche's global policy on data sharing have been met.

For more information, refer to the Roche Global Policy on Sharing of Clinical Trials Data at the following web site:

www.roche.com/roche_global_policy_on_sharing_of_clinical_study_information.pdf

### 2.3.4. Management of Study Quality

The Sponsor will implement a system to manage the quality of the study, focusing on processes and data that are essential to ensuring participant safety and data integrity. Prior to study initiation, the Sponsor will identify potential risks associated with critical trial processes and data and will implement plans for evaluating and controlling these risks. Risk evaluation and control will include the selection of risk-based parameters (e.g., adverse event rate, protocol deviation rate) and the establishment of quality tolerance limits for these parameters prior to study initiation. Detection of deviations from quality tolerance limits will trigger an evaluation to determine if action is needed. Details on the establishment and monitoring of quality tolerance limits will be provided in a Quality Tolerance Limit Management Plan.

### 2.3.5. Site Inspections

Site visits will be conducted by the Sponsor or an authorized representative for inspection of study data, participants' medical records, and eCRFs. The Investigator will permit national and local Health Authorities, Sponsor monitors, representatives, and collaborators, and the IRBs/ECs to inspect facilities and records relevant to this study.

## 3. ADMINISTRATIVE STRUCTURE

For information of the Joint Monitoring Committee, see Section 4.1.3 of the protocol.

## 4. STUDY AND SITE CLOSURE

The Sponsor (or designee) has the right to close the study site or terminate this study at any time. Reasons for terminating the study may include, but are not limited to, the following:

- The incidence or severity of adverse events in this or other studies indicates a potential health hazard to participants.
- Participant enrollment is unsatisfactory.

The Sponsor will notify the Investigator and Health Authorities if the study is placed on hold, or if the Sponsor decides to discontinue the study or development program.

Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The Investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the Sponsor or Investigator may include but are not limited to:

- Failure of the Investigator to comply with the protocol, the requirements of the IRB/IEC or local Health Authorities, the Sponsor's procedures, or GCP guidelines.
- Inadequate recruitment of participants by the Investigator.
- Discontinuation of further study treatment development.

# Appendix 2
# Adverse Events: Definitions and Procedures for Evaluating, Follow-up and Reporting

## 1. DEFINITION OF ADVERSE EVENTS

According to the E2A ICH guideline for Good Clinical Practice, an **adverse event** is any untoward medical occurrence in a participant or clinical investigation participant administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment.

An adverse event can therefore be:

- Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

**Events Meeting the AE Definition:**

- Deterioration in a laboratory value (hematology, clinical chemistry, or urinalysis) or other clinical test (e.g., ECG, X−ray) that is associated with symptoms or leads to a change in study treatment or concomitant treatment or discontinuation from study treatment (see Appendix 3, Section 4).
- Exacerbation of a chronic or intermittent pre-existing condition, including either an increase in frequency and/or intensity of the condition.
- New conditions detected or diagnosed after study treatment administration even though it may have been present before the start of the study.
- Adverse events that are related to a protocol-mandated intervention, including those that occur prior to assignment of study treatment (e.g., screening invasive procedures such as biopsies).
- "Lack of efficacy" or "failure of expected pharmacological action" per se will not be reported as an AE or SAE unless the progression is unexpectedly accelerated and not in line with the natural history of the disease. If the “Lack of efficacy” would not require safety reporting such instances will be captured in the efficacy assessments. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfill the definition of an AE or SAE.

**Events NOT Meeting the AE Definition:**

- Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the Investigator to be more severe than expected for the participant’s condition.
- The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant’s condition.

- Medical or surgical procedure (e.g., endoscopy, appendectomy): the condition that leads to the procedure is an AE.
- Situations where an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

## 2. DEFINITION OF SERIOUS ADVERSE EVENTS

If an event is not an AE per definition above, then it cannot be a serious adverse event (SAE) even if serious conditions are met (e.g., hospitalization for signs/symptoms of the disease under study, death due to progression of disease).

A serious adverse event is defined as any untoward medical occurrence that at any dose:

- **Results in death.**
- **Is life-threatening.**

  The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it was more severe.
- **Requires inpatient hospitalization or prolongation of existing hospitalization** (see Appendix 3).

  In general, hospitalization signifies that the participant has been admitted to the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious.

  Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.
- **Results in persistent or significant disability/incapacity**

  Disability means substantial disruption of the participant's ability to conduct normal life functions.

  This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g., sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.
- **Is a congenital anomaly/birth defect**.
- **Other significant events**:

Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.

Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

## 3. RECORDING OF ADVERSE EVENT AND/OR SERIOUS ADVERSE EVENT

When an AE/SAE occurs, it is the responsibility of the Investigator to review all documentation (e.g., hospital progress notes, laboratory reports, and diagnostics reports) related to the event.

The Investigator will then record all relevant AE/SAE information in the CRF.

It is **not** acceptable for the Investigator to send photocopies of the participant's medical records to Medical Monitor in lieu of completion of the eCRF.

There may be instances when copies of medical records for certain cases are requested by the Sponsor. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to the Sponsor.

The Investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

### 3.1. ASSESSMENT OF SEVERITY

The terms "severe" and "serious" are not synonymous. Severity refers to the intensity of an adverse event (rated as mild, moderate, or severe, or according to a pre-defined grading criteria [e.g., National Cancer Institute Common Terminology Criteria for Adverse Events [NCI CTCAE] criteria); the event itself may be of relatively minor medical significance (such as severe headache without any further findings).

Severity and seriousness need to be independently assessed for each adverse event recorded on the eCRF.

Serious adverse events are required to be reported by the Investigator to the Sponsor immediately (i.e., no more than 24 hours after learning of the event.

The adverse event severity grading scale for the NCI CTCAE (v5.0) will be used for assessing adverse event severity. Table 1 will be used for assessing severity for adverse events that are not specifically listed in the NCI CTCAE.

**Table 1 Adverse Event Severity Grading Scale**

| Grade | Severity |
|---|---|
| 1 | Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; or intervention not indicated |
| 2 | Moderate; minimal, local, or non-invasive intervention indicated; or limiting age-appropriate instrumental activities of daily living[a] |
| 3 | Severe or medically significant, but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; or limiting self-care activities of daily living[b,c] |
| 4 | Life-threatening consequences or urgent intervention indicated[d] |
| 5 | Death related to adverse event[d] |

NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events.

Note: Based on the NCI CTCAE (v5.0), which can be found at: https://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_8.5x11.pdf

[a] Instrumental activities of daily living refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

[b] Examples of self-care activities of daily living include bathing, dressing and undressing, feeding one's self, using the toilet, and taking medications, as performed by patients who are not bedridden.

[c] If an event is assessed as a "significant medical event," it must be reported as a serious adverse event (see Section 6 of this appendix for reporting instructions), per the definition of serious adverse event in Section 2.

[d] Grade 4 and 5 events must be reported as serious adverse events (see Section 6 for reporting instructions), per the definition of serious adverse event in Section 2. Grade 4 laboratory abnormalities would only be reported as SAEs if these meets one or more of the conditions outlined in Section 2 (Definition of Serious Adverse Events) of this appendix.

## 3.2. ASSESSMENT OF CAUSALITY

Investigators should use their knowledge of the participant, the circumstances surrounding the event, and an evaluation of any potential alternative causes to determine whether an adverse event is considered to be related to the study treatment, indicating "yes" or "no" accordingly. The following guidance should be taken into consideration:

- Temporal relationship of event onset to the initiation of study treatment.
- Course of the event, considering especially the effects of discontinuation of study treatment, or reintroduction of study treatment.
- Known association of the event with the study treatment or with similar treatments.
- Known association of the event with the disease under study.

- Presence of risk factors in the participant or use of concomitant medications known to increase the occurrence of the event.
- Presence of non-treatment-related factors that are known to be associated with the occurrence of the event.

For participant receiving combination therapy, causality will be assessed individually for each protocol-mandated therapy.

## 4. FOLLOW-UP OF AES AND SAES

The Investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the Medical Monitor to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.

If a participant dies during participation in the study or during a recognized follow-up period, the Investigator will provide the Sponsor with a copy of any post-mortem findings including histopathology.

New or updated information will be recorded in the originally completed eCRF.

The Investigator will submit any updated SAE data to the Sponsor within 24 hours of receipt of the information.

## 5. IMMEDIATE REPORTING REQUIREMENTS FROM INVESTIGATOR TO SPONSOR

Certain events require immediate reporting to allow the Sponsor to take appropriate measures to address potential new risks in a clinical trial. The Investigator must report such events to the Sponsor immediately; under no circumstances should reporting take place more than 24 hours after the Investigator learns of the event. The following is a list of events that the Investigator must report to the Sponsor within 24 hours after learning of the event, regardless of relationship to study treatment:

- Serious adverse events
- Non-serious adverse events of special interest (NSAESI)
- Pregnancies (see Section 8.3.5).

The Investigator must report new significant follow-up information for these events to the Sponsor immediately (i.e., no more than 24 hours after becoming aware of the information). New significant information includes the following:

- New signs or symptoms or a change in the diagnosis.
- Significant new diagnostic test results.

- Change in causality based on new information.
- Change in the event's outcome, including recovery.
- Additional narrative information on the clinical course of the event.

Investigators must also comply with local requirements for reporting serious adverse events to the local Health Authority and IRB/EC.

## 5.1 REPORTING REQUIREMENTS OF SERIOUS ADVERSE EVENTS, AND NON-SERIOUS ADVERSE EVENTS OF SPECIAL INTEREST

**Events that Occur prior to Study Treatment Initiation**

After informed consent has been obtained but prior to initiation of study treatment, only serious adverse events caused by a protocol-mandated intervention should be reported. The Serious Adverse Event/Adverse Event of Special Interest Reporting Form provided to Investigators should be completed and submitted to the Serious Adverse Event Responsible immediately (i.e., no more than 24 hours after learning of the event).

**Events that Occur after Study Treatment Initiation**

For reports of serious adverse events and non-serious adverse events of special interest (Section 8.3.6) that occur after initiation of study treatment (Section 8.3.1), Investigators should record all case details that can be gathered immediately (i.e., within 24 hours after learning of the event) on the appropriate Adverse Event of Special Interest/Serious Adverse Event eCRF form and submit the report via the electronic data capture (EDC) system. A report will be generated and sent to the Sponsor's Safety Risk Management department.

In the event that the EDC system is unavailable, the Serious Adverse Event/Adverse Event of Special Interest Reporting Form provided to Investigators should be completed and submitted to the Serious Adverse Event Responsible immediately (i.e., no more than 24 hours after learning of the event).

Once the EDC system is available, all information will need to be entered and submitted via the EDC system.

**Reporting of Post-Study Adverse Events and Serious Adverse Events**

After the end of the adverse event reporting period (see Section 8.3.1), all deaths, regardless of cause, should be reported through use of the Long-Term Survival Follow-Up eCRF.

In addition, if the Investigator becomes aware of a SAE that is believed to be related to prior study treatment, the event should be reported directly to the Sponsor or its designee, either by faxing or by scanning and emailing the SAE Reporting Form using the fax number or email address provided to Investigators.

## 5.2 REPORTING REQUIREMENTS FOR CASES OF ACCIDENTAL OVERDOSE

Accidental overdose and medication error (hereafter collectively referred to as "special situations"), are defined as follows:

- Accidental overdose: accidental administration of a drug in a quantity that is higher than the assigned dose.
- Medication error: accidental deviation in the administration of a drug.
    - In some cases, a medication error may be intercepted prior to administration of the drug.

Special situations are not in themselves adverse events, but may result in adverse events. Each adverse event associated with a special situation should be recorded separately on the Adverse Event eCRF. If the associated adverse event fulfills seriousness criteria, the event should be reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event). For this study, adverse events associated with special situations should be recorded as described below for each situation:

- Accidental overdose: Enter the adverse event term. Check the "Accidental overdose" and "Medication error" boxes.
- Medication error that does not qualify as an overdose: Enter the adverse event term. Check the "Medication error" box.
- Medication error that qualifies as an overdose: Enter the adverse event term. Check the "Accidental overdose" and "Medication error" boxes.

In addition, all special situations associated with the study drugs, regardless of whether they result in an adverse event, should be recorded on the Adverse Event eCRF and should be recorded as described below:

- Accidental overdose: Enter the “Blinded Drug” and "accidental overdose" as the event term. Check the "Accidental overdose" and "Medication error" boxes.
- Medication error that does not qualify as an overdose: Enter the name of the drug administered and a description of the error (e.g., wrong dose administered, wrong dosing schedule, incorrect route of administration, wrong drug, expired drug administered) as the event term. Check the "Medication error" box.
- Medication error that qualifies as an overdose: Enter the drug name and "accidental overdose" as the event term. Check the "Accidental overdose" and

"Medication error" boxes. Enter a description of the error in the additional case details.

- Intercepted medication error: Enter the drug name and "intercepted medication error" as the event term. Check the "Medication error" box. Enter a description of the error in the additional case details.

As an example, an accidental overdose that resulted in a headache would require the completion of two Adverse Event eCRF pages, one to report the accidental overdose and one to report the headache. The "Accidental overdose" and "Medication error" boxes would need to be checked on both eCRF pages.

## 6. EXPEDITED REPORTING TO HEALTH AUTHORITIES, INVESTIGATORS, INSTITUTIONAL REVIEW BOARDS, AND ETHICS COMMITTEES

The Sponsor will promptly evaluate all serious adverse events and NSAESI against cumulative product experience to identify and expeditiously communicate possible new safety findings to Investigators, IRBs, ECs, and applicable Health Authorities based on applicable legislation.

To determine reporting requirements for single adverse event cases, the Sponsor will assess the expectedness of these events through use of the reference safety information in the documents listed below:

| Drug | Document |
|---|---|
| RO7121661 | RO7121661 Investigator's Brochure |
| RO7247669 | RO7247669 Investigator’s Brochure |
| Nivolumab | EU SmPC |

The Sponsor will compare the severity of each event and the cumulative event frequency reported for the study with the severity and frequency reported in the applicable reference document.

Reporting requirements will also be based on the Investigator's assessment of causality and seriousness, with allowance for upgrading by the Sponsor as needed.

# Appendix 3
# Procedures for Recording Adverse Events

Investigators should use correct medical terminology/concepts when recording AEs on the Adverse Event eCRF. Avoid colloquialisms and abbreviations.

Only one AE term should be recorded in the event field on the Adverse Event eCRF.

## 1. DIAGNOSIS VERSUS SIGNS AND SYMPTOMS

### 1.1. INFUSION-RELATED REACTIONS

Adverse events that occur during or after study drug administration and are judged to be related to study treatment infusion should be captured as a diagnosis (e.g., infusion-related reaction [IRR]) on the Adverse Event eCRF. If possible, avoid ambiguous terms such as “systemic reaction.” Associated signs and symptoms should be recorded on the dedicated Infusion-Related Reaction eCRF. If a participant experiences both a local and systemic reaction to the same dose of study drug, each reaction should be recorded separately on the Adverse Event eCRF, with signs and symptoms also recorded separately on the dedicated Infusion-Related Reaction eCRF.

### 1.2. OTHER ADVERSE EVENTS

For AEs other than IRRs (see Section 1.1), a diagnosis (if known) should be recorded on the Adverse Event eCRF rather than individual signs and symptoms (e.g., record only liver failure or hepatitis rather than jaundice, asterixis, and elevated transaminases). However, if a constellation of signs and/or symptoms cannot be medically characterized as a single diagnosis or syndrome at the time of reporting, each individual event should be recorded on the Adverse Event eCRF. If a diagnosis is subsequently established, all previously reported AEs based on signs and symptoms should be nullified and replaced by one AE report based on the single diagnosis, with a starting date that corresponds to the starting date of the first symptom of the eventual diagnosis.

## 2. ADVERSE EVENTS OCCURRING SECONDARY TO OTHER EVENTS

In general, AEs occurring secondary to other events (e.g., cascade events or clinical sequelae) should be identified by their primary cause, with the exception of severe or serious secondary events. However, medically significant AEs occurring secondary to an initiating event that are separated in time should be recorded as independent events on the Adverse Event eCRF. For example:

- If vomiting results in mild dehydration with no additional treatment in a healthy adult, only vomiting should be reported on the eCRF.
- If vomiting results in severe dehydration, both events should be reported separately on the eCRF.

- If a severe gastrointestinal hemorrhage leads to renal failure, both events should be reported separately on the eCRF.
- If dizziness leads to a fall and subsequent fracture, all three events should be reported separately on the eCRF.

All AEs should be recorded separately on the Adverse Event eCRF if it is unclear as to whether the events are associated.

## 3. PERSISTENT OR RECURRENT ADVERSE EVENTS

A persistent AE is one that extends continuously, without resolution, between participant evaluation time-points. Such events should only be recorded once on the Adverse Event eCRF. The initial severity of the event should be recorded, and the severity should be updated to reflect the most extreme severity any time the event worsens. If the event becomes serious, the Adverse Event eCRF should be updated to reflect this.

A recurrent AE is one that resolves between participant evaluation time-points and subsequently recurs. Each recurrence of an AE should be recorded separately on the Adverse Event eCRF.

## 4. ABNORMAL LABORATORY VALUES

Not every laboratory abnormality qualifies as an adverse event. A laboratory test result should be reported as an adverse event if it meets any of the following criteria:

- Accompanied by clinical symptoms.
- Results in a change in study treatment (e.g., dosage modification, treatment interruption, or treatment discontinuation).
- Results in a medical intervention (e.g., potassium supplementation for hypokalemia) or a change in concomitant therapy.
- Clinically significant in the Investigator's judgment.

It is the Investigator's responsibility to review all laboratory findings. Medical and scientific judgment should be exercised in deciding whether an isolated laboratory abnormality should be classified as an adverse event.

If a clinically significant laboratory abnormality is a sign of a disease or syndrome (e.g., alkaline phosphatase and bilirubin 5 times the upper limit of normal [ULN] associated with cholecystitis), only the diagnosis (i.e., cholecystitis) should be recorded on the Adverse Event eCRF.

If a clinically significant laboratory abnormality is not a sign of a disease or syndrome, the abnormality itself should be recorded on the Adverse Event eCRF, along with a descriptor indicating if the test result is above or below the normal range (e.g., "elevated potassium", as opposed to "abnormal potassium"). If the laboratory abnormality can be characterized by a precise clinical term per standard definitions, the clinical term should be recorded as the AE. For example, an elevated serum potassium level of 7.0 mEq/L should be recorded as “hyperkalemia.”

Observations of the same clinically significant laboratory abnormality from visit to visit should not be repeatedly recorded on the Adverse Event eCRF, unless the etiology changes. The initial severity of the event should be recorded, and the severity or seriousness should be updated any time the event worsens.

## 5. ABNORMAL VITAL SIGN VALUES

Not every vital sign abnormality qualifies as an AE. A vital sign result should be reported as an AE if it meets any of the following criteria:

- Accompanied by clinical symptoms.
- Results in a change in study treatment (e.g., dosage modification, treatment interruption, or treatment discontinuation).
- Results in a medical intervention or a change in concomitant therapy.
- Clinically significant in the Investigator’s judgment.

It is the Investigator’s responsibility to review all vital sign findings. Medical and scientific judgment should be exercised in deciding whether an isolated vital sign abnormality should be classified as an adverse event.

If a clinically significant vital sign abnormality is a sign of a disease or syndrome (e.g., high blood pressure), only the diagnosis (i.e., hypertension) should be recorded on the Adverse Event eCRF.

Observations of the same clinically significant vital sign abnormality from visit to visit should not be repeatedly recorded on the Adverse Event eCRF, unless the etiology changes. The initial severity of the event should be recorded, and the severity or seriousness should be updated any time the event worsens.

## 6. ABNORMAL LIVER FUNCTION TESTS

The finding of an elevated ALT or AST ($>3\times$ULN) in combination with either an elevated total bilirubin ($>2\times$ULN) or clinical jaundice in the absence of cholestasis or other causes of hyperbilirubinemia is considered to be an indicator of severe liver injury.

Therefore, Investigators must report as an adverse event the occurrence of either of the following:

- Treatment-emergent ALT or AST $>3\times$ ULN in combination with total bilirubin $>2\times$ ULN.
- Treatment-emergent ALT or AST $>3\times$ ULN in combination with clinical jaundice.
- For participants who have liver metastases or are receiving hepatotoxic concomitant medications, Investigators must report as an AE the occurrence of either of the following:
    - Treatment-emergent ALT or AST $>5\times$ ULN value in combination with total bilirubin $>2\times$ ULN (of which $\geq 35\%$ is direct bilirubin).
    - Treatment-emergent ALT or AST $>5\times$ ULN value in combination with clinical jaundice.

The most appropriate diagnosis or (if a diagnosis cannot be established) the abnormal laboratory values should be recorded on the Adverse Event eCRF (see Appendix 2) and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event), either as an SAE or a non-serious adverse event of special interest (Section 8.3.6).

## 7. DEATHS

For this protocol, mortality is an efficacy endpoint. Deaths that occur during the protocol-specified adverse event reporting period (see Section 5 of Appendix 2) that are attributed by the Investigator solely to progression of squamous cell carcinoma of the esophagus should be recorded only on the Death Attributed to Progressive Disease eCRF. All other on-study deaths, regardless of relationship to study treatment, must be recorded on the Adverse Event eCRF and immediately reported to the Sponsor (see Section 5 of Appendix 2).

Death should be considered an outcome and not a distinct event. The event or condition that caused or contributed to the fatal outcome should be recorded as the single medical concept on the Adverse Event eCRF. Generally, only one such event should be reported. If the cause of death is unknown and cannot be ascertained at the time of reporting, “unexplained death” should be recorded on the Adverse Event eCRF. If the cause of death later becomes available (e.g., after autopsy), “unexplained death” should be replaced by the established cause of death. The term "sudden death" should not be used unless combined with the presumed cause of death (e.g., "sudden cardiac death").

## 8. PREEXISTING MEDICAL CONDITIONS

A preexisting medical condition is one that is present at the screening visit for this study. Such conditions should be recorded on the General Medical History and Baseline Conditions eCRF.

A preexisting medical condition should be recorded as an AE only if the frequency, severity, or character of the condition worsens during the study. When recording such events on the Adverse Event eCRF, it is important to convey the concept that the preexisting condition has changed by including applicable descriptors (e.g., “more frequent headaches”).

## 9. LACK OF EFFICACY OR WORSENING OF ADVANCED OR METASTATIC SQUAMOUS CELL CARCINOMA OF THE ESOPHAGUS

Events that are clearly consistent with the expected pattern of progression of the underlying disease should not be recorded as AEs. These data will be captured as efficacy assessment data only. In most cases, the expected pattern of progression will be based on criteria (e.g., RECIST. In rare cases, the determination of clinical progression will be based on symptomatic deterioration. However, every effort should be made to document progression using objective criteria. If there is any uncertainty as to whether an event is due to progressive disease, it should be reported as an AE.

## 10. HOSPITALIZATION OR PROLONGED HOSPITALIZATION

Any AE that results in hospitalization or prolonged hospitalization should be documented and reported as an SAE (per the definition of serious adverse event in Appendix 2), except as outlined below.

An event that leads to hospitalization under the following circumstances should not be reported as an AE or am SAE:

- Hospitalization for respite care.
- Planned hospitalization required by the protocol (e.g., for study treatment administration).
- Hospitalization for a preexisting condition, provided that all of the following criteria are met:

  The hospitalization was planned prior to the study or was scheduled during the study when elective surgery became necessary because of the expected normal progression of the disease.

  The participant has not suffered an AE.
- Hospitalization due solely to progression of the underlying cancer.

An event that leads to hospitalization under the following circumstances is not considered to be an SAE, but should be reported as an adverse event instead:

- Hospitalization for an AE that would ordinarily have been treated in an outpatient setting had an outpatient clinic been available.

## 11. PATIENT-REPORTED OUTCOME DATA (COA DATA REPORTED DIRECTLY BY PATIENTS)

Adverse event reports will not be derived from PRO data by the Sponsor, and safety analyses will not be performed using PRO data. Sites are not expected to review the PRO data.

# Appendix 4
# Clinical Laboratory Tests

The tests detailed in Table 1 will be performed by the local laboratory unless otherwise specified.

Protocol-specific requirements for inclusion or exclusion of participants are detailed in Sections 5.1 and 5.2, respectively, of the protocol.

Additional tests may be performed at any time during the study as determined necessary by the Investigator or required by local regulations.

## Table 1 Protocol-Required Safety Laboratory Assessments

| Laboratory Assessments | Parameters |
|---|---|
| Hematology | • Leucocytes, erythrocytes, hemoglobin, hematocrit, platelets, differential count (neutrophils, eosinophils, basophils, monocytes, lymphocytes, other cells). |
| Clinical chemistry | • Sodium, potassium, chloride, bicarbonate (only required if considered standard of care for the site and in situations where the participant's safety is at risk), glucose, urea or blood urea nitrogen, serum creatinine, protein, serum albumin, phosphate, calcium, total and direct bilirubin, alkaline phosphatase, alanine aminotransferase, aspartate aminotransferase, urate, lactate dehydrogenase, creatine kinase, creatine kinase MB, troponin I and/or troponin T, eGFR determined using the MDRD formula[a], GGT, magnesium, CRP, ferritin. |
| Coagulation | • INR or prothrombin time and activated partial prothrombin time; additional coagulation parameters (i.e., antithrombin III [antigenic or chromogenic], fibrinogen, fibrin degradation products, D-dimer) may be assessed according to clinical judgment. |
| Viral serology | • HIV, hepatitis B surface antigen (HBsAg), total hepatitis B core antibody (HBcAb), hepatitis C virus (HCV) antibody. |
| Lipid panel | • Cholesterol, LDL cholesterol, high-density lipoprotein cholesterol, triglycerides. |
| Thyroid hormones | • Free T4, TSH, free T3 (alternatively total T3 if free T3 is not performed) |
| Quantitative immunoglobulins | • IgA, IgG, IgM, IgE |
| Pregnancy test | • All women of childbearing potential (including those who have had a tubal occlusion/ ligation) will have a blood pregnancy test at screening. During the study treatment, a pregnancy test (urine or blood) will be performed as indicated in the SoA and at least every 4 weeks. An additional at-home pregnancy test will be conducted 5 months after the final dose, as indicated in the SoA. If a urine pregnancy test is positive, it must be confirmed by a blood pregnancy test. |

| Laboratory Assessments | Parameters |
|---|---|
| Urinalysis | • Specific gravity<br>• Dipstick: pH, glucose, protein or albumin, blood, ketones<br>• If there is a clinically significant positive result (confirmed by a positive repeated sample), urine will be sent to the laboratory for microscopy and culture. If there is an explanation for the positive dipstick results (e.g., menses), it should be recorded and there is no need to perform microscopy and culture.<br>• Microscopic examination (sediment, red blood cells, white blood cells, casts, crystals, epithelial cells, bacteria), if blood or protein is abnormal. |
| Other tests | • sCD25 (optional, only in case of a suspected hemophagocytic lymphohistiocytosis/macrophage activation syndrome)<br>• IgE and tryptase (only in case of IRRs or anaphylaxis; see SoAs in Section 1.3). |
| Auto-antibody panel | • Anti-nuclear antibody, anti-double-stranded deoxyribonucleic acid (DNA), circulating anti-neutrophil cytoplasmic antibody (cANCA), and perinuclear anti-neutrophil cytoplasmic antibody (pANCA) (panel based on local availability).<br>• The auto-antibody panel will be assessed, if possible locally. If not available locally the test can be done centrally.<br>• In participants who develop signs and/or symptoms suggestive of autoimmune disease while on treatment or Grade ≥ 2 immune-mediated AEs, the auto-antibody panel should be repeated.<br>• Participants with confirmed positive serology of at least one of the auto-antibody panel during the course of the study should be discussed between Medical Monitor and Investigators, and if judged clinically relevant could be referred to a specialist to exclude an underlying autoimmune disease. |

[a] Estimated GFR = 175 × standardized $S_{cr}^{-1.154}$ × $age^{-0.203}$ × 1.212 [if black] × 0.742 [if female]; Scr (serum creatinine) = mg/dL; age = years.

In case of Grade ≥ 2 IRR, samples as indicated in Section 1.3 of the protocol are to be analyzed by the local laboratory.

In case IgE or tryptase cannot be analyzed locally, the tests can be done centrally.

The results of each test must be entered into the CRF.

Investigators must document their review of each laboratory safety report.

Based on continuous analysis of the data in this study, any sample type not considered to be critical for safety may be stopped at any time if the data from the samples collected does not produce useful information.

## Additional Statistical Considerations for Clinical Laboratory Data

### Standard Reference Ranges and Transformation of Data

Potential analysis considerations for analyzing laboratory data includes the use of standard reference ranges and potential transformation of data for specific laboratory tests.

In this scenario, Roche standard reference ranges, rather than the reference ranges of the Investigator, can be used for specific parameters. For these parameters, the measured laboratory test result will be assessed directly using the Roche standard reference range. Certain laboratory parameters will be transformed to Roche's standard reference ranges.

A transformation will be performed on certain laboratory tests that lack sufficiently common procedures and have a wide range of Investigator ranges, e.g., enzyme tests that include AST, ALT, and alkaline phosphatase and total bilirubin. Since the standard reference ranges for these parameters have a lower limit of zero, only the upper limits of the ranges will be used in transforming the data.

### Definition of Laboratory Abnormalities

For all laboratory parameters included in the analysis described above, there exists a Roche predefined standard reference range. Laboratory values falling outside this standard reference range will be labeled "H" for high or "L" for low in participant listings of laboratory data.

In addition to the standard reference range, a marked reference range has been predefined by Roche for these laboratory parameters. The marked reference range is broader than the standard reference range. Values falling outside the marked reference range that also represent a defined change from baseline will be considered marked laboratory abnormalities (i.e., potentially clinically relevant). If a baseline value is not available for a participant, the midpoint of the standard reference range will be used as the participant's baseline value for the purposes of determining marked laboratory abnormalities. Marked laboratory abnormalities will be labeled in the participant listings as "HH" for very high or "LL" for very low.

# Appendix 5
# Contraceptive Guidance and Collection of Pregnancy Information

## 1. DEFINITIONS

### Woman of Childbearing Potential (WOCBP)

A woman is considered fertile following menarche and until becoming post-menopausal unless permanently sterile. The definition of childbearing potential may be adapted for alignment with local guidelines or requirements.

### Women in the following categories are considered to be women of non-childbearing potential

a) Pre-menarchal

b) Pre-menopausal female with one of the following:

- Documented hysterectomy.
- Documented bilateral salpingectomy.
- Documented bilateral oophorectomy.

  Note: Documentation can come from the site personnel's: review of participant's medical records, medical examination, or medical history interview.

c) Post-menopausal female

- A post-menopausal state is defined as no menses for ≥ 12 months without an alternative medical cause other than menopause. A high follicle-stimulating hormone (FSH) level in the post-menopausal range may be used to confirm a post-menopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.
- Females on HRT and whose menopausal status is in doubt will be required to use one of the non-hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of post-menopausal status before study enrollment.

## 2. CONTRACEPTION GUIDANCE

### Female Participants

Female participants of childbearing potential are eligible to participate if they agree to use highly effective method of contraception consistently and correctly as described in Table 1 below.

Per ICH M3(R2), highly effective methods of birth control are defined as those, alone or in combination, that result in a low failure rate (i.e. less than 1% per year) when used consistently and correctly as described in Table 1 below.

### Table 1 Highly Effective Contraceptive Methods

| **Highly Effective Contraceptive Methods That Are User-Dependent[a]**<br>(Failure rate of < 1% per year when used consistently and correctly) |
|---|
| Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation:<br>○ Oral<br>○ Intravaginal<br>○ Transdermal<br>• Progestogen-only hormonal contraception associated with inhibition of ovulation:<br>○ Oral<br>○ Injectable |
| **Highly Effective Methods That Are User-Independent**<br>(Failure rate of < 1% per year) |
| • Implantable progestogen-only hormonal contraception associated with inhibition of ovulation[a]<br>• Intrauterine device (IUD)<br>• Intrauterine hormone-releasing system (IUS)<br>• Bilateral tubal occlusion/ ligation<br>**Vasectomized partner**<br>A vasectomized partner is a highly effective contraception method provided that the partner is the sole male sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.<br>**Sexual abstinence**<br>Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatment. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant. |

| Acceptable Birth Control Methods Which May Not Be Considered As Highly Effective<br>(Failure rate of > 1% per year when used consistently and correctly) |
|---|
| • Progestogen-only oral hormonal contraception, where inhibition of ovulation is not the primary mode of action<br>• Male or female condom with or without spermicide [b]<br>• Cap, diaphragm or sponge with spermicide [b] |

a) Hormonal contraception may be susceptible to interaction with the IMP, which may reduce the efficacy of the contraception method.

   Typical use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for participants participating in clinical studies.

b) A combination of male condom with either cap, diaphragm or sponge with spermicide (double barrier methods) are also considered acceptable, but not highly effective, birth control methods. i.e., when the risk of teratogenicity and genotoxicity is unlikely.

## 3. PREGNANCY TESTING

For WOCBP enrolled in the study, blood sample and urine pregnancy tests will be performed according to Schedule of Activity tables (see Section 1.3). If a urine pregnancy test is positive, it must be confirmed by a blood pregnancy test.

Pregnancy testing will be performed whenever a menstrual cycle is missed or when pregnancy is otherwise suspected and according to local practice.

## 4. COLLECTION OF PREGNANCY INFORMATION

### Male participants with partners who become pregnant

The Investigator will attempt to collect pregnancy information on any male participant's female partner who becomes pregnant while the male participant is in this study or within 5 months after the final dose of study drug (see Section 8.3.5 Pregnancy).

Attempts should be made to collect and report details of the course and outcome of any pregnancy in the partner of a male participant exposed to study treatment. The Investigator will record pregnancy information on the Clinical Trial Pregnancy Reporting Form and submit it to the Sponsor within 24 hours of learning of the partner's pregnancy. When permitted by the site, the pregnant partner would need to sign an Authorization for Use and Disclosure of Pregnancy Health Information to allow for follow-up on her pregnancy. If the authorization has been signed, the Investigator should update the Clinical Trial Pregnancy Reporting Form with additional information on the course and outcome of the pregnancy when available. An Investigator who is contacted by the male participant or his pregnant partner may provide information on the risks of the pregnancy and the possible effects on the fetus, to support an informed decision in cooperation with the treating physician and/or obstetrician. The female partner will be followed to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to the Sponsor. Monitoring of the participant's partner should continue until conclusion of the pregnancy. Any termination of the pregnancy will be reported regardless of fetal status (presence or absence of anomalies) or indication for procedure.

**Female participants who become pregnant**

The Investigator will collect pregnancy information on any female participant, who becomes pregnant while participating in this study (see Section 8.3.5 Pregnancy). Information will be recorded on the appropriate form and submitted to the Sponsor within 24 hours of learning of a participant's pregnancy. The participant will be followed to determine the outcome of the pregnancy. The Investigator will collect follow-up information on the participant and the neonate, which will be forwarded to the Sponsor. Monitoring of the participant should continue until conclusion of the pregnancy. Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for procedure.

While pregnancy itself is not considered to be an AE or SAE, and should not be recorded on the AE eCRF, any pregnancy complication will be reported as an AE or SAE. A spontaneous abortion is always considered to be an SAE and will be reported as such. Any post-study pregnancy related SAE considered reasonably related to the study treatment by the Investigator, will be reported to the Sponsor as described in Appendix 2. While the Investigator is not obligated to actively seek this information in former study participants, he/she may learn of an SAE through spontaneous reporting.

Any female participant who becomes pregnant while participating in the study will discontinue study treatment.

## 5 ABORTIONS

Any spontaneous abortion should be classified as a serious adverse event (as the Sponsor considers spontaneous abortions to be medically significant events), recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5 of Appendix 2).

Any induced abortion due to maternal toxicity and/or embryo-fetal toxicity should also be classified as serious adverse event, recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5 of Appendix 2).

Elective or therapeutic abortion not associated with an underlying maternal or embryofetal toxicity (e.g., induced abortion for personal reasons) does not require expedited reporting but should be reported as outcome of pregnancy on the Clinical Trial Pregnancy Reporting Form.

## 6 CONGENITAL ANOMALIES/BIRTH DEFECTS

Any congenital anomaly/birth defect in a child born to a female participant or female partner of a male participant exposed to study treatment should be classified as a serious adverse event, recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event).

# Appendix 6
# New Response Evaluation Criteria in Solid Tumors Version 1.1 Modified Excerpt from Original Publication with Addition of Supplementary Explanations

## 1. MEASURABILITY OF TUMOR AT BASELINE

### 1.1 DEFINITIONS

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

#### 1.1.1 Measurable Tumor Lesions

Tumor 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 computed tomography (CT) or magnetic resonance imaging (MRI) scan (CT/MRI scan slice thickness/interval no greater than 5 mm).
- 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 $\geq$15 mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be not greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed. See also Section 2.2 on 'Baseline documentation of target and non-target lesions' for information on lymph node measurement.

#### 1.1.2 Non-measurable Tumor Lesions

Non-measurable tumor lesions encompass small lesions (longest diameter $<$10 mm or pathological lymph nodes with $\geq$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, peritoneal spread, and abdominal masses/abdominal organomegaly identified by physical exam that is not measurable by reproducible imaging techniques.

### 1.1.3 Special Considerations Regarding Lesion Measurability

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

Bone lesions:

- Bone scan, positron emission tomography 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) because 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 participant, these are preferred for selection as target lesions.

Lesions with previous local treatment:

- Tumor 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.

## 1.2 TARGET LESIONS: SPECIFICATIONS BY METHODS OF MEASUREMENTS

### 1.2.1 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.

### 1.2.2 Method of Assessment

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during study. Imaging based evaluation should always be the preferred option.

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 color photography including a ruler to estimate the size of the lesion is suggested.

Chest x-ray: Chest CT is preferred over chest x-ray, particularly when progression is an important endpoint, because 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.

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 on the basis of the assumption that CT slice thickness is 5 mm or less. 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.

If before enrollment it is known that a participant is unable to undergo CT scans with intravenous contrast because of allergy or renal insufficiency, the decision as to whether a non-contrast CT or MRI (without intravenous contrast) will be used to evaluate the participant at baseline and during study, should be guided by the tumor type under investigation and the anatomic location of the disease. For participants 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) will be performed, should also be based on the tumor type, anatomic location of the disease and should be optimized to allow for comparison to the previous 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 participant should be considered not evaluable from that point forward.

Ultrasound: Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement.

# 2. TUMOR RESPONSE EVALUATION

## 2.1. ASSESSMENT OF OVERALL TUMOR BURDEN AND MEASURABLE DISEASE

To assess objective response or future progression, it is necessary to estimate the overall tumor burden at baseline and use this as a comparator for subsequent measurements. Measurable disease is defined by the presence of at least one measurable lesion (as detailed in Section 1.1.1).

## 2.2. 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 2 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 participants have only one or 2 organ sites involved a maximum of 2 (one site) and 4 lesions (2 sites), respectively, will be recorded. Other lesions (albeit measurable) in that organ will be recorded as non-measurable lesions (even if size is $\geq$ 10 mm by CT scan).

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 reproducible in 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.

Lymph nodes merit special mention because they are normal anatomical structures which may be visible by imaging even if not involved by tumor. As noted in Section 1.1.1, pathological nodes which are defined as measurable and may be identified as target lesions must meet the criterion of a short axis of ≥ 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 tumor. Nodal size is normally reported as 2 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, sagittal, or coronal). The smaller of these measures is the short axis. For example, an abdominal node which is reported as being 20 mm $\times$ 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. All other pathological nodes (those with short axis ≥ 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 characterize any objective tumor 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' (see also Section 2.3.4).

In addition, it is possible to record multiple non-target lesions involving the same organ as a single item on the case report form (e.g., 'multiple enlarged pelvic lymph nodes' or 'multiple liver metastases').

## 2.3. RESPONSE CRITERIA

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

### 2.3.1. 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: At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study including baseline (nadir). 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 progressive disease.

### 2.3.2. 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, because a normal lymph node is defined as having a short axis of $< 10$ mm.

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 probably 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 and BML (below measurable limit) should be ticked (Note: It is less probable that this rule will be used for lymph nodes because 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 and BML should also be ticked).

To reiterate, however, if the radiologist is able to provide an actual measure, that should be recorded, even if it is below 5 mm and in that case BML should not be ticked (BML is equivalent to a less than sign <).

Lesions that split or coalesce on treatment: 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’.

### 2.3.3. Evaluation of Non-target Lesions

This section provides the definitions of the criteria used to determine the tumor 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, if applicable, normalization of tumor marker level). All lymph nodes must be non-pathological in size ($<$ 10 mm short axis).

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

Progressive Disease: Unequivocal progression (see Section 2.3.4) of existing non-target lesions. The appearance of one or more new lesions is also considered progression.

### 2.3.4. Special Notes on Assessment of Progression of Non-target Disease

When the participant 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 in a magnitude 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 non-target lesions is usually not sufficient to qualify 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 participant 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 participants 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 progressive disease for measurable disease: i.e., an increase in tumor 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 localized to widespread, or may be described in protocols as 'sufficient to require a change in therapy'. If 'unequivocal progression' is seen, the participant should be considered to have had overall progressive disease 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.

### 2.3.5. 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 tumor (for example, some 'new' bone lesions may be simply healing or flare of preexisting lesions). This is particularly important when the participant'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 during the study in an anatomical location that was not scanned at baseline is considered a new lesion and will indicate disease progression.

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.

## 2.4 EVALUATION OF RESPONSE

### 2.4.1 Time-Point Response (Overall Response)

It is assumed that at each protocol specified time-point, a response assessment occurs. A summary of the overall response status calculation at each time-point for participants who have measurable disease at baseline is provided in Table 1.

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

**Table 1 Time-Point Response – Target (w/wo non- target) Lesions**

| 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.

Abbreviations: w/wo = with or without.

**Table 2 Time-Point Response – Non-Target Lesions 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.

### 2.4.2 Missing Assessments and Not Evaluable Designation

When no imaging/measurement is done at all at a particular time-point, the participant is not evaluable at that time-point. If only a subset of lesion measurements is made at an assessment, usually the case is also considered not evaluable 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 progressive disease.

For example, if a participant had a baseline sum of 50 mm with 3 measured lesions and during study only 2 lesions were assessed, but those gave a sum of 80 mm, the participant will have achieved progressive disease status, regardless of the contribution of the missing lesion.

If one or more target lesions were not assessed either because the scan was not done, or could not be assessed because of poor image quality or obstructed view, the Response for Target Lesions should be “Unable to Assess” because the participant is not evaluable. Similarly, if one or more non-target lesions are indicated as ‘not assessed’, the response for non-target lesions should be “Unable to Assess” (except where there is clear progression). Overall response would be “Unable to Assess” if either the target response or the non-target response is “Unable to Assess” (except where this is clear evidence of progression) as this equates with the case being not evaluable at that time-point.

## 2 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 participants with CR may not have a total sum of ‘zero’ on the case report form (CRF).

Participants 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 participants is to be determined by evaluation of target and non-target disease as shown in Table 1 and Table 2.

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. In studies where participants with advanced disease are eligible (i.e., primary disease still or partially present), the primary tumor should be also captured under target or non-target lesions as appropriate. This is to avoid wrong assessments of complete overall response by statistical programs while the primary is still present but not evaluable.

## References

Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumors: Revised RECIST guideline (version 1.1). Eur J Cancer 2009;45(2):228-47.

# Appendix 7
# Risks Associated with Study Drugs and Guidelines for Management of Adverse Events Associated with Study Drugs

Toxicities associated or possibly associated with study drug treatment should be managed according to standard medical practice. Additional tests, such as autoimmune serology or biopsies, should be used to evaluate for a possible immunogenic etiology.

Although most immune-mediated AEs observed with immunomodulatory agents have been mild and self-limiting, such events should be recognized early and treated promptly to avoid potential major complications. Discontinuation of study drug may not have an immediate therapeutic effect, and in severe cases, immune-mediated toxicities may require acute management with topical corticosteroids, systemic corticosteroids, or other immunosuppressive agents.

The Investigator should consider the benefit–risk balance a given participant may be experiencing prior to further administration of study drug. The decision to re-challenge patients with study drug should be based on the Investigator's assessment of benefit-risk and documented by the Investigator (or an appropriate delegate). The Medical Monitor will be available to advise as needed.

## MANAGEMENT GUIDELINES

### PULMONARY EVENTS

Dyspnea, cough, fatigue, hypoxia, pneumonitis, and pulmonary infiltrates may be associated with the administration of study drug. Participants will be assessed for pulmonary signs and symptoms throughout the study and also have computed tomography (CT) scans of the chest performed at every tumor assessment.

All pulmonary events should be thoroughly evaluated for other commonly reported etiologies such as pneumonia or other infection, lymphangitic carcinomatosis, pulmonary embolism, heart failure, chronic obstructive pulmonary disease, or pulmonary hypertension. Management guidelines for pulmonary events are provided in Table 1.

**Table 1 Management Guidelines for Pulmonary Events, Including Pneumonitis**

| Event | Management |
|---|---|
| Pulmonary event, Grade 1 | • Continue study drug and monitor closely.<br>• Re-evaluate on serial imaging.<br>• Consider participant referral to pulmonary specialist. |
| Pulmonary event, Grade 2 | • Withhold study drug for up to 12 weeks after event onset. [a]<br>• Refer participant to pulmonary and infectious disease specialists and consider bronchoscopy or BAL.<br>• Initiate treatment with 1–2 mg/kg/day oral prednisone or equivalent.<br>• If event resolves to Grade 1 or better, resume study drug. [b]<br>• If event does not resolve to Grade 1 or better while withholding study drug, permanently discontinue study drug and contact Medical Monitor.<br>• For recurrent events, treat as a Grade 3 or 4 event. |
| Pulmonary event, Grade 3 or 4 | • Permanently discontinue study drug and contact Medical Monitor.<br>• Bronchoscopy or BAL is recommended.<br>• Initiate treatment with 1–2 mg/kg/day oral prednisone or equivalent.<br>• If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent.<br>• If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month. |

BAL = Bronchoscopic alveolar lavage.

[a] Study drug may be withheld for a longer period (i.e., > 12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to ≤ 10 mg/day oral prednisone or equivalent. The acceptable length of the extended period must be based on the assessment of benefit-risk by the Investigator and in alignment with the protocol requirement for duration of treatment and documented by the Investigator. The Medical Monitor will be available to advise as needed.

[b] If corticosteroids have been initiated, they must be tapered over ≥ 1 month to ≤ 10 mg/day oral prednisone or equivalent before study drug can be resumed.

## HEPATIC EVENTS

Immune-mediated hepatitis may be associated with the administration of study drug. Eligible patients must have adequate liver function, as manifested by measurements of total bilirubin and hepatic transaminases, and liver function will be monitored throughout study treatment. Management guidelines for hepatic events are provided in Table 2.

Participants with right upper-quadrant abdominal pain and/or unexplained nausea or vomiting should have liver function tests (LFTs) performed immediately and reviewed before administration of the next dose of study drug.

For participants with elevated LFTs, concurrent medication, viral hepatitis, and toxic or neoplastic etiologies should be considered and addressed, as appropriate.

## Table 2 Management Guidelines for Hepatic Events

| Event | Management |
|---|---|
| Hepatic event, Grade 1 | • Continue study drug.<br>• Monitor LFTs until values resolve to within normal limits or to baseline values. |
| Hepatic event, Grade 2 | **All events:**<br>• Monitor LFTs more frequently until return to baseline values.<br>**Events of > 5 days' duration:**<br>• Withhold study drug for up to 12 weeks after event onset. [a]<br>• Initiate treatment with 1–2 mg/kg/day oral prednisone or equivalent.<br>• If event resolves to Grade 1 or better, resume study drug. [b]<br>• If event does not resolve to Grade 1 or better while withholding study drug, permanently discontinue study drug and contact Medical Monitor. |
| Hepatic event, Grade 3 or 4 | • Permanently discontinue study drug and contact Medical Monitor.<br>• Consider patient referral to gastrointestinal specialist for evaluation and liver biopsy to establish etiology of hepatic injury.<br>• Initiate treatment with 1–2 mg/kg/day oral prednisone or equivalent.<br>• If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent.<br>If event resolves to Grade 1 or better, taper corticosteroids over ≥1 month. |

| Event | Management |
|---|---|
| **In participants with liver lesions** | |
| AST/ALT is within normal limits at baseline and increases to > 3 × ULN to ≤ 10 × ULN<br><br>or<br><br>AST/ALT is > ULN to ≤ 3 × ULN at baseline and increases to >5 × ULN to ≤ 10 × ULN<br><br>or<br><br>AST/ALT is >3 × ULN to 5 × ULN at baseline and increases to > 8 × ULN to ≤10 × ULN | Monitor LFTs more frequently until return to baseline values.<br>• Withhold study drug for up to 12 weeks after event onset[a].<br><br>Events of > 5 days' duration:<br>• Consider initiating treatment with 1−2 mg/kg/day prednisone or equivalent.<br>• If event resolves to baseline, resume study drug[b].<br>• If event does not resolve to baseline while withholding study drug, permanently discontinue study drug and contact Medical Monitor. |
| AST or ALT increases to >10×ULN or total bilirubin increases to > 3×ULN | • Permanently discontinue study drug and contact Medical Monitor<br>• Consider patient referral to GI specialist for evaluation and liver biopsy to establish etiology of hepatic injury.<br>• Initiate treatment with 1−2 mg/kg/day prednisone or equivalent<br>• If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent.<br>If event resolves to baseline, taper corticosteroids over ≥ 1 month. |

ALT = alanine aminotransferase; AST = aspartate aminotransferase; CTCAE = Common Terminology Criteria for Adverse Events; GI = Gastrointestinal; LFT = Liver function test; NCI = National Cancer Institute; ULN =-Upper limit of normal.

Note: Management guidelines are presented by adverse event severity based on NCI CTCAE and are applicable to both CTCAE Version 4.0 and CTCAE Version 5.0.

a Study drug may be withheld for a longer period (i.e., > 12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to ≤ 10 mg/day oral prednisone or equivalent. The acceptable length of the extended period must be based on the assessment of benefit-risk by the Investigator and in alignment with the protocol requirement for duration of treatment and documented by the Investigator. The Medical Monitor will be available to advise as needed.

b If corticosteroids have been initiated, they must be tapered over ≥ 1 month to ≤ 10 mg/day oral prednisone or equivalent before study drug can be resumed.

## GASTROINTESTINAL EVENTS

Immune-mediated colitis may be associated with the administration of study drug. Management guidelines for diarrhea or colitis are provided in Table 3.

All events of diarrhea or colitis should be thoroughly evaluated for other more common etiologies. For events of significant duration or magnitude or associated with signs of systemic inflammation or acute-phase reactants (e.g., increased C-reactive protein, platelet count, or bandemia): Perform sigmoidoscopy (or colonoscopy, if appropriate) with colonic biopsy, with three to five specimens for standard paraffin block to check for inflammation and lymphocytic infiltrates to confirm colitis diagnosis.

### Table 3 Management Guidelines for Gastrointestinal Events (Diarrhea or Colitis)

| Event | Management |
|---|---|
| Diarrhea or colitis, Grade 1 | • Continue study drug.<br>• Initiate symptomatic treatment.<br>• Endoscopy is recommended if symptoms persist for > 7 days.<br>• Monitor closely. |
| Diarrhea or colitis, Grade 2 | • Withhold study drug for up to 12 weeks after event onset. [a]<br>• Initiate symptomatic treatment.<br>• Participant referral to GI specialist is recommended.<br>• For recurrent events or events that persist > 5 days, initiate treatment with 1–2 mg/kg/day oral prednisone or equivalent.<br>• If event resolves to Grade 1 or better, resume study drug. [b]<br>• If event does not resolve to Grade 1 or better while withholding study drug, permanently discontinue study drug and contact Medical Monitor. |
| Diarrhea or colitis, Grade 3 | • Withhold study drug for up to 12 weeks after event onset. [a]<br>• Refer participant to GI specialist for evaluation and confirmatory biopsy.<br>• Initiate treatment with 1–2 mg/kg/day IV methylprednisolone or equivalent and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement.<br>• If event resolves to Grade 1 or better, resume study drug. [b]<br>• If event does not resolve to Grade 1 or better while withholding study drug, permanently discontinue study drug and contact Medical Monitor. |
| Diarrhea or colitis, Grade 4 | • Permanently discontinue study drug and contact Medical Monitor.<br>• Refer participant to GI specialist for evaluation and confirmation biopsy.<br>• Initiate treatment with 1–2 mg/kg/day IV methylprednisolone or equivalent and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement.<br>• If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent.<br>• If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month. |

GI = Gastrointestinal, IV = Intravenous.

[a] Study Drug may be withheld for a longer period (i.e., > 12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to ≤ 10 mg/day oral prednisone or equivalent. The acceptable length of the extended period must be based on the assessment of benefit-risk by the Investigator and in alignment with the protocol requirement for duration of treatment and documented by the Investigator. The Medical Monitor will be available to advise as needed.

[b] If corticosteroids have been initiated, they must be tapered over ≥ 1 month to ≤ 10 mg/day oral prednisone or equivalent before study drug can be resumed.

## ENDOCRINE EVENTS

Thyroid disorders, adrenal insufficiency, diabetes mellitus, and pituitary disorders may be associated with the administration of study drug. Management guidelines for endocrine events are provided in Table 4.

Participants with unexplained symptoms such as headache, fatigue, myalgias, impotence, constipation, or mental status changes should be investigated for the presence of thyroid, pituitary, or adrenal endocrinopathies. The participant should be referred to an endocrinologist if an endocrinopathy is suspected. Thyroid-stimulating hormone (TSH) and free triiodothyronine and thyroxine levels should be measured to determine whether thyroid abnormalities are present. Pituitary hormone levels and function tests (e.g., TSH, growth hormone, luteinizing hormone, follicle-stimulating hormone, testosterone, prolactin, adrenocorticotropic hormone levels, and adrenocorticotropic hormone stimulation test) and magnetic resonance imaging (MRI) of the brain (with detailed pituitary sections) may help to differentiate primary pituitary insufficiency from primary adrenal insufficiency.

### Table 4 Management Guidelines for Endocrine Events

| Event | Management |
|---|---|
| Asymptomatic hypothyroidism | • Continue study drug.<br>• Initiate treatment with thyroid replacement hormone.<br>• Monitor TSH weekly. |
| Symptomatic hypothyroidism | • Withhold study drug.<br>• Initiate treatment with thyroid replacement hormone.<br>• Monitor TSH weekly.<br>• Consider participant referral to endocrinologist.<br>• Resume study drug when symptoms are controlled and thyroid function is improving. |
| Asymptomatic hyperthyroidism | • TSH ≥ 0.1 mU/L and < 0.5 mU/L:<br>• Continue study drug.<br>• Monitor TSH every 4 weeks.<br>• TSH < 0.1 mU/L:<br>• Follow guidelines for symptomatic hyperthyroidism. |

| Event | Management |
|---|---|
| Symptomatic hyperthyroidism | • Withhold study drug.<br>• Initiate treatment with anti-thyroid drug such as methimazole or carbimazole as needed.<br>• Consider participant referral to endocrinologist.<br>• Resume study drug when symptoms are controlled and thyroid function is improving.<br>• Permanently discontinue study drug and contact Medical Monitor for life-threatening immune-mediated hyperthyroidism. |
| Symptomatic adrenal insufficiency, Grade 2–4 | • Withhold study drug for up to 12 weeks after event onset. [a]<br>• Refer participant to endocrinologist.<br>• Perform appropriate imaging.<br>• Initiate treatment with 1–2 mg/kg/day IV methylprednisolone or equivalent and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement.<br>• If event resolves to Grade 1 or better and participant is stable on replacement therapy, resume study drug. [b]<br>• If event does not resolve to Grade 1 or better or participant is not stable on replacement therapy while withholding study drug, permanently discontinue study drug and contact Medical Monitor. |
| Hyperglycemia, Grade 1 or 2 | • Continue study drug.<br>• Investigate for diabetes. If participant has Type 1 diabetes, treat as a Grade 3 event. If participant does not have Type 1 diabetes, treat as per institutional guidelines.<br>• Monitor for glucose control. |
| Hyperglycemia, Grade 3 or 4 | • Withhold study drug.<br>• Initiate treatment with insulin.<br>• Monitor for glucose control.<br>• Resume study drug when symptoms resolve and glucose levels are stable. |
| Hypophysitis (pan-hypopituitarism), Grade 2 or 3 | • Withhold study drug for up to 12 weeks after event onset. [a]<br>• Refer participant to endocrinologist.<br>• Perform brain MRI (pituitary protocol).<br>• Initiate treatment with 1–2 mg/kg/day IV methylprednisolone or equivalent and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement.<br>• Initiate hormone replacement if clinically indicated.<br>• If event resolves to Grade 1 or better, resume study drug. [b]<br>• If event does not resolve to Grade 1 or better while withholding study drug, permanently discontinue study drug and contact Medical Monitor.<br>• For recurrent hypophysitis, treat as a Grade 4 event. |

| Event | Management |
|---|---|
| Hypophysitis (pan-hypopituitarism), Grade 4 | • Permanently discontinue study drug and contact Medical Monitor.<br>• Refer participant to endocrinologist.<br>• Perform brain MRI (pituitary protocol).<br>• Initiate treatment with 1–2 mg/kg/day IV methylprednisolone or equivalent and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement.<br>• Initiate hormone replacement if clinically indicated. |

IV = Intravenous; MRI = Magnetic resonance imaging; TSH = Thyroid-stimulating hormone.

[a] Study drug may be withheld for a longer period (i.e., > 12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to ≤ 10 mg/day oral prednisone or equivalent. The acceptable length of the extended period must be based on the assessment of benefit-risk by the Investigator and in alignment with the protocol requirement for duration of treatment and documented by the Investigator. The Medical Monitor will be available to advise as needed.

[b] If corticosteroids have been initiated, they must be tapered over ≥ 1 month to ≤ 10 mg/day oral prednisone or equivalent before study drug can be resumed.

## OCULAR EVENTS

An ophthalmologist should evaluate visual complaints (e.g., uveitis, retinal events). Management guidelines for ocular events are provided in Table 5.

### Table 5 Management Guidelines for Ocular Events

| Event | Management |
|---|---|
| Ocular event, Grade 1 | • Continue study drug.<br>• Participant referral to ophthalmologist is strongly recommended.<br>• Initiate treatment with topical corticosteroid eye drops and topical immunosuppressive therapy.<br>• If symptoms persist, treat as a Grade 2 event. |
| Ocular event, Grade 2 | • Withhold study drug for up to 12 weeks after event onset. [a]<br>• Participant referral to ophthalmologist is strongly recommended.<br>• Initiate treatment with topical corticosteroid eye drops and topical immunosuppressive therapy.<br>• If event resolves to Grade 1 or better, resume study drug. [b]<br>• If event does not resolve to Grade 1 or better while withholding study drug, permanently discontinue study drug and contact Medical Monitor. |
| Ocular event, Grade 3 or 4 | • Permanently discontinue study drug and contact Medical Monitor<br>• Refer participant to ophthalmologist.<br>• Initiate treatment with 1–2 mg/kg/day oral prednisone or equivalent.<br>• If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month. |

[a] Study drug may be withheld for a longer period (i.e., > 12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to ≤ 10 mg/day oral prednisone or equivalent. The acceptable length of the extended period must be based on the assessment of benefit-risk by the Investigator and in alignment with the protocol requirement for duration of treatment and documented by the Investigator. The Medical Monitor will be available to advise as needed.

[b] If corticosteroids have been initiated, they must be tapered over ≥ 1 month to ≤ 10 mg/day oral prednisone or equivalent before study drug can be resumed.

## IMMUNE-MEDIATED MYOCARDITIS

Immune-mediated myocarditis should be suspected in any participant presenting with signs or symptoms suggestive of myocarditis, including, but not limited to, laboratory (e.g., B-type natriuretic peptide) or cardiac imaging abnormalities, dyspnea, chest pain, palpitations, fatigue, decreased exercise tolerance, or syncope. Immune-mediated myocarditis needs to be distinguished from myocarditis resulting from infection (commonly viral, e.g., in a participant who reports a recent history of gastrointestinal illness), ischemic events, underlying arrhythmias, exacerbation of preexisting cardiac conditions, or progression of malignancy.

All participants with possible myocarditis should be urgently evaluated by performing cardiac enzyme assessment, an ECG, a chest x-ray, an echocardiogram, and/or a cardiac MRI as appropriate per institutional guidelines. A cardiologist should be consulted. An endomyocardial biopsy may be considered to enable a definitive diagnosis and appropriate treatment, if clinically indicated.

Participants with signs and symptoms of myocarditis, in the absence of an identified alternate etiology, should be treated according to the guidelines in Table 6.

### Table 6 Management Guidelines for Immune-Mediated Myocarditis

| Event | Management |
|---|---|
| Immune-mediated myocarditis *(all grades)* | • Permanently discontinue study drug and contact Medical Monitor.<br>• Refer participant to cardiologist.<br>• Initiate treatment as per institutional guidelines and consider antiarrhythmic drugs, temporary pacemaker, ECMO, or VAD as appropriate.<br>• Initiate treatment with 1–2 mg/kg/day IV methylprednisolone or equivalent and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement.<br>• If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent.<br>• If event resolves to Grade 1 or better, taper corticosteroids over ≥1 month. |

ECMO = Extracorporeal membrane oxygenation; IV = Intravenous; VAD = Ventricular assist device.

## PANCREATIC EVENTS

Symptoms of abdominal pain associated with elevations of amylase and lipase, suggestive of pancreatitis, may be associated with the administration of study drug. The differential diagnosis of acute abdominal pain should include pancreatitis. Appropriate work-up should include an evaluation for ductal obstruction, as well as serum amylase and lipase tests. Management guidelines for pancreatic events, including pancreatitis, are provided in Table 7.

### Table 7 Management Guidelines for Pancreatic Events, Including Pancreatitis

| Event | Management |
|---|---|
| Amylase and/or lipase elevation, Grade 2 | Amylase and/or lipase > 1.5–2.0 × ULN:<br>• Continue study drug.<br>• Monitor amylase and lipase weekly.<br>• For prolonged elevation (e.g., > 3 weeks), consider treatment with 10 mg/day oral prednisone or equivalent.<br>Asymptomatic with amylase and/or lipase > 2.0–5.0 × ULN:<br>Treat as a Grade 3 event. |
| Amylase and/or lipase elevation, Grade 3 or 4 | • Withhold study drug for up to 12 weeks after event onset. [a]<br>• Refer participant to GI specialist.<br>• Monitor amylase and lipase every other day.<br>• If no improvement, consider treatment with 1–2 mg/kg/day oral prednisone or equivalent.<br>• If event resolves to Grade 1 or better, resume study drug. [b]<br>• If event does not resolve to Grade 1 or better while withholding study drug, permanently discontinue study drug and contact Medical Monitor.<br>• For recurrent events, permanently discontinue study drug and contact Medical Monitor. |
| Immune-mediated pancreatitis, Grade 2 or 3 | • Withhold study drug for up to 12 weeks after event onset. [a]<br>• Refer participant to GI specialist.<br>• Initiate treatment with 1–2 mg/kg/day IV methylprednisolone or equivalent and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement.<br>• If event resolves to Grade 1 or better, resume study drug. [b]<br>• If event does not resolve to Grade 1 or better while withholding study drug, permanently discontinue study drug and contact Medical Monitor.<br>• For recurrent events, permanently discontinue study drug and contact Medical Monitor. |

| Event | Management |
|---|---|
| Immune-mediated pancreatitis, Grade 4 | • Permanently discontinue study drug and contact Medical Monitor.<br>• Refer participant to GI specialist.<br>• Initiate treatment with 1–2 mg/kg/day IV methylprednisolone or equivalent and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement.<br>• If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent.<br>• If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month. |

GI = Gastrointestinal; IV = Intravenous; ULN = Upper limit of normal.

[a] Study drug may be withheld for a longer period (i.e., > 12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to ≤ 10 mg/day oral prednisone or equivalent. The acceptable length of the extended period must be based on the assessment of benefit-risk by the Investigator and in alignment with the protocol requirement for duration of treatment and documented by the Investigator. The Medical Monitor will be available to advise as needed.

[b] If corticosteroids have been initiated, they must be tapered over ≥ 1 month to ≤ 10 mg/day oral prednisone or equivalent before study drug can be resumed.

## DERMATOLOGIC EVENTS

Treatment-emergent rash may be associated with the study drug. A dermatologist should evaluate persistent and/or severe rash or pruritus. A biopsy should be considered unless contraindicated. Management guidelines for dermatologic events are provided in Table 8.

**Table 8 Management Guidelines for Dermatologic Events**

| Event | Management |
|---|---|
| Dermatologic event, Grade 1 | • Continue study drug.<br>• Consider treatment with topical corticosteroids and/or other symptomatic therapy (e.g., antihistamines). |
| Dermatologic event, Grade 2 | • Continue study drug.<br>• Consider participant referral to dermatologist.<br>• Initiate treatment with topical corticosteroids.<br>• Consider treatment with higher-potency topical corticosteroids if event does not improve. |
| Dermatologic event, Grade 3 | • Withhold study drug for up to 12 weeks after event onset. [a]<br>• Refer participant to dermatologist.<br>• Initiate treatment with 10 mg/day oral prednisone or equivalent, increasing dose to 1–2 mg/kg/day if event does not improve within 48–72 hours.<br>• If event resolves to Grade 1 or better, resume study drug. [b]<br>• If event does not resolve to Grade 1 or better while withholding study drug, permanently discontinue study drug and contact Medical Monitor. |
| Dermatologic event, Grade 4 | • Permanently discontinue study drug and contact Medical Monitor. |

[a] Study drug may be withheld for a longer period (i.e., > 12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to ≤ 10 mg/day oral prednisone or equivalent. The acceptable length of the extended period must be based on the assessment of benefit-risk by the Investigator and in alignment with the protocol requirement for duration of treatment and documented by the Investigator. The Medical Monitor will be available to advise as needed.

[b] If corticosteroids have been initiated, they must be tapered over ≥ 1 month to ≤ 10 mg/day oral prednisone or equivalent before study drug can be resumed.

## NEUROLOGIC DISORDERS

Myasthenia gravis and Guillain-Barré syndrome may be observed with study drug. Participants may present with signs and symptoms of sensory and/or motor neuropathy. Diagnostic work-up is essential for an accurate characterization to differentiate between alternative etiologies. Management guidelines for neurologic disorders are provided in Table 9.

**Table 9 Management Guidelines for Neurologic Disorders**

| Event | Management |
|---|---|
| Immune-mediated neuropathy, Grade 1 | • Continue study drug.<br>• Investigate etiology. |
| Immune-mediated neuropathy, Grade 2 | • Withhold study drug for up to 12 weeks after event onset. [a]<br>• Investigate etiology.<br>• Initiate treatment as per institutional guidelines.<br>• If event resolves to Grade 1 or better, resume study drug. [b]<br>• If event does not resolve to Grade 1 or better while withholding study drug, permanently discontinue study drug and contact Medical Monitor. |
| Immune-mediated neuropathy, Grade 3 or 4 | • Permanently discontinue study drug and contact Medical Monitor.<br>• Initiate treatment as per institutional guidelines. |
| Myasthenia gravis and Guillain-Barré syndrome (any grade) | • Permanently discontinue study drug and contact Medical Monitor.<br>• Refer participant to neurologist.<br>• Initiate treatment as per institutional guidelines.<br>• Consider initiation of 1–2 mg/kg/day oral or IV prednisone or equivalent. |

IV = Intravenous.

[a] Study drug may be withheld for a longer period (i.e., > 12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to ≤ 10 mg/day oral prednisone or equivalent. The acceptable length of the extended period must be based on the assessment of benefit-risk by the Investigator and in alignment with the protocol requirement for duration of treatment and documented by the Investigator. The Medical Monitor will be available to advise as needed.

[b] If corticosteroids have been initiated, they must be tapered over ≥ 1 month to ≤ 10 mg/day oral prednisone or equivalent before study drug can be resumed.

## IMMUNE-MEDIATED MENINGOENCEPHALITIS

Immune-mediated meningoencephalitis may be associated with the administration of study drug. Immune-mediated meningoencephalitis should be suspected in any participant presenting with signs or symptoms suggestive of meningitis or encephalitis, including, but not limited to, headache, neck pain, confusion, seizure, motor or sensory dysfunction, and altered or depressed level of consciousness. Encephalopathy from metabolic or electrolyte imbalances needs to be distinguished from potential meningoencephalitis resulting from infection (bacterial, viral, or fungal) or progression of malignancy, or secondary to a paraneoplastic process.

All participants being considered for meningoencephalitis should be urgently evaluated with a CT scan and/or MRI scan of the brain to evaluate for metastasis, inflammation, or edema. If deemed safe by the treating physician, a lumbar puncture should be performed and a neurologist should be consulted.

Participants with signs and symptoms of meningoencephalitis, in the absence of an identified alternate etiology, should be treated according to the guidelines in Table 10.

**Table 10 Management Guidelines for Immune-Mediated Meningoencephalitis**

| Event | Management |
|---|---|
| Immune-mediated meningoencephalitis, all grades | • Permanently discontinue study drug and contact Medical Monitor.<br>• Refer participant to neurologist.<br>• Initiate treatment with 1–2 mg/kg/day IV methylprednisolone or equivalent and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement.<br>• If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent.<br>• If event resolves to Grade 1 or better, taper corticosteroids over ≥1 month. |

IV = Intravenous.

## RENAL EVENTS

Immune-mediated nephritis may be associated with the administration of study drug. Eligible participants must have adequate renal function, and renal function, including serum creatinine, should be monitored throughout study treatment. Participants with abnormal renal function should be evaluated and treated for other more common etiologies (including prerenal and postrenal causes, and concomitant medications such as non-steroidal anti-inflammatory drugs). Refer the participant to a renal specialist if clinically indicated. A renal biopsy may be required to enable a definitive diagnosis and appropriate treatment.

Participants with signs and symptoms of nephritis, in the absence of an identified alternate etiology, should be treated according to the guidelines in Table 11.

## Table 11 Management Guidelines for Renal Events

| Event | Management |
|---|---|
| Renal event, Grade 1 | • Continue study drug.<br>• Monitor kidney function, including creatinine, closely until values resolve to within normal limits or to baseline values. |
| Renal event, Grade 2 | • Withhold study drug for up to 12 weeks after event onset. [a]<br>• Refer participant to renal specialist.<br>• Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day oral prednisone.<br>• If event resolves to Grade 1 or better, resume study drug. [b]<br>• If event does not resolve to Grade 1 or better while withholding study drug, permanently discontinue study drug and contact Medical Monitor. |
| Renal event, Grade 3 or 4 | • Permanently discontinue study drug and contact Medical Monitor.<br>• Refer participant to renal specialist and consider renal biopsy.<br>• Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day oral prednisone.<br>• If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent.<br>• If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month. |

[a] Study drug may be withheld for a longer period (i.e., > 12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of ≤ 10 mg/day oral prednisone. The acceptable length of the extended period must be based on the assessment of benefit-risk by the Investigator and in alignment with the protocol requirement for duration of treatment and documented by the Investigator. The Medical Monitor will be available to advise as needed.

[b] If corticosteroids have been initiated, they must be tapered over ≥ 1 month to the equivalent of ≤ 10 mg/day oral prednisone before study drug can be resumed.

## IMMUNE-MEDIATED MYOSITIS

Immune-mediated myositis may be associated with the administration of study drug. Myositis or inflammatory myopathies are a group of disorders sharing the common feature of inflammatory muscle injury; dermatomyositis and polymyositis are among the most common disorders. Initial diagnosis is based on clinical (muscle weakness, muscle pain, rash in dermatomyositis), biochemical (serum creatine kinase increase), and imaging (electromyography/MRI) features, and is confirmed with a muscle biopsy.

Participants with signs and symptoms of myositis, in the absence of an identified alternate etiology, should be treated according to the guidelines in Table 12.

### Table 12 Management Guidelines for Immune-Mediated Myositis

| Event | Management |
|---|---|
| Immune-mediated myositis, Grade 1 | • Continue study drug.<br>• Refer participant to rheumatologist or neurologist.<br>• Initiate treatment as per institutional guidelines. |
| Immune-mediated myositis, Grade 2 | • Withhold study drug for up to 12 weeks after event onset [a] and contact Medical Monitor.<br>• Refer participant to rheumatologist or neurologist.<br>• Initiate treatment as per institutional guidelines.<br>• Consider treatment with corticosteroids equivalent to 1–2 mg/kg/day IV methylprednisolone and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement.<br>• If corticosteroids are initiated and event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent.<br>• If event resolves to Grade 1 or better, resume study drug. [b]<br>• If event does not resolve to Grade 1 or better while withholding study drug, permanently discontinue study drug and contact Medical Monitor. |

| Event | Management |
|---|---|
| Immune-mediated myositis, Grade 3 | • Withhold study drug for up to 12 weeks after event onset [a] and contact Medical Monitor.<br>• Refer participant to rheumatologist or neurologist.<br>• Initiate treatment as per institutional guidelines. Respiratory support may be required in more severe cases.<br>• Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day IV methylprednisolone, or higher-dose bolus if participant is severely compromised (e.g., cardiac or respiratory symptoms, dysphagia, or weakness that severely limits mobility); convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement.<br>• If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent.<br>• If event resolves to Grade 1 or better, resume study drug. [b]<br>• If event does not resolve to Grade 1 or better while withholding study drug, permanently discontinue study drug and contact Medical Monitor.<br>• For recurrent events, treat as a Grade 4 event. |
| Immune-mediated myositis, Grade 4 | • Permanently discontinue study drug and contact Medical Monitor.<br>• Refer participant to rheumatologist or neurologist.<br>• Initiate treatment as per institutional guidelines. Respiratory support may be required in more severe cases.<br>• Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day IV methylprednisolone, or higher-dose bolus if patient is severely compromised (e.g., cardiac or respiratory symptoms, dysphagia, or weakness that severely limits mobility); convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement.<br>• If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent.<br>• If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month. |

IV = Intravenous.

[a] Study drug may be withheld for a longer period (i.e., > 12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of ≤ 10 mg/day oral prednisone. The acceptable length of the extended period must be based on the assessment of benefit-risk by the Investigator and in alignment with the protocol requirement for duration of treatment and documented by the Investigator. The Medical Monitor will be available to advise as needed.

[b] If corticosteroids have been initiated, they must be tapered over ≥ 1 month to the equivalent of ≤ 10 mg/day oral prednisone before study drug can be resumed.

## HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS AND MACROPHAGE ACTIVATION SYNDROME

Immune-mediated reactions may involve any organ system and may lead to hemophagocytic lymphohistiocytosis (HLH) and macrophage activation syndrome (MAS).

Patients with suspected HLH should be diagnosed according to published criteria by McClain and Eckstein (2014). A patient should be classified as having HLH if five of the following eight criteria are met:

- Fever $\geq$ 38.5°C
- Splenomegaly
- Peripheral blood cytopenia consisting of at least two of the following:
  - Hemoglobin $<$ 90 g/L (9 g/dL) ($<$ 100 g/L [10 g/dL] for infants aged $<$ 4 weeks)
  - Platelet count $<$ 100 $\times$ 109/L (100 000/$\mu$L)
  - ANC $<1.0\times10^9$/L (1000/$\mu$L)
- Fasting triglycerides $>$ 2.992 mmol/L (265 mg/dL) and/or fibrinogen $<$ 1.5 g/L (150 mg/dL)
- Hemophagocytosis in bone marrow, spleen, lymph node, or liver
- Low or absent natural killer cell activity
- Ferritin $>$ 500 mg/L (500 ng/mL)
- Soluble interleukin 2 (IL-2) receptor (soluble CD25) elevated $\geq$ 2 standard deviations above age-adjusted laboratory-specific norms

Participants with suspected MAS should be diagnosed according to published criteria for systemic juvenile idiopathic arthritis by Ravelli et al. 2016. A febrile patient should be classified as having MAS if the following criteria are met:

- Ferritin $>$ 684 mg/L (684 ng/mL)
- At least two of the following:
  - Platelet count $\leq$ 181 $\times$ $10^9$/L (181,000/µL)
  - AST $\geq$ 48 U/L
  - Triglycerides $>$ 1.761 mmol/L (156 mg/dL)
  - Fibrinogen $\leq$ 3.6 g/L (360 mg/dL)

Participants with suspected HLH or MAS should be treated according to the guidelines in Table 13.

## Table 13 Management Guidelines for Suspected Hemophagocytic Lymphohistiocytosis or Macrophage Activation Syndrome

| Event | Management |
|---|---|
| Suspected HLH or MAS | • Permanently discontinue study drug and contact Medical Monitor.<br>• Consider patient referral to hematologist.<br>• Initiate supportive care, including intensive care monitoring if indicated per institutional guidelines.<br>• Consider initiation of IV corticosteroids, an immunosuppressive agent, and/or anti-cytokine therapy.<br>• If event does not respond to treatment within 24 hours, contact Medical Monitor and initiate treatment as appropriate according to published guidelines (La Rosée 2015; Schram and Berliner 2015; La Rosée et al. 2019).<br>• If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month. |

HLH = Hemophagocytic lymphohistiocytosis; IV = Intravenous; MAS= Macrophage activation syndrome.

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# Appendix 8
# European Organisation for Research and Treatment of Cancer Quality-of-Life Questionnaire (EORTC QLQ-C30)

## EORTC QLQ-C30 (version 3)

We are interested in some things about you and your health. Please answer all of the questions yourself by circling the number that best applies to you. There are no "right" or "wrong" answers. The information that you provide will remain strictly confidential.

Please fill in your initials: ⌊ ⌋⌊ ⌋⌊ ⌋⌊ ⌋

Your birthdate (Day, Month, Year): ⌊ ⌋⌊ ⌋ ⌊ ⌋⌊ ⌋ ⌊ ⌋⌊ ⌋⌊ ⌋⌊ ⌋

Today's date (Day, Month, Year): 31 ⌊ ⌋⌊ ⌋ ⌊ ⌋⌊ ⌋ ⌊ ⌋⌊ ⌋⌊ ⌋⌊ ⌋

| | Not at All | A Little | Quite a Bit | Very Much |
|---|---|---|---|---|
| 1. Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase? | 1 | 2 | 3 | 4 |
| 2. Do you have any trouble taking a long walk? | 1 | 2 | 3 | 4 |
| 3. Do you have any trouble taking a short walk outside of the house? | 1 | 2 | 3 | 4 |
| 4. Do you need to stay in bed or a chair during the day? | 1 | 2 | 3 | 4 |
| 5. Do you need help with eating, dressing, washing yourself or using the toilet? | 1 | 2 | 3 | 4 |

| During the past week: | Not at All | A Little | Quite a Bit | Very Much |
|---|---|---|---|---|
| 6. Were you limited in doing either your work or other daily activities? | 1 | 2 | 3 | 4 |
| 7. Were you limited in pursuing your hobbies or other leisure time activities? | 1 | 2 | 3 | 4 |
| 8. Were you short of breath? | 1 | 2 | 3 | 4 |
| 9. Have you had pain? | 1 | 2 | 3 | 4 |
| 10. Did you need to rest? | 1 | 2 | 3 | 4 |
| 11. Have you had trouble sleeping? | 1 | 2 | 3 | 4 |
| 12. Have you felt weak? | 1 | 2 | 3 | 4 |
| 13. Have you lacked appetite? | 1 | 2 | 3 | 4 |
| 14. Have you felt nauseated? | 1 | 2 | 3 | 4 |
| 15. Have you vomited? | 1 | 2 | 3 | 4 |
| 16. Have you been constipated? | 1 | 2 | 3 | 4 |

Please go on to the next page

| During the past week: | Not at All | A Little | Quite a Bit | Very Much |
|---|---|---|---|---|
| 17. Have you had diarrhea? | 1 | 2 | 3 | 4 |
| 18. Were you tired? | 1 | 2 | 3 | 4 |
| 19. Did pain interfere with your daily activities? | 1 | 2 | 3 | 4 |
| 20. Have you had difficulty in concentrating on things, like reading a newspaper or watching television? | 1 | 2 | 3 | 4 |
| 21. Did you feel tense? | 1 | 2 | 3 | 4 |
| 22. Did you worry? | 1 | 2 | 3 | 4 |
| 23. Did you feel irritable? | 1 | 2 | 3 | 4 |
| 24. Did you feel depressed? | 1 | 2 | 3 | 4 |
| 25. Have you had difficulty remembering things? | 1 | 2 | 3 | 4 |
| 26. Has your physical condition or medical treatment interfered with your family life? | 1 | 2 | 3 | 4 |
| 27. Has your physical condition or medical treatment interfered with your social activities? | 1 | 2 | 3 | 4 |
| 28. Has your physical condition or medical treatment caused you financial difficulties? | 1 | 2 | 3 | 4 |

**For the following questions please circle the number between 1 and 7 that best applies to you**

29. How would you rate your overall health during the past week?

| 1 | 2 | 3 | 4 | 5 | 6 | 7 |
|---|---|---|---|---|---|---|
| Very poor | | | | | | Excellent |

30. How would you rate your overall quality of life during the past week?

| 1 | 2 | 3 | 4 | 5 | 6 | 7 |
|---|---|---|---|---|---|---|
| Very poor | | | | | | Excellent |

# Appendix 9
# European Organisation for Research and Treatment of Cancer Quality-of-Life Questionnaire for Esophageal Cancer (QLQ-OES18)

## EORTC QLQ – OES18

Patients sometimes report that they have the following symptoms or problems. Please indicate the extent to which you have experienced these symptoms or problems during the past week. Please answer by circling the number that best applies to you.

| During the past week: | | Not at all | A little | Quite a bit | Very much |
|---|---|---|---|---|---|
| 31. | Could you eat solid food? | 1 | 2 | 3 | 4 |
| 32. | Could you eat liquidised or soft food? | 1 | 2 | 3 | 4 |
| 33. | Could you drink liquids? | 1 | 2 | 3 | 4 |
| 34. | Have you had trouble with swallowing your saliva? | 1 | 2 | 3 | 4 |
| 35. | Have you choked when swallowing? | 1 | 2 | 3 | 4 |
| 36. | Have you had trouble enjoying your meals? | 1 | 2 | 3 | 4 |
| 37. | Have you felt full up too quickly? | 1 | 2 | 3 | 4 |
| 38. | Have you had trouble with eating? | 1 | 2 | 3 | 4 |
| 39. | Have you had trouble with eating in front of other people? | 1 | 2 | 3 | 4 |
| 40. | Have you had a dry mouth? | 1 | 2 | 3 | 4 |
| 41. | Did food and drink taste different from usual? | 1 | 2 | 3 | 4 |
| 42 | Have you had trouble with coughing? | 1 | 2 | 3 | 4 |
| 43. | Have you had trouble with talking? | 1 | 2 | 3 | 4 |
| 44. | Have you had acid indigestion or heartburn? | 1 | 2 | 3 | 4 |
| 45. | Have you had trouble with acid or bile coming into your mouth? | 1 | 2 | 3 | 4 |
| 46. | Have you had pain when you eat? | 1 | 2 | 3 | 4 |
| 47. | Have you had pain in your chest? | 1 | 2 | 3 | 4 |
| 48. | Have you had pain in your stomach? | 1 | 2 | 3 | 4 |

# Appendix 10
# European Organisation for Research and Treatment of Cancer Item Library 97 (EORTC IL97)

## EORTC IL97

We are interested in some things about you and your health. Please answer all of the questions yourself by circling the number that best applies to you. There are no "right" or "wrong" answers. The information that you provide will remain strictly confidential.

| During the past week: | Not at All | A Little | Quite a Bit | Very Much |
|---|---|---|---|---|
| 1. Have you had pain? | 1 | 2 | 3 | 4 |
| 2. Did you need to rest? | 1 | 2 | 3 | 4 |
| 3. Have you felt weak? | 1 | 2 | 3 | 4 |
| 4. Have you lacked appetite? | 1 | 2 | 3 | 4 |
| 5. Have you felt nauseated? | 1 | 2 | 3 | 4 |
| 6. Have you vomited? | 1 | 2 | 3 | 4 |
| 7. Have you had diarrhea? | 1 | 2 | 3 | 4 |
| 8. Were you tired? | 1 | 2 | 3 | 4 |
| 9. Did pain interfere with your daily activities? | 1 | 2 | 3 | 4 |
| 10. Did you feel tense? | 1 | 2 | 3 | 4 |
| 11. Did you worry? | 1 | 2 | 3 | 4 |
| 12. Did you feel irritable? | 1 | 2 | 3 | 4 |
| 13. Did you feel depressed? | 1 | 2 | 3 | 4 |
| 14. Has your physical condition or medical treatment interfered with your family life? | 1 | 2 | 3 | 4 |
| 15. Has your physical condition or medical treatment interfered with your social activities? | 1 | 2 | 3 | 4 |

**For the following questions please circle the number between 1 and 7 that best applies to you**

16. How would you rate your overall health during the past week?

| 1 | 2 | 3 | 4 | 5 | 6 | 7 |
|---|---|---|---|---|---|---|
| Very poor | | | | | | Excellent |

17. How would you rate your overall quality of life during the past week?

| 1 | 2 | 3 | 4 | 5 | 6 | 7 |
|---|---|---|---|---|---|---|
| Very poor | | | | | | Excellent |

# Appendix 11
# Patient Global Impression of Change and its Importance (PGI-CI)

**Patient Global Impression of Change and its Importance (PGI-CI)**

1. Please choose the response below that best describes your overall health because of cancer **now compared with when you started the study**.

| | |
|---|---|
| Very much improved | ☐ |
| Much improved | ☐ |
| Minimally improved | ☐ |
| No change | ☐ |
| Minimally worse | ☐ |
| Much worse | ☐ |
| Very much worse | ☐ |

2. In the previous question, you reported the change you have experienced since the start of the study. Was this change important to you?

| | |
|---|---|
| Yes | ☐ |
| No | ☐ |
| Not applicable (selected *No change*) | ☐ |

# Appendix 12
# Patient Global Impression of Severity (PGI-S)

**Patient Global Impression of Severity (PGI-S)**

1. Please choose the response below that best describes how severely your overall health has been impacted because of cancer **over the past week**.

| | |
|---|---|
| None | ☐ |
| Mild | ☐ |
| Moderate | ☐ |
| Severe | ☐ |
| Very severe | ☐ |

# Appendix 13
# Patient-Reported Outcomes Common Terminology Criteria for Adverse Events (PRO-CTCAE)

NCI PRO-CTCAE ™ ITEMS
Item Library Version 1.0
English
Form Created on 06 October 2020

As individuals go through treatment for their cancer, they sometimes experience different symptoms and side effects. For each question, please select the one response that best describes your experiences over the past 7 days.

| **1a.** In the last 7 days, what was the SEVERITY of your SHORTNESS OF BREATH at its WORST? | | | | |
|---|---|---|---|---|
| O None | O Mild | O Moderate | O Severe | O Very severe |
| **1b.** In the last 7 days, how much did your SHORTNESS OF BREATH INTERFERE with your usual or daily activities? | | | | |
| O Not at all | O A little bit | O Somewhat | O Quite a bit | O Very much |

| **2a.** In the last 7 days, what was the SEVERITY of your COUGH at its WORST? | | | | |
|---|---|---|---|---|
| O None | O Mild | O Moderate | O Severe | O Very severe |
| **2b.** In the last 7 days, how much did COUGH INTERFERE with your usual or daily activities? | | | | |
| O Not at all | O A little bit | O Somewhat | O Quite a bit | O Very much |

| **3a.** In the last 7 days, did you have any RASH? | |
|---|---|
| O Yes | O No |

| **4a.** In the last 7 days, what was the SEVERITY of your ITCHY SKIN at its WORST? | | | | |
|---|---|---|---|---|
| O None | O Mild | O Moderate | O Severe | O Very severe |

| **5a.** In the last 7 days, how OFTEN did you have ACHING MUSCLES? | | | | |
|---|---|---|---|---|
| O Never | O Rarely | O Occasionally | O Frequently | O Almost constantly |
| **5b.** In the last 7 days, what was the SEVERITY of your ACHING MUSCLES at their WORST? | | | | |
| O None | O Mild | O Moderate | O Severe | O Very severe |
| **5c.** In the last 7 days, how much did ACHING MUSCLES INTERFERE with your usual or daily activities? | | | | |
| O Not at all | O A little bit | O Somewhat | O Quite a bit | O Very much |

| | | | | |
|---|---|---|---|---|
| **6a.** In the last 7 days, how OFTEN did you have ACHING JOINTS (SUCH AS ELBOWS, KNEES, SHOULDERS)? | | | | |
| O Never | O Rarely | O Occasionally | O Frequently | O Almost constantly |
| **6b.** In the last 7 days, what was the SEVERITY of your ACHING JOINTS (SUCH AS ELBOWS, KNEES, SHOULDERS) at their WORST? | | | | |
| O None | O Mild | O Moderate | O Severe | O Very severe |
| **6c.** In the last 7 days, how much did ACHING JOINTS (SUCH AS ELBOWS, KNEES, SHOULDERS) INTERFERE with your usual or daily activities? | | | | |
| O Not at all | O A little bit | O Somewhat | O Quite a bit | O Very much |

# Appendix 14
# Correction Formulas for QTc Intervals

**Fridericia's correction for QTc Measurement - QTcF**

$$QTcF\ (ms) = \frac{QT\ (ms)}{\sqrt[3]{RR(ms)/1000}}$$

Example: QTcF of a subject with a QT of 386 ms and a RR of 848 ms

QT (ms) = 386

RR (ms) = 848

$$\frac{QT\ (ms)}{\sqrt[3]{RR(ms)/1000}} = 408\ ms$$

**Bazett's correction for QTc Measurement - QTcB**

$$QTcB\ (ms) = \frac{QT\ (ms)}{\sqrt{RR(ms)/1000}}$$

Example: QTcB of a subject with a QT of 386 ms and a RR of 848 ms

QT (ms) = 386

RR (ms) = 848

$$\frac{QT\ (ms)}{\sqrt{RR(ms)/1000}} = 419\ ms$$