Official Title: **AN EARLY-PHASE, MULTICENTER, OPEN-LABEL STUDY OF THE SAFETY AND PHARMACOKINETICS OF ATEZOLIZUMAB (MPDL3280A) IN PEDIATRIC AND YOUNG ADULT PATIENTS WITH PREVIOUSLY TREATED SOLID TUMORS**

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PROTOCOL

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MEDICAL MONITOR:	[redacted], M.D.
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PROTOCOL AMENDMENT APPROVAL

Approver's Name	Title	Date and Time (UTC)
[redacted]	Company Signatory	21-Oct-2016 14:33:33

PROTOCOL AMENDMENT, VERSION 5:
RATIONALE

Changes to the protocol, along with a rationale for each change, are summarized below.

- The atezolizumab clinical safety information has been updated to reflect the most current available data (Section 1.2.2.1).
- The International Neuroblastoma Response Criteria (INRC) used in this study is modified from the original INRC publication to clarify the definition of measurable (evaluable) disease on computed tomography and magnetic resonance imaging scans for malignant lymph nodes (Section 3.1 and Appendix 3). Notations were made to clarify this.
- The protocol was modified to include atypical teratoid rhabdoid tumor (ATRT) and rhabdoid tumor (RT) on the basis of a significant clinical response seen in a patient in the non-rhabdomyosarcoma soft tissue sarcoma cohort. Associated changes (including the addition of Response Assessment in Neuro-Oncology criteria) were made to allow for these patients to be able to enroll safely (e.g., utilization of steroids, exclusion of tumors that involve the brainstem) and to ensure that consistent data are obtained. Additional safety measures including but not limited to additional neurologic visits were added for patients enrolling in the ATRT cohort (Section 3.1, Section 3.3.7, Section 3.4.4, Section 4.1.1, Section 4.1.2, Section 4.5.2, Section 4.5.5.2, Section 5.3.5.10, Section 6.1, Section 6.6.1, and Section 6.6.2).
- The safety monitoring and reporting period has been differentiated on the basis of the category of adverse events. Serious adverse events and adverse events of special interest will be reported until 90 days after the last dose of study drug or initiation of new anti-cancer therapy, whichever occurs first. All other adverse events, regardless of relationship to study drug, will be reported until 30 days after the last dose of study drug or initiation of new anti-cancer therapy, whichever occurs first. The change was made for consistency with the atezolizumab program in adult studies and to better focus on the most relevant safety information (Section 3.1, Section 5.1, Section 5.3.1, Section 5.4.2.2, and Section 5.6).
- Bone biopsy tissue samples are now part of the acceptable tissue samples because of operational and bioanalytical updates; these samples can now be analyzed in the setting of this study (Sections 4.1.1 and 4.5.6).
- Contraception requirements were updated to require female patients to use two methods of birth control for at least 5 months after the last dose of study drug, which corresponds to five times the terminal half-life of atezolizumab and is expected to provide a complete washout of the drug from the body. Male contraception requirements were removed in consistency with updated safety requirements reported in the Investigator's Brochure (Version 8), provided that atezolizumab is not considered a genotoxic drug (Section 4.1.1).
- The criterion that excludes patients under treatment with investigational therapy (except specific cancer therapies) within 4 weeks prior to initiation of study drug was modified (Section 4.1.2). The 4-week period of withholding treatment is, in

certain instances, considered too extensive in this impaired patient population. If required, patients will be evaluated on the basis of their grade of recovery of toxicity.

- Enrollment stopping rules (Section 3.1.2) were updated in accordance to the atezolizumab Pediatric Investigational Plan.

In addition, this amendment incorporates changes as follows:

- The overall target enrollment has been modified (from approximately 40−100 to approximately 100) and the expected enrollment period updated on the basis of the updated recruitment plan (Section 3.1.1, Section 4.1, Section 6.1, and Section 9.4).
- For consistency with the atezolizumab program in adult studies, it was clarified that among adverse events requiring drug discontinuation is included any toxicity that requires interruption of treatment for $>$105 days (previously $>$42 days), which refers to no more than 105 days between infusions (Section 3.1.3, Section 4.6.2, and Section 5.1.1.1).
- Clarification of the exclusion criteria referring to any non-hematologic toxicity (excluding alopecia) from prior treatment that has not resolved to Grade $\leq$1: long-term sequelae of prior treatment (hearing loss, iatrogenic hypothyroidism, infertility, etc.) are not considered non-hematologic toxicity and are instead considered chronic medical conditions (Section 4.1.2).
- For consistency with the atezolizumab program in adult studies and updated safety requirements reported in the Investigator's Brochure (Version 8), the following exclusion criteria were amended (Section 4.1.2):

  Allowed timing of treatment with chemotherapy, differentiation therapy, or immunotherapy (such as anti-GD2 antibody treatment) prior to initiation of study drug updated to within 3 weeks instead of 4 weeks.

  Allowed timing of treatment with thoracic or mediastinal radiotherapy to within 3 weeks prior to initiation instead of 6 weeks.

  Allowed timing of treatment with hormonal therapy or biologic therapy updated to 4 weeks or 5 half-lives, whichever is shorter, instead of 4 weeks.

  Allowed timing of treatment with herbal cancer therapy updated to within 1 week prior to initiation of study drug instead of 4 weeks.

  Patients with a history of autoimmune-related hypothyroidism on a stable dose of thyroid-replacement hormone are now eligible for the study.

  Patients with controlled Type 1 diabetes mellitus on a stable insulin regimen are now eligible for the study.

  Allowed timing of use of live vaccine or live attenuated vaccine updated to within 4 weeks prior to initiation of the study or 5 months after final dose of study drug, instead of the previously stated 90 days after final dose (Section 4.1.2, Section 4.4.2, and Section 5.1).

- Pregnancy reporting was updated for female patients to a more extensive period of 5 months (Section 5.4.3.1), which corresponds to five times the terminal half-life of

atezolizumab and is expected to provide a complete washout of the drug from the body. In case of pregnancies in partners of male patients, the Sponsor will follow up the outcome of the pregnancy regardless of time after last dose (Section 5.4.3.2).

- Guidelines for the management of specific adverse events (Section 5.1.1) were amended to remove endocrine events and clarify systemic immune activation. Instruction for management of atezolizumab-specific adverse events now refers to the Investigator's Brochure.
- Changes that aim to facilitate the operational feasibility of the study and clarifications were made in the sections related to dosage, administration and compliance, prohibited therapies, tumor assessments, laboratory-related sections, patient discontinuation, adverse events requiring drug discontinuation immediately reportable to the Sponsor, immediate reporting requirements, reporting requirements, and schedules of assessments (Section 4.3.2, Section 4.4.2, Section 4.5.5.1, Section 4.5.6, Section 4.6.1, Section 5.2.4, Section 5.4, Section 5.4.2, Appendix 1, and Appendix 2).

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

PROTOCOL AMENDMENT, VERSION 5:
SUMMARY OF CHANGES

PROTOCOL SYNOPSIS

The protocol synopsis has been updated to reflect the changes to the protocol, where applicable.

SECTION 1.1: PD-L1/PD-1 PATHWAY IN CANCER

Encouraging clinical data emerging in the field of ~~tumor~~*cancer* immunotherapy have demonstrated that therapies focused on enhancing T-cell responses against cancer can result in a significant survival benefit in patients with advanced solid tumors and hematologic malignancies.

SECTION 1.2: BACKGROUND ON ATEZOLIZUMAB

Atezolizumab *(also referred to as TECENTRIQ®)* is a humanized IgG1 monoclonal antibody that targets PD-L1 and inhibits its interaction with PD-1.

SECTION 1.2.2.1: Clinical Safety

As of 10 May ~~2015~~*2016*, atezolizumab has been administered to approximately ~~3200~~*6000* adult patients with solid tumors and hematologic malignancies…

…In Study PCD4989g, as of ~~11 May 2015~~*15 December 2015*, there have been ~~558~~*629* adult patients treated with study drug ~~for a median duration of treatment of 12.14 weeks (range: 0.0 71.4)~~. The most common cancer types for these patients include non–small cell lung cancer (NSCLC; n = ~~91~~*89*), urothelial bladder cancer (n = ~~94~~*95*), triple-negative breast cancer (n = ~~78~~*111*), and renal cell carcinoma (n = ~~70~~*72*). Of the ~~558~~*629* patients *evaluable for safety* enrolled, ~~376~~ *444* patients (~~67.4~~*70.6*%) reported at least one treatment-related adverse event while receiving study drug. The most frequently observed adverse events (occurring in ≥ 10% of treated patients) included fatigue, nausea, decreased appetite, diarrhea, constipation, dyspnea, pyrexia, cough, vomiting, anemia, back pain, headache, asthenia, arthralgia, pruritus, rash, abdominal pain, peripheral edema, *urinary tract infection,* insomnia, and ~~chills~~*dizziness*. Grade ≥ 3 adverse events were reported by ~~260 of 558~~*326 of 629* patients (~~46.6~~*51.8*%), and ~~69~~*89* patients (~~12.4~~*14.1*%) experienced Grade ≥ 3 adverse events that were assessed as related to study drug by the investigators. The most frequently reported related Grade 3 and 4 adverse events included ~~dyspnea, pneumonitis, increased alanine aminotransferase, increased aspartate aminotransferase, increased gamma-glutamyl transferase, lymphocyte count decreased, cardiac tamponade, asthenia, autoimmune hepatitis, pneumonia, influenza, and hypoxia~~*fatigue, asthenia, increased aspartate aminotransferase, dyspnea, and hyponatremia*.

SECTION 1.3: STUDY RATIONALE AND BENEFIT-RISK ASSESSMENT

The expression of PD-L1 by malignant cells has been reported in many pediatric tumor types, including high-grade glioma (Wintterle et al. 2003; Wilmotte et al. 2005; Parsa et al. 2007), rhabdomyosarcoma (Wiendl et al. 2003*, Kim et al. 2008*),

non-Hodgkin's lymphoma (Yamamoto et al. 2009; Green et al. 2010; Andorsky et al. 2011), Hodgkin's lymphoma (Yamamoto et al. 2008, 2009; Green et al. 2010), ~~rhabdomyosarcoma (Kim et al. 2008),~~ soft tissue sarcoma (Kim et al. 2008), osteosarcoma (Lussier et al. 2013), Ewing sarcoma (Kim et al. 2008), and Wilms tumor (Routh et al. 2008, 2013).

SECTION 2.6: EXPLORATORY OBJECTIVES

- To evaluate potential relationships between *detectable* ATAs and other *clinical relevant* outcome measures (e.g., pharmacokinetics, safety, and efficacy)

SECTION 3.1: DESCRIPTION OF STUDY

…An independent Data Monitoring Committee (iDMC) will review the safety data of the first 5 patients and make recommendations on the appropriateness of opening the study to patients <2 years of age *(see Section* 3.1.4*)*….

Tumor assessments will be performed every two cycles *from Cycle1* through Cycle 8 and then every 4th cycle thereafter. Response will be determined by the investigator through use of *modified* International Neuroblastoma Response Criteria (mINRC) for patients with neuroblastoma (see Appendix 3), Revised Response Criteria for Malignant Lymphoma for patients with Hodgkin's lymphoma or non-Hodgkin's lymphoma (Cheson et al. 2007; see Appendix 4), *Response Assessment in Neuro-Oncology (RANO) criteria (see* Appendix 11*) for patients with atypical teratoid rhabdoid tumor* and Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST v1.1) for patients with other solid tumors (see Appendix 5)…

…All patients will be closely monitored for adverse events throughout the study and for at least ~~90~~*30* days after the last dose of study treatment *or initiation of a new anti-cancer therapy, regardless of relationship to study drug* (see Section 5.3.1). *Serious adverse events and adverse events of special interest, regardless of relationship to study drug, will be monitored for 90 days after the last dose of study drug or until initiation of new anti-cancer therapy.* All identified adverse events should be followed up until resolution, which may necessitate monitoring beyond ~~90~~*30* days after the last dose of study drug.

SECTION 3.1.1: Number of Patients

Approximately ~~40~~ 100 patients are expected be enrolled in this study, at approximately 50 investigative sites in Europe and North America….

Accrual is expected to last approximately ~~2~~*3* years.

SECTION 3.1.2: Enrollment Stopping Rules

- The Sponsor has stopped the study.
- *At least two tumor type cohorts have enrolled the minimum number of patients needed for initial response assessment.*

Some exceptions may apply to these general stopping rules, including but not limited to the following:

- Enrollment in the study ~~will~~*may* be stopped if enrollment has been open for more than 2 years and at least 20 patients have been treated with the study.

SECTION 3.1.3: Adverse Events Requiring Drug Discontinuation

- Grade ≥3 thrombocytopenia with *a Grade ≥2* bleeding *event*
- Grade ≥3 non-hematologic, non-hepatic adverse event, with the following exceptions:

  Grade 3 fevers will not mandate study drug discontinuation.

  Grade 3 mucositis or stomatitis that resolves to Grade ≤2 within 3 days will not mandate study drug discontinuation.

  Grade ≥3 nausea or vomiting that responds to standard-of-care therapy within 3 days will not mandate study drug discontinuation. *In the ATRT cohort, this may mandate study drug discontinuation if Grade ≥3 nausea and/or vomiting is subsequent to increased intracranial pressure (see* Section 4.5.3.1 *for management guidelines)….*
- Any toxicity that requires interruption of atezolizumab treatment for >~~42~~*105* days *(e.g., no more than 105 days between infusions)*, except in patients who must be tapered off corticosteroids used to treat adverse events (see Section 5.1.1.1 for details). Longer periods of treatment interruption may be considered after discussion with the Medical Monitor.

SECTION 3.3.1: Rationale for Atezolizumab Starting Dose and Dose Modification

…For atezolizumab, the nonspecific elimination pathway appears to be primary, as evidenced by linear pharmacokinetics in the dose range of 1–20 mg/kg, which includes the *approved dose (for treatment of adult patients with urothelial carcinoma) and* recommended Phase II/III dose currently under investigation in multiple cancer types (1200 mg; equivalent to a weight-based dose of 15 mg/kg assuming an adult body weight of 80 kg)…

Children aged <18 years will receive the weight-based equivalent of the *approved adult dose and* recommended Phase II/III adult dose (15 mg/kg atezolizumab every 3 weeks, with a maximum of 1200 mg). Patients who are ≥18 years old will receive ~~a flat~~*the approved adult* dose of 1200 mg. Dose adjustments may be made, if necessary, to achieve exposures corresponding to those measured in adult patients and if the safety profile is acceptable.

Dose levels for modification will be determined on the basis of the available information regarding PK exposure, ~~based on~~ interim PK analyses, and the emerging safety profile.

SECTION 3.3.2: Rationale for Inclusion of Patients ~~Over~~ Aged *> 18 Years*

SECTION 3.3.4: Rationale for Treatment beyond Progression

…Patient~~s~~ *participation in the study* should be discontinued for unacceptable toxicity or symptomatic deterioration attributed to disease progression as determined by the investigator after an integrated assessment of radiographic data and clinical status (see Section 4.5.5.2).

SECTION 3.3.7: Rationale for Separate Cohorts for Rhabdoid Tumor and Atypical Teratoid Rhabdoid Tumor

Patients with atypical teratoid rhabdoid tumor (ATRT) and rhabdoid tumor will be enrolled into separate cohorts. Although the two tumor types are often merged together, reflecting common genetic drivers, the differences in tumor microenvironment (CNS for ATRT and non-CNS for rhabdoid tumor) necessitate separating them in this protocol. This will allow for a more thorough evaluation of atezolizumab in these tumor types and account for any differences in safety and efficacy that may occur because of differences in organ location or tumor microenvironment or the presence of a blood-brain barrier.

SECTION 3.4.2: Pharmacokinetic Outcome Measures

The PK outcome measures for this study are as follows:

- Atezolizumab maximum serum concentration (C_{max}) after the infusion on Day 1 of Cycle 1 *and Cycle 4*

SECTION 3.4.4: Efficacy Outcome Measures

The primary efficacy outcome measures for this study are as follows:

- Objective response, defined as a complete or partial response for patients with measurable disease or neuroblastoma patients with evaluable disease at baseline, or a complete response for patients with non–measurable but evaluable disease at baseline (except patients with neuroblastoma) on two consecutive occasions ≥4 weeks apart, as determined by the investigator using RECIST v1.1 for patients with solid tumors (see Appendix 6), *m*INRC for patients with neuroblastoma (see Appendix 3), ~~and~~ Revised Response Criteria for Malignant Lymphoma for patients with Hodgkin's lymphoma or non-Hodgkin's lymphoma (see Appendix 4)*, and RANO criteria (see* Appendix 11*) for patients with ATRT.*
- Clinical benefit response (CBR), defined as objective response or stable disease for at least 6 months, as determined by RECIST v1.1 for patients with osteosarcoma (see Appendix 6)
- PFS, defined as the time from initiation of study drug to the first documented occurrence of progressive disease, as determined by the investigator using RECIST v1.1 for patients with solid tumors (see Appendix 6), *m*INRC for patients with neuroblastoma (see Appendix 3), ~~and~~ Revised Response Criteria for Malignant Lymphoma for patients with Hodgkin's lymphoma or non-Hodgkin's

lymphoma (see Appendix 4), *and RANO criteria (see Appendix 11) for patients with ATRT,* or death from any cause, whichever occurs first

The secondary efficacy outcome measures for this study are as follows:

- DOR, defined as the time from the first tumor assessment that supports the patient's objective response to the time of progressive disease, as determined by the investigator using RECIST v1.1 for patients with solid tumors (see Appendix 5), *m*INRC for patients with neuroblastoma (see Appendix 3), ~~and~~ Revised Response Criteria for Malignant Lymphoma for patients with Hodgkin's lymphoma or non-Hodgkin's lymphoma (see Appendix 4*), and RANO criteria (Appendix 11) for patients with ATRT,* or death from any cause, whichever occurs first
- OS, defined as the time from initiation of study drug to death from any cause
- ORR, PFS, and DOR as determined *by the* investigator using ~~and~~ immune-modified RECIST v1.1 for patients with other solid tumors (see Appendix 5) and immune-related response criteria (irRC) for patients with neuroblastoma, Hodgkin's lymphoma or non-Hodgkin's lymphoma

SECTION 4.1: PATIENTS

This study will enroll ~~at least 40~~ *approximately 100* pediatric or young adult patients with solid tumors with known or expected PD-L1 pathway involvement for which prior treatment has proven to be ineffective (i.e., relapsed or refractory disease) or intolerable and for whom there are no curative standard-of-care treatment options.

SECTION 4.1.1: Inclusion Criteria

Non-Hodgkin's lymphoma

Rhabdoid tumor

Note: Patients who have synchronous rhabdoid tumor and ATRT with no clear primary should be enrolled into the rhabdoid tumor cohort, and they should complete the additional assessments scheduled for patients with ATRT.

ATRT

Other tumor types not included in the list above with documented expression of PD-L1 on either tumor cells or immune infiltrating cells with approval of the Medical Monitor…

- Disease that is measurable as defined by RECIST v1.1, *m*INRC, Revised Response Criteria for Malignant Lymphoma, *or RANO criteria* (as appropriate) or evaluable by nuclear medicine techniques, immunocytochemistry techniques, tumor markers, or other reliable measures
- Archival tumor tissue block or 15 freshly cut, unstained, serial slides available for submission or willingness to undergo a core or excisional biopsy prior to enrollment (fine-needle aspiration, brush biopsy, ~~bone metastases samples,~~ and lavage samples are not acceptable)…

- For patients of childbearing potential: agreement to remain abstinent (refrain from heterosexual intercourse) or use two adequate methods of contraception, including at least one method with a failure rate of < 1% per year, during the treatment period and for at least ~~90 days~~*5 months* after the last dose of study drug…

- ~~For male patients: agreement to remain abstinent (refrain from heterosexual intercourse) or use contraceptive measures and agreement to refrain from donating sperm, as defined below:~~

  ~~With female partners of childbearing potential or pregnant female partners, men must remain abstinent or use a condom during the treatment period and for at least 90 days after the last dose of study drug.~~

  ~~The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not acceptable methods of contraception.~~

  ~~Men must refrain from donating sperm during the treatment period and for at least 90 days after the last dose of study drug.~~

SECTION 4.1.2: Exclusion Criteria

Patients who meet any of the following criteria will be excluded from study entry:

- Known primary CNS malignancy or symptomatic CNS metastases*, except ATRT*

  Patients with ATRT must not have tumor brainstem involvement or tumors within 10 mm of the optic chiasm; they must not have a history of intracranial hemorrhage or spinal cord hemorrhage or have had neurosurgical resection, brain biopsy, or radiation to the primary brain tumor within 28 days of Cycle 1, Day 1.

- Patients with asymptomatic untreated CNS ~~disease~~*metastases* may be enrolled after consultation with the Medical Monitor, provided all of the following criteria are met:

  Evaluable or measurable outside the CNS. *(Note: this is not required for patients with ATRT.)*

  No metastases to brain stem, midbrain, pons, medulla, or cerebellum or within 10 mm of the optic apparatus (optic nerve or chiasm). *(Note: ATRT may have metastases in the cerebellum.)*

  No history of intracranial hemorrhage or spinal cord hemorrhage

  No ongoing requirement for corticosteroids for CNS disease *except in ATRT where steroids use is permitted with approval from the Medical Monitor. Patients with ATRT must receive a stable or decreasing dose for ≥5 days prior to the baseline magnetic resonance imaging [MRI] scan and at the time of drug initiation.*

  Patients taking a stable dose of anticonvulsants are permitted…

- Treatment with chemotherapy (other than high-dose chemotherapy as described above) or differentiation therapy (such as retinoic acid) or immunotherapy (such as anti-GD2 antibody treatment) within ~~4~~*3* weeks prior to initiation of study drug or, if treatment included nitrosoureas, within 6 weeks prior to initiation of study drug

  This requirement may be waived at the investigator's request if the patient has recovered from therapeutic toxicity to the degree specified in the protocol, with approval of the Medical Monitor.
- Treatment with thoracic or mediastinal radiotherapy within ~~6~~*3* weeks prior to initiation of study drug
- Treatment with hormonal therapy (except hormone replacement therapy or oral contraceptives) or biologic therapy ~~or herbal cancer therapy~~ within 4 weeks *or 5 half-lives, whichever is shorter,* prior to initiation of study drug. *This requirement may be waived at the investigator's request if the patient has recovered from therapeutic toxicity to the degree specified in the protocol, with approval of the Medical Monitor.*
- *Treatment with herbal cancer therapy within 1 week prior to initiation of study drug*
- Treatment with investigational therapy (with the exception of cancer therapies as described above) within 4 weeks prior to initiation of study drug. *This requirement may be waived at the investigator's request if the patient has recovered from therapeutic toxicity to the degree specified in the protocol, with approval of the Medical Monitor.*
- Treatment with a live vaccine or a live attenuated vaccine (e.g., nasal spray of live attenuated influenza vaccine or FluMist®) within 4 weeks prior to initiation of study drug or anticipation that such treatment will be required during the study or within ~~90 days~~*5 months* after the final dose of study drug
- Treatment with systemic corticosteroids or other systemic immunosuppressive medications (including but not limited to prednisone, dexamethasone, cyclophosphamide, azathioprine, methotrexate, thalidomide, and anti–tumor necrosis factor [TNF] agents) ~~within 2 weeks prior to~~*at the time of* initiation of study drug, or anticipated requirement for systemic immunosuppressive medications during the study

  Patients with ATRT can be receiving concurrent treatment with corticosteroids with approval from the Medical Monitor as outlined in Section 4.4.2 and the ATRT-related exclusion criteria.
- Current treatment with therapeutic anticoagulants
- Any non-hematologic toxicity (excluding alopecia ~~or hearing loss~~) from prior treatment that has not resolved to Grade ≤1 (per NCI CTCAE v4.0) at screening

  Note: Long-term sequelae of prior treatment (e.g., hearing loss, iatrogenic hypothyroidism, infertility, etc.) are not considered non-hematologic toxicity and instead are considered chronic medical conditions….

- Known hypersensitivity to ~~any component of the study drug~~ *biopharmaceuticals produced in Chinese hamster ovary cells or any component of the atezolizumab formulation…*
- History of any autoimmune disease, including but not limited to Type 1 diabetes mellitus, autoimmune-related hypothyroidism, myasthenia gravis, myositis, autoimmune hepatitis, systemic lupus erythematosus, rheumatoid arthritis, inflammatory bowel disease, vascular thrombosis associated with anti-phospholipid syndrome, Wegener granulomatosis, Sjögren's syndrome, Guillain-Barré syndrome, multiple sclerosis, vasculitis, or glomerulonephritis

  Patients with a history of autoimmune-related hypothyroidism who are receiving a stable dose of thyroid-replacement hormone are eligible for the study.

  Patients with controlled Type 1 diabetes mellitus who are receiving a stable dose of insulin regimen are eligible for the study….

SECTION 4.3.1: Formulation, Packaging, and Handling

~~The atezolizumab drug product is provided in a single use, 20 mL USP/Ph. Eur. Type 1 glass vial as a colorless to slightly yellow, sterile, preservative free clear liquid solution intended for IV administration. The vial is designed to deliver 20 mL (1200 mg) of atezolizumab solution but may contain more than the stated volume to enable delivery of the entire 20 mL volume. The atezolizumab drug product is formulated as 60 mg/mL atezolizumab in 20 mM histidine acetate, 120 mM sucrose, 0.04% polysorbate 20, pH 5.8.~~

~~Atezolizumab must be refrigerated at 2°C 8°C (36°F 46°F) upon receipt until use. Atezolizumab vials should not be used beyond the expiration date provided by the manufacturer. No preservative is used in the atezolizumab drug product; therefore, each vial is intended for single use only. Discard any unused portion of drug remaining in a vial. Vial contents should not be frozen or shaken and should be protected from direct sunlight.~~*Atezolizumab will be supplied by the Sponsor as sterile liquid in 20-mL glass vials. The vial is designed to deliver 20 mL (1200 mg) of atezolizumab solution but may contain more than the stated volume to enable delivery of the entire 20-mL volume.*

For ~~further~~ information on the ~~storage~~*formulation* and handling of atezolizumab, see the ~~Pharmacy Manual and the Atezolizumab~~ Investigator's Brochure *and Pharmacy Manual*.

SECTION 4.3.2: Dosage, Administration, and Compliance

Patients will be weighed at the beginning of each cycle (within ~~3~~*7* days of the Day 1 dose), and the dose will be adjusted as needed. Atezolizumab infusion may be delayed up to ~~3~~*5* days to accommodate holidays, weekends, and other patient obligations. Subsequent infusions should be rescheduled accordingly. *For patients who receive the 15-mg/kg dose, the dose administered should be within 5% of the calculated dose to accommodate for any rounding that may need to occur….*

…The initial dose of atezolizumab will be ~~delivered~~*administered* over 60 (±15) minutes. If the first infusion is tolerated without infusion-associated adverse events, the second infusion may be delivered over 30 (±10) minutes. If the 30-minute infusion is well tolerated, all subsequent infusions may be ~~delivered~~*administered* over 30 (±10) minutes….

~~Refer to the Pharmacy Manual for detailed instructions on drug preparation and administration.~~*For more detailed information on drug preparation, storage, and administration, refer to the Investigator's Brochure and Pharmacy Manual.*

SECTION 4.4.2: Prohibited Therapy

Use of the following therapies is prohibited during the study:

- Any concomitant therapy intended for the treatment of solid tumors, either approved by health authorities or experimental, including chemotherapy, radiotherapy (except palliative radiotherapy), hormonal therapy, immunotherapy, biologic therapy, or herbal therapy

  Patients with rhabdoid tumor and ATRT may receive local therapy (radiation or surgery) after at least four cycles of atezolizumab with approval of the Medical Monitor….

- Live vaccines and live attenuated vaccines (prohibited during the study and for ~~90 days~~*5 months* after the last dose of study drug) …

Patients with ATRT can be receiving concurrent treatment with corticosteroids with approval from the Medical Monitor. Patients must be receiving a stable or decreasing dose for ≥5 days prior to the baseline MRI scan and at the time of drug initiation. The Medical Monitor should be informed when steroid doses are increased because of declining patient status.

In clinically indicated emergent situations (i.e., anaphylaxis), corticosteroids may be administered without notifying the Medical Monitor in advance, but the Medical Monitor should be notified within 24 hours of the event. If feasible, alternatives to these agents should be considered. *Systemic steroids used as steroid replacement therapy for adrenal insufficiency are permitted.*

SECTION 4.5.3.1: Neurologic Examinations (ATRT Only)

For patients with ATRT, a complete neurologic examination should be completed at every patient visit, including at baseline (see Schedule of Assessments in Appendix 1*). Any abnormality identified at baseline should be recorded on the General Medical History and Baseline Conditions eCRF.*

At subsequent visits (or as clinically indicated), changes from baseline abnormalities need to be reviewed carefully prior to administering the next atezolizumab dose. Atezolizumab should not be administered if there is any sign of increased intracranial pressure.

The neurologic examination should include age-appropriate evaluations of vision, including visual fields, coordination, cranial nerve function, strength and motor evaluations (including gait when appropriate), and reflexes. Discussions with the parents and/or guardian should also occur to assess for new or worsening symptoms, including but not limited to changes in physical activity, irritability, headaches, changes in appetite and/or feeding, vomiting, and nausea.

New or worsened clinically significant abnormalities should be recorded as adverse events on the Adverse Event eCRF.

SECTION 4.5.5.1: Tumor Assessments

Response will be assessed by the investigator on the basis of physical examinations, CT scans, MRI scans, fluorodeoxyglucose-positron emission tomography (FDG-PET) scans, or MIBG scans, as appropriate. ~~CT or MRI scans should include chest, abdomen, and pelvic scans; CT scans of the neck should be included if clinically indicated.~~*Tumor assessment imaging should include all areas of known disease. A chest CT is also required to be performed at each assessment.* An objective response should be confirmed by repeat assessments ≥4 weeks after initial documentation. The same *imaging techniques and*~~radiographic~~ procedure*s* used to assess disease sites at screening should be used throughout the study (e.g., the same contrast protocol for CT scans). To the extent that is feasible, assessments should be performed by the same evaluator to ensure internal consistency across visits.

SECTION 4.5.5.2: Response Criteria

All tumors will be evaluated for disease response and progressive disease with RECIST v1.1 (see Appendix 6) with the exception of those listed below.

- Neuroblastoma: *m*INRC (see Appendix 3)
- Hodgkin's lymphoma and non-Hodgkin's lymphoma: Revised Response Criteria for Malignant Lymphoma (see Appendix 4)
- *ATRT: RANO criteria (see* Appendix 11*)*

  Patients with synchronous ATRT and rhabdoid tumor with no clear primary should be enrolled into the rhabdoid tumor cohort. These patients' tumors will be evaluated with RECIST v1.1 criteria.

SECTION 4.5.6: <u>Laboratory, Biomarker, and Other Biological Samples</u>

…In situations where the total amount will exceed the amount stated above, clinical laboratory assessments should be prioritized. Any remaining blood should be sent for PK analysis and immunogenicity followed by biomarker and PD analyses.

Laboratory tests results must meet the inclusion criteria and not meet the exclusion criteria at the time of screening. If laboratory tests are performed again prior to the first dose, they must continue to meet the inclusion criteria and not meet the exclusion criteria.

…Patients without archival samples must ~~be willing to~~ undergo a core or excisional biopsy prior to enrollment. Fine-needle aspiration, brush biopsy, ~~bone marrow biopsy,~~ and lavage samples are not acceptable. *Submission of bone biopsy specimens is strongly discouraged because of complications in the assessment of such tissue. These specimens can be used only if no other tissue is available….*

- ~~Epstein Barr virus serology~~

Samples will be destroyed when the final Clinical Study Report has been completed, with the following exceptions:

- Any remaining samples collected for pharmacokinetics, biomarker assays, and ATA assays may be used for exploratory biomarker profiling, identification, and PD assay development purposes and for additional safety assessments (e.g., ATA assay) as appropriate. *These samples will be destroyed no later than 5 years after the final Clinical Study Report has been completed.* The remainder of samples obtained for study-related procedures will be destroyed no later than 5 years after the date of final closure of the clinical database unless the patient gives specific consent for the remainder of the samples to be stored for optional exploratory research….

SECTION 4.6.1: Patient Discontinuation

Every effort should be made to obtain information on patients who withdraw from the study. The primary reason for withdrawal from the study should be documented on the appropriate eCRF. *In situations where it is either unsafe or not in the best interest of the patient to complete follow-up assessments after study drug discontinuation, survival data only may be submitted during the follow-up period with approval of the Medical Monitor.* ~~However, p~~*P*atients will not be followed up for any reason after consent has been withdrawn. Patients who withdraw from the study will not be replaced.

SECTION 4.6.2: Study Drug Discontinuation

- Interruption of study treatment for >~~42~~*105* days *(e.g., more than 105 days between infusions)* because of an atezolizumab-related adverse event, except in patients who must be tapered off corticosteroids used to treat adverse events (see Section 5.1.1.1 for details). This duration may be extended after consultation with the Medical Monitor.

SECTION 5.1: SAFETY PLAN

Atezolizumab is not approved *for pediatric use* and is currently in clinical development *for different indications*. Human experience is currently limited, and the entire safety profile is not known at this time. It has not been studied in patients younger than 15 years old. The following information is based on results from nonclinical and adult clinical studies and published data on similar molecules. Refer to the Atezolizumab Investigator's Brochure for a complete summary of safety information.

Measures will be taken to ensure the safety of patients participating in this study. Eligibility criteria have been designed to exclude patients at higher risk for toxicities. Specifically, patients at risk for study-emergent autoimmune conditions or with a prior diagnosis of autoimmune disease *(except patients with a history of autoimmune-related hypothyroidism receiving a stable dose of thyroid-replacement hormone or patients with controlled Type 1 diabetes mellitus receiving a stable dose of insulin regimen)*, patients with evidence of acute or chronic infections, and patients who have received a live vaccine or a live attenuated vaccine within 4 weeks prior to initiation of study drug will be excluded from the study (see Section 4.1.2). Patients are also required to abstain from receiving a live or live attenuated vaccine during treatment and for ~~90 days~~*5 months* following the last atezolizumab dose. In addition, patients will undergo safety monitoring during the study as described in Section 4.5, Section 5, and the schedules of assessments (see Appendix 1 and Appendix 2). *Patients with ATRT will be monitored with additional visits to assess neurologic function due to the possible risk of tumor progression and/or pseudoprogression in the CNS cavities.* Adverse events, laboratory values, and vital signs must be reviewed prior to each infusion….

…~~All~~ *Serious* adverse events *and adverse events of special interest* will be recorded during the study *and for 90 days after the last dose of study treatment or until the initiation of another anti-cancer therapy, whichever occurs first. All other adverse events will be recorded during the study* and for ~~90~~*30* days after the last dose of study treatment or until the initiation of another anti-cancer therapy, whichever occurs first; treatment-related adverse events must be reported beyond this date (see Section 5.3.1). In addition, patients will continue to be followed up at defined time intervals (see schedules of assessments in Appendix 1 and Appendix 2) until termination of the study. Following discontinuation from this study, patients will be offered follow-up for adverse events and survival.

SECTION 5.1.1.1: Dose Modification and Treatment Interruption

There will be no intrapatient atezolizumab dose reductions as a result of adverse events. Study drug may be temporarily withheld if patients experience an adverse event that is considered related to atezolizumab. If study drug is withheld because of an atezolizumab-related adverse event for > ~~42~~ *105* days, the patient will be discontinued from atezolizumab treatment.…

…If patients must be tapered off corticosteroids used to treat adverse events, study treatment may be withheld for > ~~42~~ *105* days. The acceptable length of interruption will depend on agreement between the investigator and the Medical Monitor.

SECTION 5.1.1.2: Immune-Mediated Adverse Events

~~Specific guidance for investigators regarding endocrine events and systemic immune activation (SIA) are described below. For all other immune-mediated adverse events (pulmonary events [pneumonitis]; hepatic events; GI events [diarrhea/colitis]; ocular events; infusion-related reactions; pancreatic events; dermatologic events [rash]; and~~

~~neurologic disorders) refer to the Atezolizumab IB for guidance (Appendix 10 for precautions for anaphylaxis).~~

~~**Note**: The Atezolizumab IB lists recommended steroid dosing for adult patients. In the pediatric population weight based equivalent dosing adapted to children should be used~~*Management of systemic immune activation is presented below. Refer to the Atezolizumab Investigator's Brochure for details on management of atezolizumab-specific adverse events, including pulmonary events, hepatic events, gastrointestinal events, endocrine events, ocular events, infusion-related reactions, pancreatic events, dermatologic events, neurologic disorders, and immune-related meningoencephalitis.*

~~SECTION 5.1.1.3: Endocrine Events~~

~~Thyroid disorders or adrenal insufficiency has been associated with the administration of atezolizumab.~~

~~Patients with unexplained symptoms such as fatigue, myalgia, polydipsia, polyuria, impotence, mental status changes, or constipation should be investigated for the presence of thyroid, pituitary, or adrenal endocrinopathies, as well as for hyponatremia or hyperkalemia. An endocrinologist should be consulted if an endocrinopathy is suspected. Tests such as TSH and free thyroxine (T4), prolactin, and a morning cortisol level will help to differentiate primary adrenal insufficiency from primary pituitary insufficiency.~~

~~TABLE 1: Management Guidelines for Endocrine Events~~

Table 1 has been deleted. Subsequent tables have been renumbered accordingly.

SECTION 5.1.1.3: Systemic Immune Activation

Systemic immune activation is a rare condition characterized by an excessive immune response. Given the mechanism of action of atezolizumab, systemic immune activation is considered a potential risk when given in combination with other immunomodulating agents. Systemic immune activation should be included in the differential diagnosis for patients who, in the absence of an alternate etiology, develop a sepsis-like syndrome after administration of atezolizumab, and initial evaluation should include *assessing* the following:

SECTION 5.1.1.4: Central Nervous System Signs and Symptoms (ATRT Only)

For the ATRT cohort only, signs and symptoms of disease progression and pseudoprogression of this CNS tumor should be assessed at each visit. Study treatment should be interrupted immediately and patients should be treated with steroids and/or other medications to reduce intracranial pressure as per institutional guidelines in the case of signs and symptoms of increased intracranial pressure considered to be related to atezolizumab, including but not limited to vomiting, headache, changes in mental status, and vision changes. The Medical Monitor should be contacted within 24 hours

if CNS signs and symptoms considered to be related to atezolizumab occur. Patients should be treated with steroids and/or other medications to reduce intracranial pressure as per institutional guidelines.

~~**SECTION 5.2.4: Adverse Events Requiring Drug Discontinuation (Immediately Reportable to the Sponsor)**~~

~~Adverse events requiring drug discontinuation (defined in Section 3.1.3), 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 Section 5.4.2 for reporting instructions).~~

SECTION 5.3.1: Adverse Event Reporting Period

After initiation of study drug, all *serious* adverse events *and adverse events of special interest, regardless of relationship to study drug,* will be reported until 90 days after the last dose of study drug *or initiation of new anti-cancer therapy, whichever occurs first. All other adverse events, regardless of relationship to study drug, will be reported until 30 days after the last dose of study drug or initiation of new anti-cancer therapy, whichever occurs first.* After this period, the investigator should report any serious adverse events that are believed to be related to prior study drug treatment (see Section 5.6).

SECTION 5.3.5.10: Lack of Efficacy or Worsening of Cancer

Events that are clearly consistent with the expected pattern of disease evolution should not be recorded as adverse events. These data will be captured as efficacy assessment data only. In most cases, the expected pattern of progression will be based on *m*INRC, Revised Response Criteria for Malignant Lymphoma, ~~or~~ RECIST v1.1*, or RANO criteria* as appropriate. In rare cases, the determination of clinical progression will be based on symptomatic deterioration. However, every effort should be made to document progression through use of objective criteria. If there is any uncertainty as to whether an event is a result of progressive disease, it should be reported as an adverse event.

SECTION 5.4: IMMEDIATE REPORTING REQUIREMENTS FROM INVESTIGATOR TO SPONSOR

- ~~Adverse events requiring drug discontinuation~~

SECTION 5.4.2: Reporting Requirements for Serious Adverse Events and Adverse Events of Special Interest, ~~and Adverse Events Leading to Drug Discontinuation~~

SECTION 5.4.2.2: Events That Occur after Study Drug Initiation

After initiation of study drug, serious adverse events and adverse events of special interest*, regardless of relationship to study drug,* will be reported until 90 days after the last dose of study drug *or initiation of new anti-cancer therapy, whichever occurs first. All other adverse events, regardless of relationship to study drug, will be reported until 30 days after the last dose of study drug or initiation of new anti-cancer therapy, whichever occurs first.*

The investigator should also report any serious adverse events that are believed to be related to prior study drug treatment even if these occur after the abovementioned reporting periods. Investigators should record all case details that can be gathered immediately (i.e., within 24 hours after learning of the event) on the Adverse Event eCRF and submit the report via the electronic data capture (EDC) system. A report will be generated and sent to Roche Safety Risk Management by the EDC system.

SECTION 5.4.3.1: Pregnancies in Patients

Patients of childbearing potential will be instructed to immediately inform the investigator if they become pregnant during the study or within ~~90 days~~ *5 months* after the last dose of study drug.

SECTION 5.4.3.2: Pregnancies in Partners of Male Patients

Male patients will be instructed through the Informed Consent Form to immediately inform the investigator if their partner becomes pregnant during the study or ~~within 90 days~~ after the last dose of study drug.

SECTION 5.6: POST-STUDY ADVERSE EVENTS

The Sponsor should be notified if the investigator becomes aware of any serious adverse event that occurs after the end of the adverse event reporting period (defined as 90 days after the last dose of study drug *or until initiation of new anti-cancer therapy for serious adverse events and adverse events of special interest and 30 days for all other adverse events*), if the event is believed to be related to prior study drug treatment.

~~The investigator should report these events directly to the Sponsor or its designee, either by faxing or by scanning and e-mailing the Serious Adverse Event/Adverse Event of Special Interest Reporting Form using the fax number or e-mail address provided to investigators.~~*These events should be reported through use of the Adverse Event eCRF. However, if the EDC system is not available, the investigator should report these events directly to the Sponsor or its designee, either by faxing or by scanning and emailing the Serious Adverse Event/Adverse Event of Special Interest Reporting Form using the fax number or email address provided to investigators.*

SECTION 6.1: DETERMINATION OF SAMPLE SIZE
TABLE 3: Sample Size and Responder Requirements for Initial Response Assessment

Table 3 heading of column 2 has been changed as follows: Historical Control ~~Overall~~*Objective* Response Rate. The last 2 rows of text regarding rhabdoid tumor and atypical teratoid rhabdoid tumor were added.

Overall, approximately ~~40~~ *100* patients will be enrolled in the study.

SECTION 6.4: PHARMACOKINETIC ANALYSES

…Descriptive statistics will include mean, median, range, ~~and~~ standard deviation, *coefficient of variation, geometric mean, and geometric mean coefficient of variation* as appropriate….

SECTION 6.5: IMMUNOGENICITY ANALYSES

The immunogenicity analyses will include patients with at least one ATA assessment. The numbers and proportions of ATA-positive patients and ATA-negative patients during both the treatment and follow-up periods will be summarized. Patients are considered to be ATA positive if they are ATA negative *or missing* at baseline but develop an ATA response following study drug administration (treatment-induced ATA response), or if they are ATA positive at baseline and the titer of one or more post-baseline samples is at least 4-fold greater (i.e., ≥0.60 titer units) than the titer of the baseline sample (treatment-enhanced ATA response). Patients are considered to be ATA negative if they are ATA negative *or missing* at baseline and all post-baseline samples are negative, or if they are ATA positive at baseline but do not have any post-baseline samples with a titer that is at least 4-fold greater than the titer of the baseline sample (treatment unaffected).

SECTION 6.6.1: Primary Efficacy Endpoint

The primary endpoints for efficacy are ORR and PFS. For patients with measurable disease or patients with neuroblastoma who have evaluable disease at baseline, an objective response is defined as a complete or partial response on two consecutive occasions ≥4 weeks apart, as determined by the investigator using RECIST v1.1 for patients with solid tumors (see Appendix 6), *m*INRC for patients with neuroblastoma (see Appendix 3), Revised Response Criteria for Malignant Lymphoma for patients with Hodgkin's lymphoma or non-Hodgkin's lymphoma (see Appendix 4)*, and RANO criteria (see Appendix 11) for patients with ATRT*.

For patients with non-measurable but evaluable disease at baseline (except *patients with* neuroblastoma ~~patients~~), an objective response is defined as a complete response on two consecutive occasions ≥ 4 weeks apart, as determined by the investigator using RECIST v1.1 for patients with solid tumors (see Appendix 6), Revised Response Criteria for Malignant Lymphoma for patients with Hodgkin's lymphoma or non-Hodgkin's lymphoma (see Appendix 4)*, and RANO criteria (see Appendix 11) for patients with ATRT*.

… PFS is defined as the time from initiation of study drug to the first documented occurrence of disease progression, as determined by the investigator using RECIST v1.1 for patients with solid tumors (see Appendix 6), *m*INRC for patients with neuroblastoma (see Appendix 3), Revised Response Criteria for Malignant Lymphoma for patients with Hodgkin's lymphoma or non-Hodgkin's lymphoma (see Appendix 4), *and RANO criteria (see Appendix 11) for patients with ATRT,* or death from any cause, whichever occurs first.

SECTION 6.6.2: Secondary Efficacy Endpoints

For patients who achieve an objective response, DOR is defined as the time from the first tumor assessment that supports the patient's objective response to the time of progressive disease, as determined by the investigator using *m*INRC for patients with neuroblastoma (see Appendix 3), Revised Response Criteria for Malignant Lymphoma for patients with Hodgkin's lymphoma or non-Hodgkin's lymphoma (see Appendix 4), *RANO criteria (see Appendix 11) for patients with ATRT,* and RECIST v1.1 for patients with other solid tumors (see Appendix 6), or death from any cause, whichever occurs first.

SECTION 9.4: ADMINISTRATIVE STRUCTURE

This study will be sponsored by Roche and managed with the support of a contract research organization, which will provide clinical monitoring, sample management, and project management support. Approximately ~~40–~~*1*00 patients are expected be enrolled in this study, at approximately 50 investigative sites in Europe and North America.

SECTION 9.5: PUBLICATION OF DATA AND PROTECTION OF TRADE SECRETS

Regardless of the outcome of a study, the Sponsor is dedicated to openly providing information on the study to health care professionals and to the public, both at scientific congresses and in peer-reviewed journals. The Sponsor will comply with all requirements for publication of study results. ~~For more information, refer to the Roche Global Policy on Sharing of Clinical Trials Data at the following Web site:~~

~~http://www.rochetrials.com/pdf/RocheGlobalDataSharingPolicy.pdf~~

APPENDIX 1: Schedule of Assessments

The schedule of assessments has been revised to reflect the changes to the protocol.

APPENDIX 2: Schedule of Pharmacokinetic, Pharmacodynamic, and Immunogenicity Assessments

Appendix 2 has been updated to reflect changes in the protocol that update timepoints and sample types.

APPENDIX 3: *Modified* International Neuroblastoma Response Criteria

Appendix 3 has been updated to reflect changes in the protocol that clarify the definition of measurable disease in malignant lymph nodes.

APPENDIX 11: *Response Assessment in Neuro-Oncology Criteria*

Appendix 11 has been added to the protocol.

SAMPLE INFORMED CONSENT FORM

The sample Informed Consent Form has been revised to reflect the changes to the protocol.

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PROTOCOL AMENDMENT ACCEPTANCE FORM

TITLE:	**AN EARLY-PHASE, MULTICENTER, OPEN-LABEL STUDY OF THE SAFETY AND PHARMACOKINETICS OF ATEZOLIZUMAB (MPDL3280A) IN PEDIATRIC AND YOUNG ADULT PATIENTS WITH PREVIOUSLY TREATED SOLID TUMORS**
PROTOCOL NUMBER:	GO29664
VERSION NUMBER:	5
EUDRACT NUMBER:	2014-004697-41
IND NUMBER:	124026
TEST PRODUCT:	Atezolizumab (RO5541267)
MEDICAL MONITOR:	[redacted], M.D.
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 retain the signed original of this form for your study files. Please return a copy as instructed by your local study monitor.

PROTOCOL SYNOPSIS

TITLE:	**AN EARLY-PHASE, MULTICENTER, OPEN-LABEL STUDY OF THE SAFETY AND PHARMACOKINETICS OF ATEZOLIZUMAB (MPDL3280A) IN PEDIATRIC AND YOUNG ADULT PATIENTS WITH PREVIOUSLY TREATED SOLID TUMORS**
PROTOCOL NUMBER:	GO29664
VERSION NUMBER:	5
EUDRACT NUMBER:	2014-004697-41
IND NUMBER:	124026
TEST PRODUCT:	Atezolizumab (RO5541267)
PHASE:	Early Phase
INDICATION:	Solid tumors
SPONSOR:	F. Hoffmann-La Roche Ltd

Objectives

Safety Objective

The safety objective for this study is as follows:

- To evaluate the safety and tolerability of atezolizumab in pediatric and young adult patients, focusing on the nature, frequency, and severity of serious and non-serious adverse events, as well as effects on laboratory values and vital signs

Pharmacokinetic Objective

The pharmacokinetic (PK) objective for this study is as follows:

- To characterize the pharmacokinetics of atezolizumab

Immunogenicity Objective

The immunogenicity objective for this study is as follows:

- To evaluate the immune response to atezolizumab on the basis of the incidence of anti-therapeutic antibodies (ATAs)

Efficacy Objectives

The efficacy objectives for this study are as follows:

- To evaluate the anti-cancer activity of atezolizumab, as measured by objective response rate (ORR), progression-free survival (PFS), duration of objective response (DOR), and clinical benefit response rate (only for osteosarcoma)
- To evaluate the anti-cancer activity of atezolizumab, as measured by overall survival (OS)

Dose Assessment Objective

The dose-assessment objective for this study is as follows:

- To assess the optimal dose of atezolizumab in pediatric and young adult patients on the basis of safety, PK, and efficacy outcome measures

Exploratory Objectives

The exploratory objectives for this study are as follows:

- To explore if programmed death–ligand 1 (PD-L1) expression on tumor and/or tumor-infiltrating cells at baseline is predictive of response to atezolizumab

- To explore the relationship between atezolizumab exposure and changes in levels of pharmacodynamic (PD) biomarkers including but not limited to cytokines, circulating tumor DNA (ctDNA) concentration, and T-cell subpopulations
- To explore non-inherited biomarkers that may be predictive of response to atezolizumab (i.e., predictive biomarkers), may be associated with progression to a more severe disease state (i.e., prognostic biomarkers), acquired resistance to atezolizumab, or susceptibility to developing adverse events; may provide evidence of atezolizumab activity; or may increase the knowledge and understanding of disease biology
- To explore inherited biomarkers (i.e., variants in germline DNA) that may be predictive of response to atezolizumab (i.e., predictive biomarkers); may be associated with progression to a more severe disease state (i.e., prognostic biomarkers), acquired resistance to atezolizumab, or susceptibility to developing adverse events; or may increase the knowledge and understanding of disease biology
- To evaluate potential relationships between *detectable* ATAs and other *clinical relevant* outcome measures (e.g., pharmacokinetics, safety, and efficacy)

Study Design

Description of Study

The study is an early-phase, multicenter, open-label, single-arm study designed to evaluate the safety, tolerability, pharmacokinetics, immunogenicity, and preliminary efficacy of atezolizumab in pediatric and young adult patients with solid tumors with known or expected PD-L1 pathway involvement for which prior treatment has proven to be ineffective (i.e., relapsed or refractory) or intolerable and for whom no curative standard-of-care treatment options exist.

Number of Patients

Approximately 100 patients are expected be enrolled in this study, at approximately 50 investigative sites in Europe and North America. Of those who are enrolled, at least 20 patients < 18 years of age will be treated with study drug, and at least 40 patients across all tumor type cohorts will be treated and available for response assessment (at least two tumor type cohorts must enroll a minimum of 10 patients).

Target Population

Inclusion Criteria

Patients must meet the following criteria for study entry:

- Histologically or cytologically confirmed solid tumor of a type listed below (tumor types with known or expected PD-L1 pathway involvement) (including Hodgkin's and non-Hodgkin's lymphoma), for which prior treatment had proven to be ineffective (i.e., relapsed or refractory) or intolerable. Patients must have had histologic or cytologic confirmation of malignancy at the time of diagnosis or relapse.

  Neuroblastoma

  Rhabdomyosarcoma

  Non-rhabdomyosarcoma soft tissue sarcoma

  Osteosarcoma

  Ewing sarcoma

  Wilms tumor

  Hodgkin's lymphoma

  Non-Hodgkin's lymphoma

  Rhabdoid tumor

  Note: Patients who have synchronous rhabdoid tumor and atypical teratoid rhabdoid tumor (ATRT) with no clear primary should be enrolled into the rhabdoid tumor cohort, and they should complete the additional assessments scheduled for patients with ATRT.

  ATRT

  Other tumor types not included in the list above with documented expression of PD-L1 on either tumor cells or immune infiltrating cells with approval of the Medical Monitor

Other tumor types not included in the list above without documented expression of PD-L1 can be included with approval of the Medical Monitor and should not exceed 20% of the total sample size.

- Signed Informed Consent Form
- Signed Child's or Young Adult's Assent Form when appropriate, as determined by patient's age and individual site and country standards
- Age at study entry <30 years

  The first 5 patients must be $\geq$2 years of age (i.e., patients must have reached their 2nd birthday) to ensure safety and tolerability before patients $<$2 years of age receive their first dose of study drug. These first 5 patients must be followed for either two cycles of treatment or until drug discontinuation, whichever is shorter, prior to enrolling younger patients.

  The Sponsor may decide to stop enrollment of patients who are ≥ 18 years old at any time during the study to ensure adequate enrollment of patients < 18 years old.

  Patients who are ≥ 18 years old and are eligible for an adult PD-L1 treatment protocol will be preferentially enrolled onto those adult studies.
- In exceptional cases of relapsed pediatric tumors in patients ≥ 30 years of age, the Sponsor will consider waiving the age requirement with approval of the Medical Monitor. This waiver is restricted to patients with pediatric-specific diseases (e.g., neuroblastoma), for whom clinical trials are unlikely to be available and will not be extended to patients with tumors that typically occur both in children and adults (i.e., high-grade glioma).
- Able to comply with the study protocol, in the investigator's judgment
- Weight ≥ 3 kg
- Disease that is measurable as defined by Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST v1.1), *modified* International Neuroblastoma Response Criteria (mINRC), Revised Response Criteria for Malignant Lymphoma, *or Response Assessment in Neuro-Oncology (RANO) criteria* (as appropriate) or evaluable by nuclear medicine techniques, immunocytochemistry techniques, tumor markers, or other reliable measures
- Archival tumor tissue block or 15 freshly cut, unstained, serial slides available for submission or willingness to undergo a core or excisional biopsy prior to enrollment (fine-needle aspiration, brush biopsy, and lavage samples are not acceptable)

  Patients with fewer than 15 slides available may be eligible for study entry following discussion with the Medical Monitor.
- Lansky Performance Status (patients <16 years old) or Karnofsky Performance Status (patients ≥ 16 years old) ≥ 50
- Life expectancy ≥ 3 months, in the investigator's judgment
- For patients of childbearing potential: agreement to remain abstinent (refrain from heterosexual intercourse) or use two adequate methods of contraception, including at least one method with a failure rate of $<1\%$ per year, during the treatment period and for at least *5 months* after the last dose of study drug

  Examples of contraceptive methods with a failure rate of <1% per year include established, proper use of hormonal contraceptives that inhibit ovulation, hormone-releasing intrauterine devices (IUDs), and copper IUDs.

  The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not acceptable methods of contraception.

  Barrier methods must always be supplemented with the use of a spermicide.
- Adequate hematologic and end organ function, defined by the following laboratory results obtained within 28 days prior to initiation of study drug:

  ANC $\geq 0.75 \times 10^9$/L (unsupported)

  Platelet count $\geq 75 \times 10^9$/L (unsupported)

Hemoglobin ≥ 8 g/dL (transfusion permitted)

Bilirubin $\leq 1.5 \times$ upper limit of normal (ULN) for age

AST and ALT $\leq 2.5 \times$ ULN for age

Serum creatinine $\leq 1.5 \times$ ULN for age or creatinine clearance (or radioisotope glomerular filtration rate) > 70 mL/min/1.73 m^2

INR and aPTT ≤ 1.5 institutional ULN for age

Patients receiving therapeutic anticoagulants are excluded from the study.

- Fractional shortening $\geq 30\%$ or left ventricular ejection fraction $\geq 50\%$ at baseline, as determined by echocardiography or multigated acquisition scan within 28 days prior to initiation of study drug

Exclusion Criteria

Patients who meet any of the following criteria will be excluded from study entry:

- Known primary CNS malignancy or symptomatic CNS metastases*, except ATRT*

  Patients with ATRT must not have tumor brainstem involvement or tumors within 10 mm of the optic chiasm; they must not have a history of intracranial hemorrhage or spinal cord hemorrhage or have had neurosurgical resection, brain biopsy, or radiation to the primary brain tumor within 28 days of Cycle 1, Day 1.

- Patients with asymptomatic untreated CNS *metastases* may be enrolled after consultation with the Medical Monitor, provided all of the following criteria are met:

  Evaluable or measurable outside the CNS. *(Note: this is not required for patients with ATRT).*

  No metastases to brain stem, midbrain, pons, medulla, or cerebellum or within 10 mm of the optic apparatus (optic nerve or chiasm). *(Note: ATRT may have metastases in the cerebellum.)*

  No history of intracranial hemorrhage or spinal cord hemorrhage

  No ongoing requirement for corticosteroids for CNS disease *except in ATRT where steroids use is permitted with approval from the Medical Monitor. Patients with ATRT must receive a stable or decreasing dose for ≥ 5 days prior to the baseline magnetic resonance imaging scan and at the time of drug initiation.*

  Patients taking a stable dose of anticonvulsants are permitted

  No neurosurgical resection or brain biopsy within 28 days prior to Cycle 1, Day 1

- Patients with asymptomatic treated CNS metastases may by enrolled after consultation with the Medical Monitor, provided all the criteria listed above in the above CNS-related exclusion criteria are met as well as the following:

  Radiographic demonstration of improvement upon the completion of CNS-directed therapy and no evidence of interim progression between the completion of CNS-directed therapy and the screening radiographic study

  No stereotactic radiation or whole-brain radiation within 28 days prior to Cycle 1, Day 1

  Screening CNS radiographic study ≥ 4 weeks from completion of radiotherapy and ≥ 2 weeks from discontinuation of corticosteroids

- For patients with lymphoma, known CNS lymphoma, or leptomeningeal disease
- Treatment with high-dose chemotherapy and hematopoietic stem-cell rescue within 3 months prior to initiation of study drug

  This requirement may be waived at the investigator's request if the patient has recovered from therapeutic toxicity to the degree specified in the protocol, with approval of the Medical Monitor.

- Prior allogeneic hematopoietic stem-cell transplantation or prior solid-organ transplantation

- Treatment with chemotherapy (other than high-dose chemotherapy as described above) or differentiation therapy (such as retinoic acid) or immunotherapy (such as anti-GD2 antibody treatment) within *3* weeks prior to initiation of study drug or, if treatment included nitrosoureas, within 6 weeks prior to initiation of study drug

  This requirement may be waived at the investigator's request if the patient has recovered from therapeutic toxicity to the degree specified in the protocol, with approval of the Medical Monitor.
- Treatment with thoracic or mediastinal radiotherapy within *3* weeks prior to initiation of study drug
- Treatment with hormonal therapy (except hormone replacement therapy or oral contraceptives), immunotherapy, or biologic therapy within 4 weeks *or 5 half-lives, whichever is shorter, prior to initiation of study drug. This requirement may be waived at the investigator's request if the patient has recovered from therapeutic toxicity to the degree specified in the protocol, with approval of the Medical Monitor.*
- *Treatment with herbal cancer therapy within 1 week prior to initiation of study drug*
- Treatment with investigational therapy (with the exception of cancer therapies as described above) within 4 weeks prior to initiation of study drug. *This requirement may be waived at the investigator's request if the patient has recovered from therapeutic toxicity to the degree specified in the protocol, with approval of the Medical Monitor.*
- Treatment with a live vaccine or a live attenuated vaccine (e.g., nasal spray of live attenuated influenza vaccine or FluMist®) within 4 weeks prior to initiation of study drug or anticipation that such treatment will be required during the study or within *5 months* after the final dose of study drug
- Prior treatment with CD137 agonists or immune checkpoint blockade therapies, including anti–CTLA-4, anti–programmed death–1 (PD-1), or anti–PD-L1 therapeutic antibodies
- Treatment with systemic immunostimulatory agents (including but not limited to interferons or interleukin 2) within 6 weeks or five drug elimination half-lives prior to Day 1 of Cycle 1, whichever is longer
- Treatment with systemic corticosteroids or other systemic immunosuppressive medications (including but not limited to prednisone, dexamethasone, cyclophosphamide, azathioprine, methotrexate, thalidomide, and anti–tumor necrosis factor agents) *at the time of* initiation of study drug, or anticipated requirement for systemic immunosuppressive medications during the study

  Patients with ATRT can be receiving concurrent treatment with corticosteroids with approval from the Medical Monitor and the ATRT-related exclusion criteria.
- Current treatment with therapeutic anticoagulants
- Any non-hematologic toxicity (excluding alopecia) from prior treatment that has not resolved to Grade ≤ 1 (per National Cancer Institute Common Terminology Criteria for Adverse Events Version 4.0) at screening

  Note: Long-term sequelae of prior treatment (e.g., hearing loss, iatrogenic hypothyroidism, infertility, etc.) are not considered non-hematologic toxicity and instead are considered chronic medical conditions.
- Evidence of progression of neurologic deficit, in the investigator's judgment, within 1 week prior to initiation of study drug
- Major surgical procedure, significant traumatic injury within 4 weeks prior to initiation of study drug, or anticipation of need for major surgical procedure during the course of the study

  Placement of a vascular access device is permitted if the site has healed prior to initiation of study drug.

  Biopsy tissue collections are permitted if all bleeding parameters (including PT/INR and aPTT) are within normal limits and procedure is safe in the judgment of the investigator.
- Known active infection (excluding fungal infection of the nail beds) within 28 days prior to initiation of study drug that has not completely resolved

- Pregnant or lactating or intending to become pregnant during the study

  Patients of childbearing potential must have a negative serum pregnancy test result within 1 week prior to initiation of study drug.
- Known hypersensitivity *to biopharmaceuticals produced in Chinese hamster ovary cells or any component of the atezolizumab formulation*
- Any other disease, metabolic or psychological dysfunction, physical examination finding, or clinical laboratory finding giving reasonable suspicion of a disease or condition that contraindicates use of an investigational drug or places the patient at unacceptable risk from treatment complications
- Current drug or alcohol use or dependence that would interfere with adherence to study requirements, in the opinion of the investigator
- History of severe allergic or anaphylactic reaction to monoclonal antibody therapies (or recombinant antibody–related fusion proteins)
- History of clinically significant cardiac or pulmonary dysfunction
- History of any autoimmune disease, including but not limited to Type 1 diabetes mellitus, autoimmune-related hypothyroidism, myasthenia gravis, myositis, autoimmune hepatitis, systemic lupus erythematosus, rheumatoid arthritis, inflammatory bowel disease, vascular thrombosis associated with anti-phospholipid syndrome, Wegener granulomatosis, Sjögren's syndrome, Guillain-Barré syndrome, multiple sclerosis, vasculitis, or glomerulonephritis

  Patients with a history of autoimmune-related hypothyroidism who are receiving a stable dose of thyroid-replacement hormone are eligible for the study.

  Patients with controlled Type 1 diabetes mellitus who are receiving a stable dose of insulin regimen are eligible for the study.
- History of severe eczema
- History of Kawasaki disease
- History of Fanconi anemia, Beckwith-Wiedemann, ataxia telangiectasia, or other genetic syndromes that may have immune or hematologic susceptibilities
- History of severe asthma or presence of uncontrolled asthma at time of screening evaluation

  Severe asthma is defined as presence of symptoms throughout the day, multiple nighttime awakenings during the week, use of a short-acting β2 agonist several times a day, and/or limitations with normal daily activity. In addition, any asthma that does not meet the above definition but is felt to be severe in the eyes of the investigator should also be excluded.
- History of idiopathic pulmonary fibrosis (including pneumonitis), drug-induced pneumonitis, organizing pneumonia (i.e., bronchiolitis obliterans, cryptogenic organizing pneumonia), cystic fibrosis, or evidence of active pneumonitis on screening chest computed tomography scan
- Dyspnea at rest or requirement for supplemental oxygen
- Uncontrolled seizures

End of Study

The end of this study is defined as the date when last patient last visit occurs or 5 years after the last patient is enrolled, whichever occurs first. The Sponsor reserves the right to present interim data to health authorities for compliance purposes.

Outcome Measures

Safety Outcome Measures

The safety outcome measures for this study are as follows:

- Nature, frequency, severity, and timing of adverse events, including serious adverse events and adverse events of special interest

- Changes in vital signs, physical findings, and clinical laboratory results during and following administration of atezolizumab
- Growth patterns (relative to age-specific standards for height and weight)
- Development patterns (relative to onset of menarche [for females] and pubertal changes)
- Change in tetanus toxoid antibody titers at study discontinuation as compared with pretreatment values

Pharmacokinetic Outcome Measures

The PK outcome measures for this study are as follows:

- Atezolizumab maximum serum concentration (C_{max}) after the infusion on Day 1 of Cycle 1 *and Cycle 4*
- Atezolizumab minimum serum concentration (C_{min}) prior to the infusion on Day 1 of Cycles 2, 3, 4, 8, 12, and 16 and every 8 cycles thereafter
- Atezolizumab serum concentration at washout (90 or more days after the last dose)
- Atezolizumab area under the concentration-time curve for serum concentration-time profile in Cycle 1 will be estimated using a population PK model, as appropriate.

Immunogenicity Outcome Measure

The immunogenicity outcome measure for this study is as follows:

- Incidence of ATAs during the study relative to the prevalence of ATAs at baseline

Efficacy Outcome Measures

The primary efficacy outcome measures for this study are as follows:

- Objective response, defined as a complete or partial response for patients with measurable disease or neuroblastoma patients with evaluable disease at baseline, or a complete response for patients with non-measurable but evaluable disease at baseline (except patients with neuroblastoma) on two consecutive occasions $\geq$4 weeks apart, as determined by the investigator using RECIST v1.1 for patients with solid tumors, *m*INRC for patients with neuroblastoma, Revised Response Criteria for Malignant Lymphoma for patients with Hodgkin's lymphoma or non-Hodgkin's lymphoma, *and RANO criteria for patients with ATRT*.
- Clinical benefit response, defined as objective response or stable disease for at least 6 months, as determined by RECIST v1.1 for patients with osteosarcoma
- PFS, defined as the time from initiation of study drug to the first documented occurrence of progressive disease, as determined by the investigator using RECIST v1.1 for patients with solid tumors, *m*INRC for patients with neuroblastoma, Revised Response Criteria for Malignant Lymphoma for patients with Hodgkin's lymphoma or non-Hodgkin's lymphoma, *and RANO criteria for patients with ATRT,* or death from any cause, whichever occurs first

The secondary efficacy outcome measures for this study are as follows:

- DOR, defined as the time from the first tumor assessment that supports the patient's objective response to the time of progressive disease, as determined by the investigator using RECIST v1.1 for patients with solid tumors, *m*INRC for patients with neuroblastoma, Revised Response Criteria for Malignant Lymphoma for patients with Hodgkin's lymphoma or non-Hodgkin's lymphoma, *and RANO criteria for patients with ATRT*, or death from any cause, whichever occurs first
- OS, defined as the time from initiation of study drug to death from any cause
- ORR, PFS, and DOR as determined *by the* investigator using immune-modified RECIST v1.1 for patients with other solid tumors and immune-related response criteria for patients with neuroblastoma, Hodgkin's lymphoma, or non-Hodgkin's lymphoma

Dose Assessment Outcome Measure

The dose assessment outcome measure for this study is as follows

- Assessment of atezolizumab dose using integrated data gathered from safety, PK, biomarker, and efficacy outcomes

Exploratory Outcome Measures

The exploratory outcome measures for this study are as follows:

- Descriptive analyses of PD-L1 expression (as defined by immunohistochemistry [IHC] score), infiltrating T-cell activity, T-cell subpopulations, B-cell and NK cell absolute counts in baseline tumor samples
- Correlation between PD-L1 expression (both overall expression and by tumor type) at baseline, as defined by IHC score, and efficacy outcome measures
- Levels of potential PD biomarkers (including but not limited to cytokines, ctDNA concentration, and T-cell subpopulations) measured in plasma and whole blood collected at baseline; at Cycles 1, 2, 3, 8, and 12 and every 8 cycles thereafter; and at the time of progressive disease
- Correlation between non-inherited and inherited biomarkers in plasma, whole blood, or tumor tissue (including but not limited to PD-L1, PD-1, CD4, CD8, FoxP3, cytokines, ctDNA concentration, ctDNA mutations, and T-cell receptor sequencing) and safety, PK, or efficacy outcome measures
- Changes in T, B, and NK cell numbers (TBNK assay) in whole blood
- Correlation between ATA status and PK, PD, safety, or efficacy outcome measures
- Descriptive analyses of PD-L1 expression (as defined by IHC score), infiltrating T-cell activity, T-cell subpopulations, B-cell and NK cell absolute counts in any available tumor samples obtained at the time of progressive disease

Investigational Medicinal Products

Patients will receive atezolizumab by intravenous (IV) infusion on Day 1 of each 3-week cycle. The dosing regimen in this study aims to achieve similar atezolizumab exposures in children and adolescents ($<$ 18 years) to those of adults receiving the recommended Phase II/III dose of 1200 mg every 3 weeks. Patients who are $<$18 years old will receive 15 mg/kg atezolizumab (maximum dose 1200 mg) every 3 weeks. Dose adjustments may be made if necessary to achieve exposures corresponding to those measured in adult patients and if the safety profile is acceptable. Patients $\geq$ 18 years old who are enrolled will receive a flat dose of 1200 mg atezolizumab.

Statistical Methods

Primary Analysis

No formal hypothesis testing is planned in this study. Safety analyses will be performed on the safety-evaluable population, which is defined as patients who receive any amount of study drug. Subgroup safety analyses by tumor type will also be conducted as appropriate.

Study treatment exposure (such as treatment duration, total dose received, and number of cycles and dose modifications) will be summarized with descriptive statistics. Descriptive statistics (mean, median, standard deviation, 25th percentile, 75th percentile, and range) will be presented for continuous variables, and proportions will be presented for categorical variables.

Determination of Sample Size

A minimum of 40 patients will be enrolled in this study across all tumor types. In addition, at least two tumor type cohorts must enroll a minimum of 10 patients. To make a preliminary assessment of the efficacy of the study drug, two response assessments are planned: an initial response assessment and an additional response assessment. Taking into account historical control ORRs for each pediatric tumor type, the minimum number of patients in the initial response assessment and the minimum number of responders needed for cohort expansion and advancement to the additional response assessment were calculated and presented by tumor type. The selection of expansion cohorts for additional response assessment, as well as

the number of patients needed for the additional response assessment, will also take into account practical considerations (e.g., enrollment feasibility), biomarker analysis, safety profiles, and any other relevant information. The maximum number of patients per tumor type cohort will be 40. Similar consideration will be given to other rare pediatric tumor types that are enrolled in the study.

Overall, approximately 100 patients will be enrolled in the study.

Interim Analyses

Interim PK analyses will be conducted after the first 5 and 20 patients have completed Cycle 1, along with an ongoing evaluation of safety. An additional interim PK analysis will be conducted after the first 5 patients < 6 years old (if available) have completed Cycle 1. After a minimum of 20 patients have completed Cycle 1, an interim PK and safety analysis will be conducted.

Interim efficacy analyses will be conducted whenever a tumor type cohort has enrolled the number of patients required for initial response assessment and patients have been followed up for approximately 6 months.

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
ATA	anti-therapeutic antibody
ATRT	atypical teratoid rhabdoid tumor
AUC	area under the concentration–time curve
C_{max}	maximum concentration
C_{min}	minimum concentration
CBR	clinical benefit response
CBRR	clinical benefit response rate
CT	computed tomography
ctDNA	circulating tumor DNA
DOR	duration of objective response
EC	Ethics Committee
eCRF	electronic Case Report Form
EDC	electronic data capture
FDA	U.S. Food and Drug Administration
FDG-PET	fluorodeoxyglucose positron emission tomography
FFPE	formalin-fixed paraffin-embedded
FPI	first patient in
HIPAA	Health Insurance Portability and Accountability Act
HIV	human immunodeficiency virus
IC	tumor-infiltrating immune cell
ICH	International Conference on Harmonisation
IND	Investigational New Drug
IHC	immunohistochemistry
IL-2	interleukin 2
iDMC	independent Data Monitoring Committee
IMP	investigational medicinal product
IFN	interferon
irAE	immune-related adverse event
IRB	Institutional Review Board
irRC	immune-related response criteria
IUD	intrauterine device
IV	intravenous
IxRS	interactive voice or Web response system
LPLV	last patient last visit
LVEF	left ventricular ejection fraction
MIBG	metaiodobenzoguanine
mINRC	modified International Neuroblastoma Response Criteria

Abbreviation	Definition
MRI	magnetic resonance imaging
MUGA	multigated acquisition
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NSCLC	non–small cell lung cancer
ORR	objective response rate
OS	overall survival
PD	pharmacodynamic
PD-L1	programmed death–ligand 1
PD-1	programmed death–1
PFS	progression-free survival
PK	pharmacokinetic
RCR	Roche Clinical Repository
RANO	Response Assessment in Neuro-Oncology
RECIST	Response Evaluation Criteria in Solid Tumors
SNP	single-nucleotide polymorphism
TAM	tumor associated macrophage
TNF	tumor necrosis factor
ULN	upper limit of normal

1. BACKGROUND

1.1 PD-L1/PD-1 PATHWAY IN CANCER

Encouraging clinical data emerging in the field of *cancer* immunotherapy have demonstrated that therapies focused on enhancing T-cell responses against cancer can result in a significant survival benefit in patients with advanced solid tumors and hematologic malignancies (Hodi et al. 2010; Kantoff et al. 2010; Schadendorf et al. 2013). Therefore, immunomodulation represents a promising new strategy for cancer therapy that results in improved anti-tumor activity.

Programmed death−ligand 1 (PD-L1) expression is prevalent in many human tumors (e.g., lung, ovarian, melanoma, colon carcinoma, non-Hodgkin's lymphoma) and its overexpression on tumor cells has been associated with poor prognosis in patients with some cancers (Thompson et al. 2006; Hamanashi et al. 2007; Okazaki and Honjo 2007; Hino et al. 2010). PD-L1 is one of two ligands (PD-L1 and PD-L2) that bind programmed death−1 (PD-1), an inhibitory receptor expressed on T cells following T-cell activation in states of chronic stimulation such as in chronic infection or cancer (Blank et al. 2005; Keir et al. 2008). Ligation of PD-L1 with PD-1 inhibits T-cell proliferation, cytokine production, and cytolytic activity, leading to the functional inactivation of T cells. Aberrant expression of PD-L1 on tumor cells has been reported to impede anti-tumor immunity and results in immune evasion (Blank and Mackensen 2007). Therefore, interruption of the PD-L1/PD-1 pathway represents an attractive strategy to reinvigorate tumor-specific T-cell immunity.

Blockade of PD-L1 or PD-1 with monoclonal antibodies results in strong and often rapid anti-tumor effects in several mouse tumor models (Iwai et al. 2002; Strome et al. 2003). These data suggest that tumor-specific T cells may be present in the tumor microenvironment in an inactive or repressed state, and inhibition of the PD-L1/PD-1 pathway reinvigorates tumor-specific T-cell responses. Reports from Phase I oncology studies of molecules targeting either PD-L1 or PD-1 have demonstrated activity in patients with advanced stage and metastatic disease refractory to standard therapy (Brahmer et al. 2012; Topalian et al. 2012). Immune-related adverse events (irAEs) reported from the two recent studies were consistent with the role of the PD-L1/PD-1 pathway in regulating peripheral tolerance. See the Atezolizumab Investigator's Brochure for safety data.

1.2 BACKGROUND ON ATEZOLIZUMAB

Atezolizumab *(also referred to as TECENTRIQ®)* is a humanized IgG1 monoclonal antibody that targets PD-L1 and inhibits its interaction with PD-1. Atezolizumab also blocks the binding of PD-L1 to B7-1, an interaction that is reported to provide additional inhibitory signals to T cells (Butte et al. 2007). Therapeutic blockade of PD-L1 binding by atezolizumab is expected to enhance the magnitude and quality of the tumor-specific T-cell responses, resulting in improved anti-tumor activity. Atezolizumab was engineered to impair its binding to Fcγ receptors, to minimize depletion of tumor-specific

T cells that express high levels of PD-L1 (and PD-1). Also, unlike PD-1 antibodies, atezolizumab preserves the PD-L2 and PD-1 interaction, potentially reducing the risk of host tissue injury from T-cell activation while still overcoming the immunosuppressive effect of tumor-specific PD-L1 signaling.

Atezolizumab consists of two heavy chains (448 amino acids) and two light chains (214 amino acids) and is produced in Chinese hamster ovary cells. Atezolizumab was engineered to eliminate Fc-effector function via a single amino acid substitution (asparagine to alanine) at position 298 on the heavy chain, which results in a non-glycosylated antibody that has minimal binding to Fc receptors and consequently eliminates detectable Fc-effector function and depletion of cells expressing PD-L1. Atezolizumab targets PD-L1 and inhibits its interaction with its receptor, PD-1. Atezolizumab also blocks the binding of PD-L1 to B7.1, an interaction that is reported to provide additional inhibitory signals to T cells (Butte et al. 2007). Atezolizumab is being investigated as a potential therapy against solid tumors and hematologic malignancies in humans.

1.2.1 Nonclinical Studies with Atezolizumab

The nonclinical strategy of the atezolizumab program was to demonstrate in vitro and in vivo activity, to determine in vivo pharmacokinetic (PK) behavior, to evaluate the safety profile, and to identify a Phase I starting dose. Comprehensive pharmacology, PK, and toxicology evaluations were performed with atezolizumab. The safety, pharmacokinetics, and toxicokinetics of atezolizumab were investigated in mice and cynomolgus monkeys to support intravenous (IV) administration and to aid in projecting the appropriate starting dose in humans. Given the similar binding of atezolizumab for cynomolgus monkey and human PD-L1, the cynomolgus monkey was selected as the primary and relevant nonclinical model for understanding the safety, pharmacokinetics, and toxicokinetics of atezolizumab.

Overall, the nonclinical pharmacokinetics and toxicokinetics observed for atezolizumab supported entry into clinical studies, including providing adequate safety factors for the proposed Phase I starting doses. The results of the toxicology program were consistent with the anticipated pharmacologic activity of downmodulating the PD-L1/PD-1 pathway; heightened immune responses and the potential to increase immune-associated inflammatory lesions were identified as possible safety risks in patients. Refer to the Atezolizumab Investigator's Brochure for details on the nonclinical studies.

1.2.2 Clinical Studies with Atezolizumab

Clinical data for atezolizumab are currently available from five Phase I or II clinical trials in patients with solid tumors and hematologic malignancies. For each of these studies, treatment and/or analyses are ongoing. Three of these studies use atezolizumab as a single agent, and two use atezolizumab in combination.

1.2.2.1 Clinical Safety

As of 10 May *2016*, atezolizumab has been administered to approximately *6000* adult patients with solid tumors and hematologic malignancies. The safety profile is mainly based on the ongoing Study PCD4989g (GO27831), in which atezolizumab is being used as single-agent therapy in adult patients with locally advanced or metastatic solid tumors or hematologic malignancies. Across all these patients, fatigue was the most frequently reported adverse event. In studies that investigated atezolizumab in combination, the incidence of adverse events in the treatment arms with combined use was consistent with the known safety profiles of the individual study drugs. Currently, no maximum tolerated dose, no dose-limiting toxicities, and no clear dose-related trends in the incidence of adverse events have been observed.

In Study PCD4989g, as of *15 December 2015*, there have been *629* adult patients treated with study drug. The most common cancer types for these patients include non–small cell lung cancer (NSCLC; n=*89*), urothelial bladder cancer (n=*95*), triple-negative breast cancer (n=*111*), and renal cell carcinoma (n=*72*). Of the *629* patients *evaluable for safety* enrolled, *444* patients (*70.6*%) reported at least one treatment-related adverse event while receiving study drug. The most frequently observed adverse events (occurring in ≥10% of treated patients) included fatigue, nausea, decreased appetite, diarrhea, constipation, dyspnea, pyrexia, cough, vomiting, anemia, back pain, headache, asthenia, arthralgia, pruritus, rash, abdominal pain, peripheral edema, *urinary tract infection,* insomnia, and *dizziness*. Grade ≥3 adverse events were reported by *326 of 629* patients (*51.8*%), and *89* patients (*14.1*%) experienced Grade ≥3 adverse events that were assessed as related to study drug by the investigators. The most frequently reported related Grade 3 and 4 adverse events included *fatigue, asthenia, increased aspartate aminotransferase, dyspnea, and hyponatremia*.

No safety information has been established in pediatric populations.

Refer to the Atezolizumab Investigator's Brochure for details on adverse events observed in patients who were treated with atezolizumab.

1.2.2.2 Clinical Activity

As of the data cutoff date of 1 January 2014, efficacy analyses were performed on 291 efficacy-evaluable adult patients enrolled in Study PCD4989g (single-agent atezolizumab administered to patients with locally advanced or metastatic solid tumors or hematologic malignancies). These patients had been treated by 1 July 2013 to ensure each patient had a minimum of 6 months' follow-up. Objective responses with atezolizumab monotherapy were observed in a broad range of malignancies, including NSCLC, renal cell carcinoma, melanoma, bladder cancer, colorectal cancer, head and neck cancer, gastric cancer, breast cancer, and sarcoma. Altogether, there were 47 adult patients with a measurable response with a median duration of response of

75.7 weeks. The majority of these responses have been durable with 72.3% (34 of 47 patients) of responses ongoing as of the clinical cutoff date.

Analyses of tumor-infiltrating immune cells (IC) for PD-L1 expression on baseline tumor tissue have been performed for Study PCD4989g. Preliminary results suggest that across multiple tumor types, PD-L1 expression in IC is likely to be associated with response to atezolizumab (Herbst et al. 2014).

Refer to the Atezolizumab Investigator's Brochure for additional details on clinical activity in patients who were treated with atezolizumab.

1.3 STUDY RATIONALE AND BENEFIT-RISK ASSESSMENT

Pediatric cancer that is recurrent or refractory represents an area of high unmet medical need. Despite the progress made after 40 years of clinical research that used combinations of chemotherapy, radiotherapy, and surgery, disease-free survival and overall survival rates have not significantly improved for children with relapsed or refractory tumors.

The expression of PD-L1 by malignant cells has been reported in many pediatric tumor types, including high-grade glioma (Wintterle et al. 2003; Wilmotte et al. 2005; Parsa et al. 2007), rhabdomyosarcoma (Wiendl et al. 2003, *Kim et al. 2008*), non-Hodgkin's lymphoma (Yamamoto et al. 2009; Green et al. 2010; Andorsky et al. 2011), Hodgkin's lymphoma (Yamamoto et al. 2008, 2009; Green et al. 2010), soft tissue sarcoma (Kim et al. 2008), osteosarcoma (Lussier et al. 2013), Ewing sarcoma (Kim et al. 2008), and Wilms tumor (Routh et al. 2008, 2013).

Although the functional role of PD-L1 expression in the pediatric tumor microenvironment is unknown, there are strong surrogate markers of putative sensitivity to PD-L1 blockade for pediatric cancers. PD-L1 is highly expressed on tumor-infiltrating leukocytes and tumor-associated macrophages (TAMs) (Zou et al. 2008; Chen et al. 2012; Berghoff et al. 2013; Melero et al. 2013). Pediatric tumors are highly infiltrated by TAMs and contain a paucity of dendritic cells compared with adult tumors (Vakkila et al. 2006). These TAMs are reported to have a prognostic role in pediatric tumors, including malignant glioma (Nishie et al. 1999; Bloch et al. 2013), neuroblastoma (Asgharzadeh et al. 2012), Ewing sarcoma (Fujiwara et al. 2011), Hodgkin's lymphoma (Barros et al. 2012), and high-grade osteosarcoma (Endo-Munoz et al. 2012), although the latter is controversial because of the complexity of identification between TAMs and osteoclasts (Buddingh et al. 2011). In addition to roles in invasion, angiogenesis, and metastasis (Pollard 2004; Ono 2008; Wynn et al. 2013), TAMs have an important immunosuppressive role in the solid tumor microenvironment (Sica and Bronte 2007; Jaiswal et al. 2010; Ruhrberg and De Palma 2010). Impeding the immunosuppressive activity of TAMs with an anti–PD-L1 antibody is therefore of therapeutic interest for pediatric cancers.

Encouraging clinical data emerging in the field of cancer immunotherapy have demonstrated that therapies focused on enhancing T-cell responses against cancer can result in a significant survival benefit in patients with advanced cancer (Hodi et al. 2010; Kantoff et al. 2010). In addition, encouraging results are being reported in early-phase clinical trials targeting the PD-L1/PD-1 pathway in adult patients with refractory late-stage cancer (Berger et al. 2008; Brahmer et al. 2012; Topalian et al. 2012).

The preliminary nonclinical data indicate that pediatric and young adult patients diagnosed with relapsed and refractory solid tumors may benefit from the addition of an immune checkpoint inhibitor like atezolizumab. In addition, atezolizumab has an acceptable toxicity profile in adults, in line with other PD-L1/PD-1 blocking agents. Given the poor long-term survival of children and young adults diagnosed with relapsed and refractory solid tumors, the potential benefit of atezolizumab is expected to outweigh the risk in this population.

2. OBJECTIVES

This study will evaluate the safety, tolerability, pharmacokinetics, immunogenicity, and preliminary efficacy of atezolizumab administered by IV infusion every 3 weeks to pediatric and young adult patients with solid tumors for which prior treatment has proven to be ineffective (i.e., relapsed or refractory) or intolerable and for whom there is no effective standard treatment available. Specific objectives for the study are outlined below.

2.1 SAFETY OBJECTIVE

The safety objective for this study is as follows:

- To evaluate the safety and tolerability of atezolizumab in pediatric and young adult patients, focusing on the nature, frequency, and severity of serious and non-serious adverse events, as well as effects on laboratory test values and vital signs

2.2 PHARMACOKINETIC OBJECTIVE

The PK objective for this study is as follows:

- To characterize the pharmacokinetics of atezolizumab

2.3 IMMUNOGENICITY OBJECTIVE

The immunogenicity objective for this study is as follows:

- To evaluate the immune response to atezolizumab on the basis of the incidence of anti-therapeutic antibodies (ATAs)

2.4 EFFICACY OBJECTIVES

The efficacy objectives for this study are as follows:

- To evaluate the anti-cancer activity of atezolizumab, as measured by objective response rate (ORR), progression-free survival (PFS), duration of objective response (DOR; see Section 3.4.4 for information on response assessment tools), and clinical benefit response rate (CBRR, only for osteosarcoma—see Section 3.4.4 for definition).
- To evaluate the anti-cancer activity of atezolizumab, as measured by overall survival (OS)

2.5 DOSE ASSESSMENT OBJECTIVE

The dose-assessment objective for this study is as follows:

- To assess the optimal dose of atezolizumab in pediatric and young adult patients on the basis of safety, PK, and efficacy outcome measures (see Section 3.4)

2.6 EXPLORATORY OBJECTIVES

The exploratory objectives for this study are as follows:

- To explore if PD-L1 expression on tumor and/or tumor-infiltrating cells at baseline is predictive of response to atezolizumab
- To explore the relationship between atezolizumab exposure and changes in levels of pharmacodynamic (PD) biomarkers including but not limited to cytokines, circulating tumor DNA (ctDNA) concentration, and T-cell subpopulations
- To explore non-inherited biomarkers that may be predictive of response to atezolizumab (i.e., predictive biomarkers); may be associated with progression to a more severe disease state (i.e., prognostic biomarkers), acquired resistance to atezolizumab, or susceptibility to developing adverse events; may provide evidence of atezolizumab activity; or may increase the knowledge and understanding of disease biology
- To explore inherited biomarkers (i.e., variants in germline DNA) that may be predictive of response to atezolizumab (i.e., predictive biomarkers); may be associated with progression to a more severe disease state (i.e., prognostic biomarkers), acquired resistance to atezolizumab, or susceptibility to developing adverse events; or may increase the knowledge and understanding of disease biology
- To evaluate potential relationships between *detectable* ATAs and other *clinical relevant* outcome measures (e.g., pharmacokinetics, safety, and efficacy)

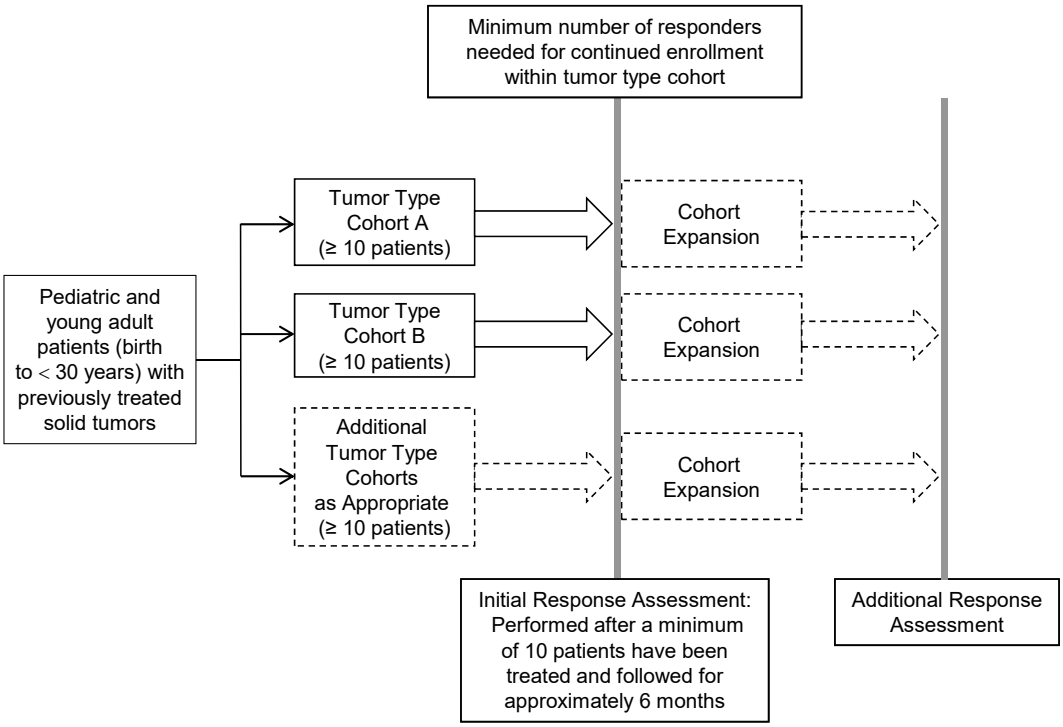
3. STUDY DESIGN

3.1 DESCRIPTION OF STUDY

The study is an early-phase, multicenter, open-label, single-arm study designed to evaluate the safety, tolerability, pharmacokinetics, immunogenicity, and preliminary efficacy of atezolizumab in pediatric and young adult patients with solid tumors with

known or expected PD-L1 pathway involvement for which prior treatment has proven to be ineffective (i.e., relapsed or refractory) or intolerable and for whom no curative standard-of-care treatment options exist.

Figure 1 Study Schema: Two Phases of Response Assessment



Pediatric and young adult patients with pediatric-type tumors with known or expected PD-L1 pathway involvement (age: birth to <30 years) will be enrolled via an interactive voice or Web response system (IxRS). The first 5 patients must be ≥2 years of age (i.e., the first 5 patients must have reached their second birthday at the time of enrollment) to ensure safety and tolerability prior to dosing in children <2 years of age. These first 5 patients must be followed for either two cycles of treatment or until drug discontinuation, whichever is shorter, prior to enrolling younger patients. An independent Data Monitoring Committee (iDMC) will review the safety data of the first 5 patients and make recommendations on the appropriateness of opening the study to patients <2 years of age *(see Section 3.1.4)*.

Patients will receive atezolizumab by IV infusion on Day 1 of each 3-week cycle. The dosing regimen in this study aims to achieve similar atezolizumab exposures in children and adolescents (<18 years) to those of adults receiving the recommended Phase II/III dose of 1200 mg every 3 weeks. Patients who are <18 years old will receive 15 mg/kg atezolizumab (maximum dose 1200 mg) every 3 weeks. Dose adjustments may be made, if necessary to achieve exposures corresponding to those measured in

adult patients and if the safety profile is acceptable. Patients ≥18 years old who are enrolled will receive a flat dose of 1200 mg atezolizumab. There must be at least 24 hours between the initial treatment doses of the first 5 patients regardless of tumor type to allow for evaluation of immediate immune activating events before additional patients are exposed to atezolizumab. There must also be at least 24 hours between treatment doses for the first 3 patients within each tumor type cohort.

Atezolizumab treatment may be continued for a maximum duration of 8 months as long as patients experience clinical benefit as assessed by the investigator—in the absence of unacceptable toxicity or symptomatic deterioration attributed to progressive disease—on the basis of an integrated assessment of radiographic data, biopsy results (if available), and clinical status. Patients who continue to experience clinical benefit at 8 months may continue treatment with approval of the Medical Monitor. If an individual patient continues to experience clinical benefit beyond 2 years of radiologic progressive disease (see Section 3.3.4), the Sponsor and treating physician will apply for additional approval from health authorities for continued treatment.

Tumor assessments will be performed every two cycles *from Cycle1* through Cycle 8 and then every 4th cycle thereafter. Response will be determined by the investigator through use of *modified* International Neuroblastoma Response Criteria (mINRC) for patients with neuroblastoma (see Appendix 3), Revised Response Criteria for Malignant Lymphoma for patients with Hodgkin's lymphoma or non-Hodgkin's lymphoma (Cheson et al. 2007; see Appendix 4), *Response Assessment in Neuro-Oncology (RANO) criteria (see* Appendix 11*) for patients with atypical teratoid rhabdoid tumor* and Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST v1.1) for patients with other solid tumors (see Appendix 5).

All patients will be closely monitored for adverse events throughout the study and for at least *30* days after the last dose of study treatment *or initiation of a new anti-cancer therapy, regardless of relationship to study drug* (see Section 5.3.1). *Serious adverse events and adverse events of special interest, regardless of relationship to study drug, will be monitored for 90 days after the last dose of study drug or until initiation of new anti-cancer therapy.* All identified adverse events should be followed up until resolution, which may necessitate monitoring beyond *30* days after the last dose of study drug. In addition, the Sponsor should be notified if the investigator becomes aware of any serious adverse event that occurs after the end of the adverse event reporting period, if the event is believed to be related to prior study drug treatment. Adverse events will be graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, Version 4.0 (NCI CTCAE v4.0). An iDMC will be established to monitor patient safety throughout the study (see Section 3.1.4).

Safety assessments will include the incidence, nature, and severity of adverse events; changes in vital signs; and laboratory abnormalities graded per NCI CTCAE v4.0. Serum samples will be collected to monitor atezolizumab pharmacokinetics and to detect

the presence of antibodies to atezolizumab. PK sampling time points have been optimized on the basis of a preliminary population PK model using the adult data. A sample of archived tumor tissues, as well as blood samples, will be collected for future exploratory biomarker assessments.

Schedules of assessments are provided in Appendix 1 and Appendix 2.

Patients with pediatric solid tumors, including Hodgkin's and non-Hodgkin's lymphoma, may be enrolled into the study (see Section 4.1 for patient inclusion and exclusion criteria). Each tumor type will be considered a distinct tumor type cohort. An initial response assessment will be performed after a minimum of 10 patients have been enrolled in a tumor type cohort and followed up for approximately 6 months, to determine whether further enrollment is needed within that tumor type cohort (cohort expansion) for additional response assessment. A minimum number of responders will be needed for cohort expansion and advancement to the additional response assessment (see Table 3 for more details). Cohort expansion, including the number of patients needed for the additional response assessment, will also take into account practical considerations (e.g., enrollment feasibility), biomarker analysis, safety profiles, and any other relevant information. The maximum number of patients enrolled in any tumor cohort will be 40.

In addition to the planned efficacy analyses mentioned above, interim PK analyses will also be performed. An initial interim PK analysis will be conducted after the first 5 patients have completed Cycle 1, irrespective of age and tumor type cohort. An additional interim PK analysis will be conducted after 5 patients who are $<$ 6 years old (if available) have completed Cycle 1. Following these analyses, dose modifications may be considered for all patients, if warranted, to match adult exposures and to ensure an optimal safety profile. After a minimum of 20 patients have completed Cycle 1, PK and safety analyses will also be conducted.

3.1.1 Number of Patients

Approximately 100 patients are expected be enrolled in this study, at approximately 50 investigative sites in Europe and North America. Of those who are enrolled, at least 20 patients who are $<$18 years of age will be treated with study drug, and at least 40 patients across all tumor type cohorts will be treated and available for response assessment (at least two tumor type cohorts must enroll a minimum of 10 patients).

Accrual is expected to last approximately 3 years.

3.1.2 Enrollment Stopping Rules

Enrollment in a tumor type cohort may be stopped if any one of the following criteria is met:

- The number of patients needed for initial response assessment is reached and the number of responders does not meet the requirement for additional tumor type cohort expansion.

- The number of patients needed for additional response assessment is reached.
- The Sponsor has stopped the study.
- *At least two tumor type cohorts have enrolled the minimum number of patients needed for initial response assessment.*

Some exceptions may apply to these general stopping rules, including but not limited to the following:

- Enrollment in the study *may* be stopped if enrollment has been open for more than 2 years and at least 20 patients have been treated with the study.
- Enrollment in a tumor type cohort may be extended if there is strong evidence of a positive efficacy signal in a slow-enrolling and rare tumor type cohort, thus allowing for additional data to be collected.

3.1.3 Adverse Events Requiring Drug Discontinuation

Events that require study drug discontinuation reflect the known and expected toxicities of the mechanism of action of atezolizumab, in addition to accounting for serious unexpected adverse events that may occur. The following events require discontinuation of study drug if they occur at any time while undergoing treatment and are considered by the investigator to be related to atezolizumab (see Table 1 for causality assessment). For situations of unclear attribution to study drug, investigators are encouraged to perform additional tests to determine the underlying etiology and most appropriate attribution.

Any one of the following events will require study drug discontinuation if they are assessed by the investigator to be related to atezolizumab:

- Grade ≥ 4 neutropenia (ANC $< 0.5 \times 10^9$/L) that lasts > 7 days
- Grade ≥ 4 neutropenia with documented infection
- Grade ≥ 3 febrile neutropenia that lasts > 5 days
- Grade ≥ 4 thrombocytopenia that lasts > 48 hours or any thrombocytopenia requiring a platelet transfusion, with the following exception:

  For patients who have undergone autologous hematopoietic stem cell transplantation or ^{131}I-MIBG (metaiodobenzoguanine) therapy, Grade ≥ 4 thrombocytopenia that lasts > 7 days or any thrombocytopenia that requires a platelet transfusion on two or more separate dates will require study drug discontinuation.
- Grade ≥ 3 thrombocytopenia with *a Grade ≥ 2* bleeding *event*
- Elevation of serum hepatic transaminase levels (ALT or AST) $\geq 5 \times$ the upper limit of normal (ULN)

  For patients with elevated hepatic transaminase levels at baseline as a result of liver metastases, hepatic transaminase $\geq 5 \times$ baseline and $< 10 \times$ baseline

for >3 days, or any hepatic transaminase $\geq 10 \times$ baseline will require study drug discontinuation.

- Elevation of serum bilirubin level $\geq 3 \times$ ULN
- Grade ≥ 3 non-hematologic, non-hepatic adverse event, with the following exceptions:

  Grade 3 fevers will not mandate study drug discontinuation.

  Grade 3 mucositis or stomatitis that resolves to Grade ≤ 2 within 3 days will not mandate study drug discontinuation.

  Grade ≥ 3 nausea or vomiting that responds to standard-of-care therapy within 3 days will not mandate study drug discontinuation. *In the ATRT cohort, this may mandate study drug discontinuation if Grade ≥ 3 nausea and/or vomiting is subsequent to increased intracranial pressure (see* Section 4.5.3.1 *for management guidelines).*

  Grade 3 fatigue that lasts for ≤ 3 days will not mandate study drug discontinuation.

  Grade 3 laboratory test abnormalities that are asymptomatic and considered by the investigator not to be clinically significant will not mandate study drug discontinuation.

  Patients with Grade 3 rash may continue treatment with atezolizumab according to guidelines outlined in the Atezolizumab Investigator's Brochure.

- Conditions (regardless of grade) suggestive of an autoimmune disorder, including but not limited to rheumatoid arthritis, Type I diabetes, vasculitis, neuritis, and neuropathies including myasthenia gravis, Guillain-Barré syndrome, systemic lupus erythematosus, Sjögren's syndrome, and multiple sclerosis.

  The following conditions may continue treatment with atezolizumab according to the guidelines outlined in Section 5.1.1 and the Atezolizumab Investigator's Brochure:

  Hepatitis (elevation of transaminases), rash, pancreatitis (elevated amylase/lipase), pneumonitis/pulmonary toxicity, endocrinopathies, colitis (presence of diarrhea), eye toxicities, and systemic immune activation

- Pericardial effusion (any grade) if not attributable to disease
- Any toxicity that requires interruption of atezolizumab treatment for >105 days *(e.g., no more than 105 days between infusions)*, except in patients who must be tapered off corticosteroids used to treat adverse events (see Section 5.1.1.1 for details). Longer periods of treatment interruption may be considered after discussion with the Medical Monitor.

3.1.4 Independent Data Monitoring Committee

An iDMC will be set up to evaluate safety data during the study. The iDMC will evaluate study safety data on a periodic basis, approximately every 6 months from the point of first patient in (FPI). They will also have a scheduled review following enrollment of the

first 5 patients (mandated to be ≥2 years old). After this review, they will make recommendations on the appropriateness of enrolling patients who are <2 years old. Members of the iDMC will be external to the Sponsor and the Investigator and will follow a charter that outlines their roles and responsibilities. Following their review, the iDMC will provide a recommendation as to whether the study may continue, whether amendment(s) to the protocol should be implemented, or whether the study should be stopped. The IDMC may also contribute to the selection of tumor types to be included in the cohort expansion. Specific details, such as committee composition, communication plan, and member roles and responsibilities, will be detailed in an iDMC Charter.

3.2 END OF STUDY

The end of this study is defined as the date when the last patient last visit (LPLV) occurs or 5 years after the last patient is enrolled, whichever occurs first. The Sponsor reserves the right to present interim data to health authorities for compliance purposes.

For an individual patient, the completion of the study (i.e., the last visit) will occur when the patient withdraws consent, has been lost to follow-up, or dies or when the study is stopped.

The primary analysis will be conducted after the enrollment has been completed and all enrolled patients have been followed up for at least 6 months. A Clinical Study Report will be submitted to health authorities.

3.3 RATIONALE FOR STUDY DESIGN

3.3.1 Rationale for Atezolizumab Starting Dose and Dose Modification

The pharmacokinetics of atezolizumab in the pediatric population are expected to be similar to those in adults on the basis of the observation of linear pharmacokinetics, suggestive of nonspecific elimination, in the clinically relevant dose range. Therefore, a pediatric dosing scheme for atezolizumab that provides reliable and adequate exposure for maximal efficacy while minimizing the potential for adverse events may be predictable from PK data in adults, provided that effects of body size are well characterized.

Few studies in the literature have investigated developmental changes in absorption, distribution, and elimination of therapeutic proteins. Tissue distribution of therapeutic proteins occurs primarily through transvascular transport processes such as convection and diffusion, which are not expected to be significantly affected by differences in body composition as a function of age (Anderson and Lynn 2009; Tabrizi et al. 2010; Xu et al. 2013). The distribution of a therapeutic protein may be influenced by binding to plasma proteins or tissue targets; however, differences in antigen production or degradation rates may not be sufficient to alter the distribution of an antibody-based therapeutic protein that exceeds a 100-fold molar ratio relative to the targeted antigen

(Xu et al. 2013). Therefore, clinically meaningful differences in monoclonal antibody distribution are not expected between adult and pediatric patients after taking into account differences in body size. Monoclonal antibodies are metabolized by the same catabolic pathways as endogenous proteins and are eliminated by nonspecific Fc receptor–mediated catabolism and/or target-mediated disposition (Tabrizi et al. 2006; Mould and Green 2010). For atezolizumab, the nonspecific elimination pathway appears to be primary, as evidenced by linear pharmacokinetics in the dose range of 1–20 mg/kg, which includes the *approved dose (for treatment of adult patients with urothelial carcinoma) and* recommended Phase II/III dose currently under investigation in multiple cancer types (1200 mg; equivalent to a weight-based dose of 15 mg/kg assuming an adult body weight of 80 kg). Because infants and children are able to maintain homeostasis of immunoglobulins, it is presumed that they are able to break down therapeutic monoclonal antibodies if Fc receptor–mediated catabolism is the major pathway. Thus, no age-related developmental differences in disposition are expected for therapeutic proteins with nonspecific elimination as the major pathway. A primary elimination pathway for atezolizumab via Fc receptor–mediated catabolism suggests that the pharmacokinetics of monoclonal antibodies in pediatric patients can be predicted from adult data, particularly in children who are >6 years of age (Xu et al. 2013).

Of the potential covariates that may affect the pharmacokinetics of antibody-based therapeutic proteins, body size (weight or body surface area) is the most frequently identified and clinically relevant covariate (Dirks and Meibohm 2010). A review of the PK characteristics of 12 approved therapeutic proteins showed comparable steady-state peak and trough concentrations and terminal half-life between pediatric and adult patients after adjustment for body size (Xu et al. 2013). Age alone does not appear to affect the clearance of monoclonal antibodies (Dirks and Meibohm 2010; Xu et al. 2013). Because the total clearance of antibody-based therapeutic proteins does not increase in proportion to increasing body weight, a 2-fold increase in body weight usually results in a less than 2-fold increase in clearance (Bai et al. 2012; Xu et al. 2013). Therefore, the lightest pediatric patients who received the same body weight–based dose level of atezolizumab may have a lower drug exposure than adults. Furthermore, because the development of ATAs has been associated with changes in pharmacokinetics for some adult patients in the lower-dose cohorts of Study PCD4989g (i.e., 0.3, 1, and 3 mg/kg), the possibility for lower exposure may be exacerbated, particularly in the lightest children. Children aged <18 years will receive the weight-based equivalent of the *approved adult dose and* recommended Phase II/III adult dose (15 mg/kg atezolizumab every 3 weeks, with a maximum of 1200 mg). Patients who are ≥18 years old will receive *the approved adult* dose of 1200 mg. Dose adjustments may be made, if necessary, to achieve exposures corresponding to those measured in adult patients and if the safety profile is acceptable.

Dose levels for modification will be determined on the basis of the available information regarding PK exposure, interim PK analyses, and the emerging safety profile.

3.3.2 Rationale for Inclusion of Patients Aged $>$18 Years

The Sponsor expects that the majority of enrolled patients will be $<$18 years old. However, there may be young adult patients with "pediatric-type" tumors who are treated in pediatric oncology facilities. In a specific analysis of adolescent and young adult patients in the United States, limited clinical trial participation correlated with the relative lack of improvement in survival prolongation and cancer death rates (Bleyer et al. 2006). The lower participation of adolescent and young adult patients in clinical trials has created significant knowledge gaps with respect to cancer biology, treatment, and other factors affecting the survival of adolescent and young adult patients with cancer. As part of the Sponsor's commitment to the development of personalized medicine, adolescent and young adult patients up to the age of 30 years (and in exceptional cases of relapsed pediatric tumors, beyond 30 years) will be included in this study.

3.3.3 Rationale for Exploratory Analysis of Immunogenicity

ATAs to atezolizumab have been observed in adult patients in all dose cohorts in Study PCD4989g, and their development was associated with changes in pharmacokinetics for some patients in the lower-dose cohorts (0.3, 1, and 3 mg/kg). Patients who were treated at the 10-, 15-, and 20-mg/kg dose levels maintained the expected target trough levels of drug despite the detection of ATAs. To date, no relationship has been observed between the development of measurable ATAs and the safety or efficacy of atezolizumab. Monitoring and characterization of ATA responses and their potential impact on pharmacokinetics, safety, and activity are continuing in all clinical studies of atezolizumab.

With respect to immunogenicity, patient-related factors such as disease, genetics, immune status, concomitant use of immunomodulators, and previous use of a monoclonal antibody or a structurally related therapeutic protein may vary considerably between pediatric and adult patients, resulting in differences in immunogenicity. To date, there are no data addressing immunogenicity with immune checkpoint inhibitors in the pediatric population, and predictions based on adult data cannot therefore be made. Thus, the occurrence of ATAs will be closely monitored in this study.

3.3.4 Rationale for Treatment beyond Progression

Conventional response criteria may not adequately assess the activity of immunotherapeutic agents because progressive disease (by initial radiographic evaluation) does not necessarily reflect therapeutic failure. Because of the potential for pseudoprogression or tumor immune infiltration, this study will allow patients to continue to receive study treatment after apparent radiographic progression, provided the benefit-risk ratio is judged to be favorable. In Study PCD4989g, several patients with NSCLC who had disease progression according to RECIST v1.1 criteria continued to receive atezolizumab treatment and demonstrated durable anti-tumor activity. In addition, in some patients who responded, the growth of known lesions or the appearance of new radiographic lesions were shown to contain immune cells and no viable cancer cells in

the biopsy tissue sample. Patient *participation in the study* should be discontinued for unacceptable toxicity or symptomatic deterioration attributed to disease progression as determined by the investigator after an integrated assessment of radiographic data and clinical status (see Section 4.5.5.2).

It is recommended that radiological disease progression be confirmed at a subsequent tumor assessment to take into account the potential for pseudoprogression or tumor immune infiltration. In addition, it is highly recommended that evidence of progressive disease in patients who respond should be confirmed by a biopsy tissue sample from the growing or new lesion when feasible.

3.3.5 Rationale for Mandatory Collection of Tumor Specimens

Development of a predictive diagnostic assay that enables prospective identification of patients who are likely to respond to treatment with atezolizumab may allow for pre-selection of patients likely to benefit from treatment with atezolizumab in future clinical studies.

Published results suggest that expression of PD-L1 in tumors correlates with response to anti–PD-1 therapy (Topalian et al. 2012). This correlation was also observed with atezolizumab in preliminary data from Study PCD4989g (see Section 1.2.2.2; Herbst et al. 2014). In this study, tumor specimens from patients meeting eligibility criteria will be retrospectively tested for PD-L1 expression by a central laboratory.

Other exploratory markers, such as potential predictive and prognostic markers that are related to response or clinical benefit of atezolizumab, tumor immunobiology, and tumor type markers, may also be analyzed.

3.3.6 Rationale for Blood Sampling for Biomarkers

An exploratory objective is to evaluate changes in surrogate PD biomarkers in blood samples that are relevant because of the target expression. Changes in PD biomarkers such as cytokines, ctDNA concentration, and T-cell subpopulations may provide evidence for biological activity of atezolizumab in humans. In addition, potential correlations of these PD markers with safety and anti-tumor activity of atezolizumab will be explored.

3.3.7 *Rationale for Separate Cohorts for Rhabdoid Tumor and Atypical Teratoid Rhabdoid Tumor*

Patients with atypical teratoid rhabdoid tumor (ATRT) and rhabdoid tumor will be enrolled into separate cohorts. Although the two tumor types are often merged together, reflecting common genetic drivers, the differences in tumor microenvironment (CNS for ATRT and non-CNS for rhabdoid tumor) necessitate separating them in this protocol. This will allow for a more thorough evaluation of atezolizumab in these tumor types and account for any differences in safety and efficacy that may occur

because of differences in organ location or tumor microenvironment or the presence of a blood-brain barrier.

3.4 OUTCOME MEASURES

3.4.1 Safety Outcome Measures

The safety outcome measures for this study are as follows:

- Nature, frequency, severity, and timing of adverse events, including serious adverse events and adverse events of special interest
- Changes in vital signs, physical findings, and clinical laboratory test results during and following administration of atezolizumab
- Growth patterns (relative to age-specific standards for height and weight)
- Development patterns (relative to onset of menarche [for females] and pubertal changes)
- Change in tetanus toxoid antibody titers at study discontinuation as compared with pretreatment values

3.4.2 Pharmacokinetic Outcome Measures

The PK outcome measures for this study are as follows:

- Atezolizumab maximum serum concentration (C_{max}) after the infusion on Day 1 of Cycle 1 *and Cycle 4*
- Atezolizumab minimum serum concentration (C_{min}) prior to the infusion on Day 1 of Cycles 2, 3, 4, 8, 12, and 16 and every 8 cycles thereafter
- Atezolizumab serum concentration at washout (90 or more days after the last dose)
- Atezolizumab area under the concentration-time curve (AUC) for serum concentration-time profile in Cycle 1 will be estimated using a population PK model, as appropriate.

3.4.3 Immunogenicity Outcome Measure

The immunogenicity outcome measure for this study is as follows:

- Incidence of ATAs during the study relative to the prevalence of ATAs at baseline

3.4.4 Efficacy Outcome Measures

The primary efficacy outcome measures for this study are as follows:

- Objective response, defined as a complete or partial response for patients with measurable disease or neuroblastoma patients with evaluable disease at baseline, or a complete response for patients with non–measurable but evaluable disease at baseline (except patients with neuroblastoma) on two consecutive occasions ≥4 weeks apart, as determined by the investigator using RECIST v1.1 for patients with solid tumors (see Appendix 6), *m*INRC for patients with neuroblastoma (see Appendix 3), Revised Response Criteria for Malignant

Lymphoma for patients with Hodgkin's lymphoma or non-Hodgkin's lymphoma (see Appendix 4), and RANO criteria (see Appendix 11) for patients with ATRT.

- Clinical benefit response (CBR), defined as objective response or stable disease for at least 6 months, as determined by RECIST v1.1 for patients with osteosarcoma (see Appendix 6)
- PFS, defined as the time from initiation of study drug to the first documented occurrence of progressive disease, as determined by the investigator using RECIST v1.1 for patients with solid tumors (see Appendix 6), *m*INRC for patients with neuroblastoma (see Appendix 3), Revised Response Criteria for Malignant Lymphoma for patients with Hodgkin's lymphoma or non-Hodgkin's lymphoma (see Appendix 4), and RANO criteria (see Appendix 11) for patients with ATRT, or death from any cause, whichever occurs first

The secondary efficacy outcome measures for this study are as follows:

- DOR, defined as the time from the first tumor assessment that supports the patient's objective response to the time of progressive disease, as determined by the investigator using RECIST v1.1 for patients with solid tumors (see Appendix 5), *m*INRC for patients with neuroblastoma (see Appendix 3), Revised Response Criteria for Malignant Lymphoma for patients with Hodgkin's lymphoma or non-Hodgkin's lymphoma (see Appendix 4), and RANO criteria (Appendix 11) for patients with ATRT, or death from any cause, whichever occurs first
- OS, defined as the time from initiation of study drug to death from any cause
- ORR, PFS, and DOR as determined by the investigator using immune-modified RECIST v1.1 for patients with other solid tumors (see Appendix 5) and immune-related response criteria (irRC) for patients with neuroblastoma, Hodgkin's lymphoma or non-Hodgkin's lymphoma

3.4.5 Dose Assessment Outcome Measure

The dose assessment outcome measure for this study is as follows:

- Assessment of atezolizumab dose with the use of integrated data gathered from safety, PK, biomarker, and efficacy outcomes

3.4.6 Exploratory Outcome Measures

The exploratory outcome measures for this study are as follows:

- Descriptive analyses of PD-L1 expression (as defined by immunohistochemistry [IHC] score), infiltrating T-cell activity, T-cell subpopulations, and B-cell and NK cell absolute counts in baseline tumor samples
- Correlation between PD-L1 expression (both overall expression and by tumor type) at baseline, as defined by IHC score, and efficacy outcome measures
- Levels of potential PD biomarkers (including but not limited to cytokines, ctDNA concentration, and T-cell subpopulations) will be measured in plasma and whole blood collected at baseline; at Cycles 1, 2, 3, 8, and 12 and every 8 cycles thereafter; and at the time of progressive disease.

- Correlation between non-inherited and inherited biomarkers in plasma, whole blood, or tumor tissue (including but not limited to PD-L1, PD-1, CD4, CD8, FoxP3, cytokines, ctDNA concentration, ctDNA mutations, and T-cell receptor sequencing) and safety, PK, or efficacy outcome measures
- Changes in T, B, and NK cell numbers (TBNK assay) in whole blood
- Correlation between ATA status and PK, PD, safety, or efficacy outcome measures
- Descriptive analyses of PD-L1 expression (as defined by IHC score), infiltrating T-cell activity, T-cell subpopulations, and B-cell and NK cell absolute counts in any available tumor samples obtained at the time of progressive disease

4. MATERIALS AND METHODS

4.1 PATIENTS

This study will enroll *approximately 100* pediatric or young adult patients with solid tumors with known or expected PD-L1 pathway involvement for which prior treatment has proven to be ineffective (i.e., relapsed or refractory disease) or intolerable and for whom there are no curative standard-of-care treatment options.

4.1.1 Inclusion Criteria

Patients must meet the following criteria for study entry:

- Histologically or cytologically confirmed solid tumor of a type listed below (tumor types with known or expected PD-L1 pathway involvement) (including Hodgkin's and non-Hodgkin's lymphoma), for which prior treatment had proven to be ineffective (i.e., relapsed or refractory disease) or intolerable. Patients must have had histologic or cytologic confirmation of malignancy at the time of diagnosis or relapse.

  Neuroblastoma

  Rhabdomyosarcoma

  Non-rhabdomyosarcoma soft tissue sarcoma

  Osteosarcoma

  Ewing sarcoma

  Wilms tumor

  Hodgkin's lymphoma

  Non-Hodgkin's lymphoma

  Rhabdoid tumor

  Note: Patients who have synchronous rhabdoid tumor and ATRT with no clear primary should be enrolled into the rhabdoid tumor cohort, and they should complete the additional assessments scheduled for patients with ATRT.

  ATRT

Other tumor types not included in the list above with documented expression of PD-L1 on either tumor cells or immune infiltrating cells with approval of the Medical Monitor

Other tumor types not included in the list above without documented expression of PD-L1 can be included with approval of the Medical Monitor and should not exceed 20% of the total sample size

- Signed Informed Consent Form
- Signed Child's or Young Adult's Assent Form when appropriate, as determined by patient's age and individual site and country standards
- Age at study entry <30 years

  The first 5 patients must be $\geq$2 years of age (i.e., patients must have reached their 2nd birthday) to ensure safety and tolerability before patients $<$2 years of age receive their first dose of study drug. These first 5 patients must be followed for either two cycles of treatment or until drug discontinuation, whichever is shorter, prior to enrollment of younger patients.

  The Sponsor may decide to stop enrollment of patients who are ≥ 18 years old at any time during the study to ensure adequate enrollment of patients who are <18 years old.

  Patients who are ≥ 18 years old and are eligible for an adult PD-L1 treatment protocol will be preferentially enrolled in those adult studies.
- In exceptional cases of patients with relapsed pediatric tumors who are ≥ 30 years of age, the Sponsor will consider waiving the age requirement with approval of the Medical Monitor. This waiver is restricted to patients with pediatric-specific diseases (e.g., neuroblastoma), for whom clinical trials are unlikely to be available, and will not be extended to patients with tumors that typically occur both in children and adults (i.e., high-grade glioma).
- Able to comply with the study protocol, in the investigator's judgment
- Weight is ≥ 3 kg
- Disease that is measurable as defined by RECIST v1.1, mINRC, Revised Response Criteria for Malignant Lymphoma, $or\ RANO\ criteria$ (as appropriate) or evaluable by nuclear medicine techniques, immunocytochemistry techniques, tumor markers, or other reliable measures
- Archival tumor tissue block or 15 freshly cut, unstained, serial slides available for submission or willingness to undergo a core or excisional biopsy prior to enrollment (fine-needle aspiration, brush biopsy, and lavage samples are not acceptable)

  Patients with fewer than 15 slides available may be eligible for study entry following discussion with the Medical Monitor. See Section 4.5.6 for detailed tissue requirements.
- Lansky Performance Status (patients who are <16 years old) or Karnofsky Performance Status (patients who are ≥ 16 years old) ≥ 50 (see Appendix 8 and Appendix 9)

- Life expectancy is ≥ 3 months, in the investigator's judgment
- For patients of childbearing potential: agreement to remain abstinent (refrain from heterosexual intercourse) or use two adequate methods of contraception, including at least one method with a failure rate of $< 1\%$ per year, during the treatment period and for at least *5 months* after the last dose of study drug

  Examples of contraceptive methods with a failure rate of $< 1\%$ per year include established, proper use of hormonal contraceptives that inhibit ovulation, hormone-releasing intrauterine devices (IUDs), and copper IUDs.

  The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not acceptable methods of contraception.

  Barrier methods must always be supplemented with the use of a spermicide.
- Adequate hematologic and end organ function, defined by the following laboratory results obtained within 28 days prior to initiation of study drug:

  ANC $\geq 0.75 \times 10^9$/L (unsupported)

  Platelet count $\geq 75 \times 10^9$/L (unsupported)

  Hemoglobin ≥ 8 g/dL (transfusion permitted)

  Bilirubin $\leq 1.5 \times$ ULN for age

  AST and ALT $\leq 2.5 \times$ ULN for age

  Serum creatinine $\leq 1.5 \times$ ULN for age or creatinine clearance (or radioisotope glomerular filtration rate) > 70 mL/min/1.73 m^2

  INR and aPTT ≤ 1.5 institutional ULN for age

  Patients receiving therapeutic anticoagulants are excluded from the study.
- Fractional shortening $\geq 30\%$ or left ventricular ejection fraction (LVEF) $\geq 50\%$ at baseline, as determined by echocardiography or multigated acquisition (MUGA) scan within 28 days prior to initiation of study drug

4.1.2 Exclusion Criteria

Patients who meet any of the following criteria will be excluded from study entry:

- Known primary CNS malignancy or symptomatic CNS metastases*, except ATRT*

  Patients with ATRT must not have tumor brainstem involvement or tumors within 10 mm of the optic chiasm; they must not have a history of intracranial hemorrhage or spinal cord hemorrhage or have had neurosurgical resection, brain biopsy, or radiation to the primary brain tumor within 28 days of Cycle 1, Day 1.

- Patients with asymptomatic untreated CNS *metastases* may be enrolled after consultation with the Medical Monitor, provided all of the following criteria are met:

  Evaluable or measurable outside the CNS. *(Note: this is not required for patients with ATRT.)*

  No metastases to brain stem, midbrain, pons, medulla, or cerebellum or within 10 mm of the optic apparatus (optic nerve or chiasm). *(Note: ATRT may have metastases in the cerebellum.)*

  No history of intracranial hemorrhage or spinal cord hemorrhage

  No ongoing requirement for corticosteroids for CNS disease *except in ATRT where steroids use is permitted with approval from the Medical Monitor. Patients with ATRT must receive a stable or decreasing dose for ≥5 days prior to the baseline magnetic resonance imaging [MRI] scan and at the time of drug initiation.*

  Patients taking a stable dose of anticonvulsants are permitted

  No neurosurgical resection or brain biopsy within 28 days prior to Cycle 1, Day 1

- Patients with asymptomatic treated CNS metastases may by enrolled after consultation with the Medical Monitor, provided all the criteria listed above in the above CNS-related exclusion criteria are met as well as the following:

  Radiographic demonstration of improvement upon the completion of CNS-directed therapy and no evidence of interim progression between the completion of CNS-directed therapy and the screening radiographic study

  No stereotactic radiation or whole-brain radiation within 28 days prior to Cycle 1, Day 1

  Screening CNS radiographic study ≥4 weeks from completion of radiotherapy and ≥2 weeks from discontinuation of corticosteroids

- For patients with lymphoma, known CNS lymphoma, or leptomeningeal disease
- Treatment with high-dose chemotherapy and hematopoietic stem-cell rescue within 3 months prior to initiation of study drug

  This requirement may be waived at the investigator's request if the patient has recovered from therapeutic toxicity to the degree specified in the protocol, with approval of the Medical Monitor.

- Prior allogeneic hematopoietic stem-cell transplantation or prior solid-organ transplantation

- Treatment with chemotherapy (other than high-dose chemotherapy as described above) or differentiation therapy (such as retinoic acid) or immunotherapy (such as anti-GD2 antibody treatment) within *3* weeks prior to initiation of study drug or, if treatment included nitrosoureas, within 6 weeks prior to initiation of study drug

  This requirement may be waived at the investigator's request if the patient has recovered from therapeutic toxicity to the degree specified in the protocol, with approval of the Medical Monitor.
- Treatment with thoracic or mediastinal radiotherapy within *3* weeks prior to initiation of study drug
- Treatment with hormonal therapy (except hormone replacement therapy or oral contraceptives) or biologic therapy within 4 weeks *or 5 half-lives, whichever is shorter,* prior to initiation of study drug. *This requirement may be waived at the investigator's request if the patient has recovered from therapeutic toxicity to the degree specified in the protocol, with approval of the Medical Monitor.*
- *Treatment with herbal cancer therapy within 1 week prior to initiation of study drug*
- Treatment with a long-acting hematopoietic growth factor within 2 weeks prior to initiation of study drug or a short-acting hematopoietic growth factor within 1 week prior to initiation of study drug
- Treatment with investigational therapy (with the exception of cancer therapies as described above) within 4 weeks prior to initiation of study drug. *This requirement may be waived at the investigator's request if the patient has recovered from therapeutic toxicity to the degree specified in the protocol, with approval of the Medical Monitor.*
- Treatment with a live vaccine or a live attenuated vaccine (e.g., nasal spray of live attenuated influenza vaccine or FluMist®) within 4 weeks prior to initiation of study drug or anticipation that such treatment will be required during the study or within *5 months* after the final dose of study drug
- Prior treatment with CD137 agonists or immune checkpoint blockade therapies, including anti–CTLA-4, anti–PD-1, or anti–PD-L1 therapeutic antibodies
- Treatment with systemic immunostimulatory agents (including but not limited to interferons or interleukin 2 [IL-2]) within 6 weeks or five drug elimination half-lives prior to Day 1 of Cycle 1, whichever is longer
- Treatment with systemic corticosteroids or other systemic immunosuppressive medications (including but not limited to prednisone, dexamethasone, cyclophosphamide, azathioprine, methotrexate, thalidomide, and anti–tumor necrosis factor [TNF] agents) *at the time of* initiation of study drug, or anticipated requirement for systemic immunosuppressive medications during the study

  Patients with ATRT can be receiving concurrent treatment with corticosteroids with approval from the Medical Monitor as outlined in Section 4.4.2 and the ATRT-related exclusion criteria.
- Current treatment with therapeutic anticoagulants

- Any non-hematologic toxicity (excluding alopecia) from prior treatment that has not resolved to Grade ≤1 (per NCI CTCAE v4.0) at screening

  Note: Long-term sequelae of prior treatment (e.g., hearing loss, iatrogenic hypothyroidism, infertility, etc.) are not considered non-hematologic toxicity and instead are considered chronic medical conditions.

- Evidence of progression of neurologic deficit, in the investigator's judgment, within 1 week prior to initiation of study drug
- Major surgical procedure, significant traumatic injury within 4 weeks prior to initiation of study drug, or anticipation of need for major surgical procedure during the course of the study

  Placement of a vascular access device is permitted if the site has healed prior to initiation of study drug.

  Biopsy tissue collections are permitted if all bleeding parameters (including PT/INR and aPTT) are within normal limits and procedure is safe in the judgment of the investigator.

- Known active infection (excluding fungal infection of the nail beds) within 28 days prior to initiation of study drug that has not completely resolved
- Pregnant or lactating or intending to become pregnant during the study

  Patients of childbearing potential must have a negative serum pregnancy test result within 1 week prior to initiation of study drug.

- Known hypersensitivity to *biopharmaceuticals produced in Chinese hamster ovary cells or any component of the atezolizumab formulation*
- Any other disease, metabolic or psychological dysfunction, physical examination finding, or clinical laboratory finding giving reasonable suspicion of a disease or condition that contraindicates use of an investigational drug or places the patient at unacceptable risk from treatment complications
- Current drug or alcohol use or dependence that would interfere with adherence to study requirements, in the opinion of the investigator
- History of severe allergic or anaphylactic reaction to monoclonal antibody therapies (or recombinant antibody–related fusion proteins)
- History of clinically significant cardiac or pulmonary dysfunction
- History of any autoimmune disease, including but not limited to Type 1 diabetes mellitus, autoimmune-related hypothyroidism, myasthenia gravis, myositis, autoimmune hepatitis, systemic lupus erythematosus, rheumatoid arthritis, inflammatory bowel disease, vascular thrombosis associated with anti-phospholipid syndrome, Wegener granulomatosis, Sjögren's syndrome, Guillain-Barré syndrome, multiple sclerosis, vasculitis, or glomerulonephritis

  Patients with a history of autoimmune-related hypothyroidism who are receiving a stable dose of thyroid-replacement hormone are eligible for the study.

Patients with controlled Type 1 diabetes mellitus who are receiving a stable dose of insulin regimen are eligible for the study.

- History of severe eczema
- History of Kawasaki disease
- History of Fanconi anemia, Beckwith-Wiedemann, ataxia telangiectasia, or other genetic syndromes that may have immune or hematologic susceptibilities
- History of severe asthma or presence of uncontrolled asthma at time of screening evaluation

  Severe asthma is defined as presence of symptoms throughout the day, multiple nighttime awakenings during the week, use of a short-acting β2 agonist several times a day, and/or limitations with normal daily activity. In addition, any asthma that does not meet the above definition but is felt to be severe in the eyes of the investigator should also be excluded.
- History of idiopathic pulmonary fibrosis (including pneumonitis), drug-induced pneumonitis, organizing pneumonia (i.e., bronchiolitis obliterans, cryptogenic organizing pneumonia), cystic fibrosis, or evidence of active pneumonitis on screening chest computed tomography (CT) scan
- Dyspnea at rest or requirement for supplemental oxygen
- Uncontrolled seizures

4.2 METHOD OF TREATMENT ASSIGNMENT AND BLINDING

This is an open-label study. Dose assignments will be based on age.

4.3 STUDY TREATMENT

4.3.1 Formulation, Packaging, and Handling

Atezolizumab will be supplied by the Sponsor as sterile liquid in 20-mL glass vials. The vial is designed to deliver 20 mL (1200 mg) of atezolizumab solution but may contain more than the stated volume to enable delivery of the entire 20-mL volume.

For information on the *formulation* and handling of atezolizumab, see the Investigator's Brochure *and Pharmacy Manual*.

4.3.2 Dosage, Administration, and Compliance

The dose of atezolizumab is 15 mg/kg (maximum, 1200 mg) for patients aged <18 years. An interim analysis will be performed after 5 patients of <6 years of age have completed the first cycle. Dose adjustments may be made, if necessary, to achieve exposures corresponding to those measured in adult patients and if the safety profile is acceptable (see Section 5.1.1.1). Patients aged ≥18 years will receive a flat dose of 1200 mg of atezolizumab. Atezolizumab will be administered by IV infusion once every 3 weeks. Patients will be weighed at the beginning of each cycle (within *7* days of the Day 1 dose), and the dose will be adjusted as needed. Atezolizumab infusion may be delayed up to *5* days to accommodate holidays, weekends, and other patient obligations. Subsequent

infusions should be rescheduled accordingly. *For patients who receive the 15-mg/kg dose, the dose administered should be within 5% of the calculated dose to accommodate for any rounding that may need to occur.*

Administration of atezolizumab will be performed in a setting with emergency medical facilities and staff who are trained to monitor for and respond to medical emergencies. In addition, there must be at least 24 hours between the initial treatment doses of the first 5 patients regardless of tumor type to allow for evaluation of immediate immune activating events before additional patients are exposed to atezolizumab. There must also be at least 24 hours of treatment doses for the first 3 patients within each tumor type cohort.

Atezolizumab will be delivered in variable-size 0.9% NaCl IV infusion bags. The size of the infusion bag for each dose is listed below and will accommodate fluid restrictions needed for smaller patients.

Dose (mg)	Infusion Bag Size (mL)
600–1200	250
240–599	100
45–239	25

The initial dose of atezolizumab will be *administered* over 60 (±15) minutes. If the first infusion is tolerated without infusion-associated adverse events, the second infusion may be delivered over 30 (±10) minutes. If the 30-minute infusion is well tolerated, all subsequent infusions may be *administered* over 30 (±10) minutes. For the first infusion, the patient's vital signs (heart rate, respiratory rate, blood pressure, temperature, and pulse oximetry) should be determined within 60 minutes before, during (every 15 [±5] minutes), and 30 (±10) minutes after the end of infusion. For subsequent infusions, vital signs will be collected within 60 minutes before infusion and at the end of the infusion (± 10 minutes). Patients or their caregivers will be informed about the possibility of delayed post-infusion symptoms and instructed to contact their study physician if they develop such symptoms.

No premedication will be allowed for the first dose of atezolizumab. Premedication, including acetaminophen, diphenhydramine, or other standard-of-care medications, may be administered for Cycles ≥2 at the discretion of the treating physician after consultation with the Medical Monitor. Corticosteroids cannot be administered as premedication. Patients who are receiving acetaminophen, diphenhydramine, or other medications for symptom management may continue to receive their scheduled medications without interruption.

Guidelines for dosage modification and treatment interruption and for the management of specific adverse events, including infusion-related reactions, are provided in Section 5.1.1.

Any overdose or incorrect administration of study drug should be noted on the Study Drug Administration electronic Case Report Form (eCRF). Adverse events associated with an overdose or incorrect administration of study drug should be recorded on the Adverse Event eCRF.

For more detailed information on drug preparation, storage, and administration, refer to the Investigator's Brochure and Pharmacy Manual.

4.3.3 Investigational Medicinal Product Accountability

All investigational medicinal product (IMP) required for completion of this study (i.e., atezolizumab) will be provided by the Sponsor where required by local health authority regulations. The study site will acknowledge receipt of IMP, using the IxRS to confirm the shipment condition and content. Any damaged shipments will be replaced.

IMP will either be disposed of at the study site according to the study site's institutional standard operating procedure or returned to the Sponsor with the appropriate documentation. The site's method of IMP destruction must be agreed to by the Sponsor. 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 IMP received at, dispensed from, returned to, and disposed of by the study site should be recorded on the drug accountability log and IxRS.

4.3.4 Post-Study Access to Atezolizumab

The Sponsor will offer post-study access to the study drug (atezolizumab) free of charge to eligible patients in accordance with the Roche Global Policy on Continued Access to Investigational Medicinal Product, as outlined below.

A patient will be eligible to receive study drug after the end of the study if all of the following conditions are met:

- The patient has a life-threatening or severe medical condition and requires continued study drug treatment for his or her well-being
- There are no appropriate alternative treatments available to the patient
- The patient and his or her doctor comply with and satisfy any legal or regulatory requirements that apply to them

A patient will not be eligible to receive study drug after the end of the study if any of the following conditions are met:

- The study drug is commercially marketed in the patient's country and is reasonably accessible to the patient (e.g., is covered by the patient's insurance or wouldn't otherwise create a financial hardship for the patient)
- The Sponsor has discontinued development of the study drug or data suggest that the study drug is not effective for solid tumors
- The Sponsor has reasonable safety concerns regarding the study drug as treatment for solid tumors
- Provision of study drug is not permitted under the laws and regulations of the patient's country

The Roche Global Policy on Continued Access to Investigational Medicinal Product is available at the following Web site:

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

4.4 CONCOMITANT THERAPY AND FOOD

4.4.1 Permitted Therapy

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

Patients who use oral contraceptives, hormone-replacement therapy, prophylactic anticoagulation therapy, or maintenance therapies other than prohibited therapies listed in Section 4.4.2 should continue their use, including stress dosing as clinically indicated.

Pain medications may be administered according to local standard practice guidelines while the patient is in the study.

Patients who experience infusion-associated symptoms should receive supportive care with oxygen, β-agonists, antihistamines, antipyretics, or corticosteroids, as considered appropriate by the investigator (see the Atezolizumab Investigator's Brochure, Section 5.1.1, and Appendix 10 for more information).

Systemic corticosteroids may attenuate potential beneficial immunologic effects of treatment with atezolizumab; however, they may be administered, as described in Section 5.1.1.2, after consultation with the Medical Monitor. If feasible, alternatives to corticosteroids should be considered. Premedication, excluding corticosteroids, may be administered for Cycles ≥2 at the discretion of the treating physician after consultation with the Medical Monitor.

Palliative radiotherapy may be given to patients (e.g., treatment of known bone metastases) provided it does not interfere with assessment of tumor target lesions. It is not required to withhold atezolizumab during palliative radiotherapy.

Patients may receive inactivated vaccines if deemed necessary by the treating physician. Influenza vaccination can be given during influenza season (approximately October to March in the Northern Hemisphere). Acceptable influenza vaccines include TIV and QIV (injection of trivalent or quadrivalent killed vaccine). However, LAIV and Q/LAIV (nasal spray of live attenuated influenza vaccine such as FluMist®) must be avoided.

4.4.2 Prohibited Therapy

Use of the following therapies is prohibited during the study:

- Any concomitant therapy intended for the treatment of solid tumors, either approved by health authorities or experimental, including chemotherapy, radiotherapy (except palliative radiotherapy), hormonal therapy, immunotherapy, biologic therapy, or herbal therapy

  Patients with rhabdoid tumor and ATRT may receive local therapy (radiation or surgery) after at least four cycles of atezolizumab with approval of the Medical Monitor.

- Traditional herbal or homeopathic or natural medicines

  Ingredients for such medicines have not been fully studied, and their use may result in unanticipated drug-drug interactions that may cause or confound assessment of toxicity.

- Immunostimulatory agents, including but not limited to interferon (IFN)-α, IFN-γ, anti-TNF-α, or IL-2 (prohibited during the study and for 10 weeks after the last dose of atezolizumab)

  These agents, in combination with atezolizumab, could potentially increase the risk for autoimmune conditions.

- Immunosuppressive medications, including but not limited to cyclophosphamide, azathioprine, methotrexate, and thalidomide

  These agents could potentially alter the activity and the safety of atezolizumab.

- Live vaccines and live attenuated vaccines (prohibited during the study and for *5 months* after the last dose of study drug)

Initiation of granulocyte colony-stimulating factors (e.g., granulocyte colony-stimulating factor, granulocyte/macrophage colony-stimulating factor, and/or pegfilgrastim) should be discussed with the Medical Monitor.

Systemic corticosteroids may attenuate potential beneficial immunologic effects of treatment with atezolizumab but may be administered at the discretion of the treating physician after consultation with the Medical Monitor, as described in Section 5.1.1.2.

Patients with ATRT can be receiving concurrent treatment with corticosteroids with approval from the Medical Monitor. Patients must be receiving a stable or decreasing dose for ≥5 days prior to the baseline MRI scan and at the time of drug initiation. The Medical Monitor should be informed when steroid doses are increased because of declining patient status.

In clinically indicated emergent situations (i.e., anaphylaxis), corticosteroids may be administered without notifying the Medical Monitor in advance, but the Medical Monitor should be notified within 24 hours of the event. If feasible, alternatives to these agents should be considered. *Systemic steroids used as steroid replacement therapy for adrenal insufficiency are permitted.*

4.5 STUDY ASSESSMENTS

See Appendix 1 and Appendix 2 for the schedules of assessments performed during the study.

Unless otherwise stated, the baseline measurement for any given assessment will be defined as the last value obtained before the first dose of study drug. After treatment initiation, changes from baseline abnormalities should be recorded in patient notes. New or worsened clinically significant abnormalities should be recorded as adverse events on the Adverse Event eCRF. Patients should be assessed for toxicity prior to each dose; dosing will occur only if the clinical assessment and local laboratory test values are acceptable.

If the timing of a protocol-mandated study visit coincides with a holiday and/or weekend that precludes the visit, the visit should be scheduled on the nearest following feasible date, with subsequent visits rescheduled accordingly.

4.5.1 Informed Consent Forms and Screening Log

Written informed consent, and assent when applicable, for participation in the study must be obtained before performing any study-specific screening tests or evaluations. Informed Consent Forms and Child's Informed Assent Forms for enrolled patients and for patients who are not subsequently enrolled will be maintained at the study site.

All screening evaluations must be completed and reviewed to confirm that patients meet all eligibility criteria before enrollment. The investigator will maintain a screening log to record details of all patients screened and to confirm eligibility or record reasons for screening failure, as applicable.

4.5.2 Medical History and Demographic Data

Medical history includes clinically significant diseases, surgeries, cancer history (including prior cancer therapies, current cancer stage, and procedures), menstrual history, fertility history, and puberty history. In addition, all medications (e.g., prescription drugs, over-the-counter drugs, herbal or homeopathic remedies,

nutritional supplements) used by the patient within 7 days prior to initiation of study drug will be recorded.

Demographic data will include age, sex, and self-reported race/ethnicity as permitted by local regulatory authorities.

4.5.3 Physical Examinations and Assessments

A complete physical examination should include an evaluation of the head, eyes, ears, nose, and throat and the cardiovascular, dermatological, musculoskeletal, respiratory, gastrointestinal, genitourinary, and neurological systems. Any abnormality identified at baseline should be recorded on the General Medical History and Baseline Conditions eCRF.

The Lansky Performance Status should be performed for patients who are <16 years old, and the Karnofsky Performance Status should be performed for patients who are ≥ 16 years old.

At subsequent visits (or as clinically indicated), changes from baseline abnormalities should be recorded in patient notes. New or worsened clinically significant abnormalities should be recorded as adverse events on the Adverse Event eCRF.

Fractional shortening or LVEF should be determined within 28 days prior to initiation of study drug by either echocardiography or MUGA scan.

During the treatment period, weight will be measured at the beginning of each cycle. During the follow-up period, weight should be measured every 3 months for the first 2 years, every 6 months during the 3rd year, and yearly thereafter.

During the treatment period, height, head circumference (until the age of 3 years), and Tanner stage should be measured every four cycles (approximately every 3 months). During the follow-up period, height, head circumference, and Tanner stage should be measured every 3 months for the first 2 years, every 6 months during the 3rd year, and yearly thereafter. Tanner staging should be performed until the patient has reached Tanner Stage V.

4.5.3.1 *Neurologic Examinations (ATRT Only)*

For patients with ATRT, a complete neurologic examination should be completed at every patient visit, including at baseline (see Schedule of Assessments in Appendix 1*). Any abnormality identified at baseline should be recorded on the General Medical History and Baseline Conditions eCRF.*

At subsequent visits (or as clinically indicated), changes from baseline abnormalities need to be reviewed carefully prior to administering the next atezolizumab dose.

Atezolizumab should not be administered if there is any sign of increased intracranial pressure.

The neurologic examination should include age-appropriate evaluations of vision, including visual fields, coordination, cranial nerve function, strength and motor evaluations (including gait when appropriate), and reflexes. Discussions with the parents and/or guardian should also occur to assess for new or worsening symptoms, including but not limited to changes in physical activity, irritability, headaches, changes in appetite and/or feeding, vomiting, and nausea.

New or worsened clinically significant abnormalities should be recorded as adverse events on the Adverse Event eCRF.

4.5.4 Vital Signs

Age-appropriate equipment should be used to obtain vital signs and assessments and adjusted for growth. Vital signs will include measurements of respiratory rate, pulse rate, systolic and diastolic blood pressures, oxygen saturation by pulse oximetry, and temperature.

For the first infusion of atezolizumab, vital signs should be determined within 60 minutes before, every 15 (±5) minutes during, and 30 (±10) minutes after the end of infusion. For subsequent infusions, vital signs should be recorded within 60 minutes before infusion and at the end of infusion (±10) minutes, but vital signs do not need to be obtained during the infusion if the prior infusion was tolerated without symptoms.

4.5.5 Tumor and Response Evaluations

4.5.5.1 Tumor Assessments

All known sites of disease must be documented at screening and re-assessed at each subsequent tumor evaluation. Baseline tumor assessments should be performed within 28 days prior to initiation of study drug (Day 1 of Cycle 1). Tumor assessments must be performed during the last week of Cycles 2, 4, 6, and 8 and every 4th cycle thereafter (i.e., within 7 days prior to Day 1 of the next cycle). At the investigator's discretion, unscheduled tumor assessments may be performed at any time if progressive disease is suspected. For patients who continue treatment beyond radiographic progressive disease because of possible pseudoprogression, a follow-up scan must be performed after 2 cycles or earlier if clinically indicated.

Response will be assessed by the investigator on the basis of physical examinations, CT scans, MRI scans, fluorodeoxyglucose-positron emission tomography (FDG-PET) scans, or MIBG scans, as appropriate. *Tumor assessment imaging should include all areas of known disease. A chest CT is also required to be performed at each assessment.* An objective response should be confirmed by repeat assessments ≥4 weeks after initial documentation. The same *imaging techniques and* procedure*s* used to assess disease sites at screening should be used throughout the study (e.g., the same contrast protocol

for CT scans). To the extent that is feasible, assessments should be performed by the same evaluator to ensure internal consistency across visits.

Patients with neuroblastoma must have a MIBG scan and bilateral bone marrow aspirates and/or biopsies done for disease evaluation. If the enrollment bone marrow aspirates and/or biopsy tissue samples are negative for disease, subsequent bone marrow aspirates and/or biopsy tissue samples are not needed. Patients with evidence of bone marrow disease at screening require bone marrow evaluation with scheduled disease evaluations until they have had two consecutive evaluations that are negative for disease. Patients with neuroblastoma should also have urine catecholamine test results (including homovanillic acid and vanillylmandelic acid) sent at screening and with all responses assessments.

Patients with lymphoma should undergo FDG-PET imaging at screening and with each response assessment. For lymphoma patients with a clinical suspicion of bone marrow involvement, bilateral bone marrow aspirates and/or biopsies should be performed at screening. Patients who have documented bone marrow involvement at screening should have subsequent bilateral bone marrow evaluations performed with each response assessment until the first negative bone marrow evaluation.

Patients without neuroblastoma or lymphoma who have a clinical suspicion of bone marrow involvement should also have bilateral bone marrow aspirates and/or biopsies performed at screening. Patients who have documented bone marrow involvement at screening should have subsequent bone marrow evaluations performed with each response assessment until the first negative bone marrow evaluation.

4.5.5.2 Response Criteria

All tumors will be evaluated for disease response and progressive disease with RECIST v1.1 (see Appendix 6) with the exception of those listed below.

- Neuroblastoma: *m*INRC (see Appendix 3)
- Hodgkin's lymphoma and non-Hodgkin's lymphoma: Revised Response Criteria for Malignant Lymphoma (see Appendix 4)
- *ATRT: RANO criteria (see Appendix 11)*

  Patients with synchronous ATRT and rhabdoid tumor with no clear primary should be enrolled into the rhabdoid tumor cohort. These patients' tumors will be evaluated with RECIST v1.1 criteria.

Patients who enroll with evaluable but not measurable disease will have a modified response assessment. For such patients, partial response cannot be determined; therefore, response will be limited to complete response, stable disease, or progressive disease.

During treatment, patients who show evidence of clinical benefit will be permitted to continue atezolizumab treatment after criteria for progressive disease for their specified response assessment are met, if they meet all of the following criteria:

- Evidence of clinical benefit as assessed by the investigator and agreed upon by the Medical Monitor
- Absence of symptoms or signs (including worsening laboratory test values) indicating unequivocal progression of disease
- No decline in Lansky or Karnofsky Performance Status that can be attributed to disease progression
- Absence of tumor progression at critical anatomical sites (e.g., leptomeningeal disease) that cannot be managed by protocol-allowed medical interventions

Patients and/or their parents or guardians must sign a consent acknowledging treatment continuation after possible worsening disease in order to continue to receive atezolizumab. Patients for whom radiographic disease progression is confirmed at a subsequent tumor assessment may be considered for continued study treatment at the discretion of the investigator if they have evidence of clinical benefit and continue to meet the criteria above. If an individual patient continues to experience clinical benefit beyond 2 years of radiologic progressive disease (see Section 3.3.4), the Sponsor and treating physician will apply for additional approval from health authorities for continued treatment.

Collection of an optional tumor biopsy sample, if clinically feasible, at the time of first radiographic progression on atezolizumab treatment is encouraged in order to evaluate the utility of the biopsy tumor sample in distinguishing pseudoprogression or tumor immune infiltration from true progressive disease.

4.5.6 Laboratory, Biomarker, and Other Biological Samples

Assessments that require blood draws should be monitored closely to ensure that institutional guidance regarding total blood volume taken for samples is maintained. In situations where no institutional guidance is available, no more than 2.5% of the total blood volume should be taken at one time and no more than 5% of the total blood volume should be taken over a 30-day period (total blood volume is defined as 80 mL/kg). Institutions should use micro-sampling systems to minimize the amount of blood drawn when able. In situations where the total amount will exceed the amount stated above, clinical laboratory assessments should be prioritized. Any remaining blood should be sent for PK analysis and immunogenicity followed by biomarker and PD analyses.

Laboratory tests results must meet the inclusion criteria and not meet the exclusion criteria at the time of screening. If laboratory tests are performed again prior to the first dose, they must continue to meet the inclusion criteria and not meet the exclusion criteria.

Samples for the following laboratory tests will be sent to the study site's local laboratory for analysis:

- Hematology (WBC count, hemoglobin, platelet count, 3-cell differential count [absolute neutrophils, monocytes, and lymphocytes])
- Serum chemistry (sodium, potassium, magnesium, chloride, bicarbonate, glucose, BUN or urea, creatinine, total protein, albumin, phosphorus, calcium, total bilirubin [if abnormal, fractionate sample for direct and indirect], alkaline phosphatase, ALT, AST, LDH, amylase, and lipase)
- Creatinine clearance should be done as clinically indicated. If radioisotope glomerular filtration rate is routinely performed at the institution to measure patients' creatinine clearance, this test can be used to assess renal function at screening, per the eligibility criteria. Otherwise, serum creatinine is sufficient to document renal function at screening.
- Coagulation panel (INR, aPTT, PT)
- Urinalysis (specific gravity, glucose, protein, blood) in children who are >3 years of age
- Pregnancy test

  All patients of childbearing potential will undergo a serum pregnancy test at screening (prior to Cycle 1) within 1 week prior to initial dose. Urine or serum pregnancy test will be performed prior to all subsequent cycles.
- Thyroid function testing (thyroid-stimulating hormone, free T3, free T4)
- Viral serology at screening (hepatitis B surface antigen, hepatitis B surface antibody, total hepatitis B core antibody, hepatitis C antibody, human immunodeficiency virus (HIV)-1, and HIV-2 antibody)

  If a patient is positive for hepatitis B core antibody at screening, a test for hepatitis B virus DNA should be performed prior to Day 1 of Cycle 1.

  If a patient is positive for hepatitis C antibody at screening, a test for hepatitis C virus RNA should be performed prior to Day 1 of Cycle 1.

The following samples will be sent to a central laboratory or the Sponsor or selected designee for analysis:

- Archival or fresh primary tumor tissue samples for exploratory research on candidate biomarkers, including but not limited to PD-L1, PD-1, and CD8

  For patients with archival samples: Representative formalin-fixed paraffin-embedded (FFPE) tumor specimens in paraffin blocks or at least 15 freshly cut, unstained, serial slides (blocks preferred), with an associated pathology report, are required for study entry. The specimen should be of good tissue quality and have sufficient viable tumor content as determined by the institutional pathologist. Patients with fewer than 15 slides available may be eligible for study entry following discussion with the Medical Monitor. The tumor specimen and associated pathology report must be confirmed to be available prior to patient participation in any study-specific screening procedures and must be shipped within 30 days of first dosing.

  Patients will be encouraged to submit all available FFPE tumor specimens from prior surgeries and biopsies performed as part of routine medical care. If a patient has multiple archival specimens available but wants to submit only one sample, the specimen obtained closest to the start of treatment should be used.

  Patients without archival samples must undergo a core or excisional biopsy prior to enrollment. Fine-needle aspiration, brush biopsy, and lavage samples are not acceptable. *Submission of bone biopsy specimens is strongly discouraged because of complications in the assessment of such tissue. These specimens can be used only if no other tissue is available.*

  Unused archival tumor blocks will be returned to the sites at the end of the study or upon site request.

- PK assay

  Serum samples will be assayed for atezolizumab concentration with use of a validated immunoassay. Any residual PK samples can be used for additional ATA testing if needed.

- ATA assays

  Serum samples will be assayed for the presence of ATAs to atezolizumab with use of a validated immunoassay.

- In children who have been vaccinated, tetanus toxoid IgG antibody titers
- Plasma samples for exploratory research on candidate biomarkers, including but not limited to the following: cytokines (e.g., IL-2 and IFN-γ), ctDNA concentration, ctDNA mutations (e.g., *KRAS*, *P53*, *PTEN*)
- Whole blood samples for analysis of immune cell expression of biomarkers, including but not limited to the following: PD-L1, CD4, CD8, FoxP3, IFN-γ

- A whole blood sample for molecular analysis of mutations and single-nucleotide polymorphisms (SNPs) is required ONLY for patients who consent to submitting optional on-study tissue (tissue submission described in Section 4.5.7). This sample may be used for the analysis of novel mutations detected in tumor tissue in order to verify the somatic nature of this mutation and SNPs that might be associated with safety, efficacy, or pharmacokinetics of the drug.
- Whole blood samples for TBNK cell enumeration

Serum samples will be obtained at baseline and held for possible testing in patients who develop immune-related or inflammatory adverse events during the study. The samples will be analyzed as needed to determine baseline values for the following:

- Auto-antibody testing

  Anti-nuclear antibody

  Anti–double-stranded DNA

  Circulating anti-neutrophil cytoplasmic antibody

  Perinuclear anti-neutrophil cytoplasmic antibody

For sampling procedures, storage conditions, and shipment instructions, see the Laboratory Manual.

Samples will be destroyed when the final Clinical Study Report has been completed, with the following exceptions:

- Any remaining samples collected for pharmacokinetics, biomarker assays, and ATA assays may be used for exploratory biomarker profiling, identification, and PD assay development purposes and for additional safety assessments (e.g., ATA assay) as appropriate. *These samples will be destroyed no later than 5 years after the final Clinical Study Report has been completed.* The remainder of samples obtained for study-related procedures will be destroyed no later than 5 years after the date of final closure of the clinical database unless the patient gives specific consent for the remainder of the samples to be stored for optional exploratory research. If the patient provides consent for optional exploratory research, the samples will be destroyed no later than 15 years after the date of final closure of the clinical database.

4.5.7 Samples for Roche Clinical Repository

4.5.7.1 Overview of the Roche Clinical Repository

The Roche Clinical Repository (RCR) is a centrally administered group of facilities used for the long-term storage of human biologic specimens, including body fluids, solid tissues, and derivatives thereof (e.g., DNA, RNA, proteins, peptides). The collection and analysis of RCR specimens 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.

Specimens for the RCR will be collected from patients who give specific consent to participate in this optional research. RCR specimens will be used to achieve the following objectives:

- To study the association of biomarkers with efficacy, adverse events, or progressive disease
- To increase knowledge and understanding of disease biology
- To study drug 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

4.5.7.2 Approval by the Institutional Review Board or Ethics Committee

Collection and submission of biological samples to the RCR is contingent upon the review and approval of the exploratory research and the RCR portion of the Informed Consent Form by each site's Institutional Review Board (IRB) or Ethics Committee (EC) and, if applicable, an appropriate regulatory body. If a site has not been granted approval for RCR sampling, this section of the protocol (Section 4.5.7) will not be applicable at that site.

4.5.7.3 Sample Collection

The following samples will be collected for research purposes, including but not limited to research on dynamic (non-inherited) biomarkers related to atezolizumab or solid tumors:

- Fresh tissue from study biopsies and residual tissue from non–study-related procedures, will be collected from the primary tumor location, metastatic site, or site of local recurrence or advancement for analyses that may include DNA or RNA extraction. Samples should be obtained at the following timepoints: prior to drug initiation, 4–6 weeks after the first dose of drug, and at the time of progressive disease (if applicable). Patient may choose to consent to any or all of these timepoints.

  A minimum of three fresh tissue cores should be acquired using an 18-gauge needle. If not feasible, one or two cores may be acceptable after discussion with the Medical Monitor.

Patients consenting to the optional study biopsy will also be required to provide a mandatory whole blood sample listed under the main protocol (Section 4.5.6).

For all samples, dates of consent should be recorded on the associated RCR page of the eCRF. For sampling procedures, storage conditions, and shipment instructions, see the Laboratory Manual.

RCR specimens will be destroyed no later than 15 years after the date of final closure of the associated clinical database. The RCR storage period will be in accordance with the IRB/EC-approved Informed Consent Form and applicable laws (e.g., health authority requirements).

The dynamic biomarker specimens will be subject to the confidentiality standards described in Section 8.4.

4.5.7.4 Confidentiality

Data generated from RCR specimens must be available for inspection upon request by representatives of national and local health authorities and Roche monitors, representatives, and collaborators, as appropriate.

Patient medical information associated with RCR specimens is confidential and may be disclosed to third parties only as permitted by the Informed Consent Form (or separate authorization for use and disclosure of personal health information) signed by the patient, unless permitted or required by law.

Data derived from RCR specimen analysis on individual patients will generally not be provided to study investigators unless a request for research use is granted. The aggregate results of any research conducted using RCR specimens will be available in accordance with the effective Roche policy on study data publication.

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

4.5.7.5 Consent to Participate in the Roche Clinical Repository

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

The investigator should document whether or not the patient has given consent to participate by completing the RCR Research Sample Informed Consent eCRF.

In the event of an RCR participant's death or loss of competence, the participant's specimens and data will continue to be used as part of the RCR research.

4.5.7.6 Withdrawal from the Roche Clinical Repository

Patients who give consent to provide RCR specimens have the right to withdraw their specimens from the RCR at any time for any reason. If a patient wants to withdraw consent to the testing of his or her specimens, the investigator must inform the Medical Monitor in writing of the patient's wishes through use of the RCR Subject Withdrawal Form and, if the study is ongoing, must enter the date of withdrawal on the RCR Research Sample Withdrawal of Informed Consent eCRF. The patient will be provided with instructions on how to withdraw consent after the study is closed. A patient's withdrawal from Study GO29664 does not, by itself, constitute withdrawal of specimens from the RCR. Likewise, a patient's withdrawal from the RCR does not constitute withdrawal from Study GO29664.

4.5.7.7 Monitoring and Oversight

RCR specimens 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 specimens as specified in this protocol and in the Informed Consent Form. Roche monitors and auditors will have direct access to appropriate parts of records relating to patient participation in the RCR for the purposes of verifying the data provided to Roche. 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 RCR samples.

4.6 PATIENT, TREATMENT, STUDY, AND SITE DISCONTINUATION

4.6.1 Patient Discontinuation

Patients have the right to voluntarily withdraw from the study (or be withdrawn by their patients or caregivers, if the patient is a minor) at any time for any reason. In addition, the investigator has the right to withdraw a patient from the study treatment at any time. Reasons for withdrawal from the study may include but are not limited to the following:

- Patient withdrawal of consent (or withdrawal of consent by their patients or caregivers, if the patient is a minor) at any time
- Any medical condition that the investigator or Sponsor determines may jeopardize the patient's safety if he or she continues in the study
- Investigator or Sponsor determines it is in the best interest of the patient.
- Patient non-compliance with the study procedures (e.g., dosing instructions, study visits)

Every effort should be made to obtain information on patients who withdraw from the study. The primary reason for withdrawal from the study should be documented on the appropriate eCRF. *In situations where it is either unsafe or not in the best interest of the patient to complete follow-up assessments after study drug discontinuation, survival data only may be submitted during the follow-up period with approval of the*

Medical Monitor. Patients will not be followed up for any reason after consent has been withdrawn. Patients who withdraw from the study will not be replaced.

4.6.2 Study Drug Discontinuation

Patients must discontinue study drug if they experience any of the following:

- Symptomatic deterioration attributed to disease progression as determined by the investigator after integrated assessment of radiographic data, biopsy results, and clinical status
- Unacceptable toxicity despite per-protocol treatment interruptions
- Pregnancy
- Withdrawal of consent
- Interruption of study treatment for >105 days *(e.g., more than 105 days between infusions)* because of an atezolizumab-related adverse event, except in patients who must be tapered off corticosteroids used to treat adverse events (see Section 5.1.1.1 for details). This duration may be extended after consultation with the Medical Monitor.

Patients who discontinue study drug for any reason will be asked to return to the clinic for a study drug discontinuation visit and undergo follow-up assessments (see the schedule of assessments in Appendix 1). If treatment with another anti-cancer treatment is scheduled to begin within 90 days after the last dose of atezolizumab, assessments at this visit should be performed before the patient starts the other treatment, if possible. Patients who discontinue for reasons other than progressive disease should continue follow-up assessments, including tumor assessments, using the long-term follow-up schedule (e.g., every 3 months for the first 2 years, every 6 months during Year 3, etc.) until radiographic documentation of progressive disease, they start another treatment, or consent is withdrawn. For patients who continue receiving study drug beyond radiographic progressive disease, assessments should be continued until they stop taking study drug. The primary reason for study drug discontinuation should be documented on the appropriate eCRF.

4.6.3 Study and Site Discontinuation

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 adverse events in this or other studies indicates a potential health hazard to patients.
- Patient enrollment is unsatisfactory.

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

The Sponsor has the right to close a site at any time. Reasons for closing a site may include but are not limited to the following:

- Excessively slow recruitment
- Poor protocol adherence
- Inaccurate or incomplete data recording
- Non-compliance with the International Conference on Harmonisation (ICH) guideline for Good Clinical Practice
- No study activity (i.e., all patients have completed and all obligations have been fulfilled)

5. ASSESSMENT OF SAFETY

5.1 SAFETY PLAN

Atezolizumab is not approved *for pediatric use* and is currently in clinical development *for different indications*. Human experience is currently limited, and the entire safety profile is not known at this time. It has not been studied in patients younger than 15 years old. The following information is based on results from nonclinical and adult clinical studies and published data on similar molecules. Refer to the Atezolizumab Investigator's Brochure for a complete summary of safety information.

Measures will be taken to ensure the safety of patients participating in this study. Eligibility criteria have been designed to exclude patients at higher risk for toxicities. Specifically, patients at risk for study-emergent autoimmune conditions or with a prior diagnosis of autoimmune disease *(except patients with a history of autoimmune-related hypothyroidism receiving a stable dose of thyroid-replacement hormone or patients with controlled Type 1 diabetes mellitus receiving a stable dose of insulin regimen)*, patients with evidence of acute or chronic infections, and patients who have received a live vaccine or a live attenuated vaccine within 4 weeks prior to initiation of study drug will be excluded from the study (see Section 4.1.2). Patients are also required to abstain from receiving a live or live attenuated vaccine during treatment and for *5 months* following the last atezolizumab dose. In addition, patients will undergo safety monitoring during the study as described in Section 4.5, Section 5, and the schedules of assessments (see Appendix 1 and Appendix 2). *Patients with ATRT will be monitored with additional visits to assess neurologic function due to the possible risk of tumor progression and/or pseudoprogression in the CNS cavities.* Adverse events, laboratory values, and vital signs must be reviewed prior to each infusion.

An iDMC will monitor patient safety throughout the study.

Administration of atezolizumab will be performed in a setting with emergency medical facilities and staff who are trained to monitor for and respond to medical emergencies. In addition, there must be at least 24 hours between the initial treatment doses of the first 5 patients regardless of tumor type to allow for evaluation of immediate immune

activating events before additional patients are exposed to atezolizumab. There must also be at least 24 hours of treatment doses for the first 3 patients within each tumor type cohort.

Serious adverse events *and adverse events of special interest* will be recorded during the study *and for 90 days after the last dose of study treatment or until the initiation of another anti-cancer therapy, whichever occurs first. All other adverse events will be recorded during the study* and for *30* days after the last dose of study treatment or until the initiation of another anti-cancer therapy, whichever occurs first; treatment-related adverse events must be reported beyond this date (see Section 5.3.1). In addition, patients will continue to be followed up at defined time intervals (see schedules of assessments in Appendix 1 and Appendix 2) until termination of the study. Following discontinuation from this study, patients will be offered follow-up for adverse events and survival.

5.1.1 Management of Specific Adverse Events

The potential safety issues anticipated in this study, as well as measures intended to avoid or minimize such toxicities, are outlined in the following sections. Toxicities possibly associated with atezolizumab treatment should be managed according to the management guidelines described in the Atezolizumab Investigator's Brochure in conjunction with standard medical practice. However, the guidelines are not intended to replace clinical judgment. Additional tests, such as autoimmune serology or biopsies, should be used to determine a possible immunogenic etiology, in accordance with pediatric standard-of-care practice. Guidelines for managing adverse events, including criteria for treatment interruption or discontinuation, are provided below and described in the Atezolizumab Investigator's Brochure.

5.1.1.1 Dose Modification and Treatment Interruption

There will be no intrapatient atezolizumab dose reductions as a result of adverse events. Study drug may be temporarily withheld if patients experience an adverse event that is considered related to atezolizumab. If study drug is withheld because of an atezolizumab-related adverse event for > 105 days, the patient will be discontinued from atezolizumab treatment.

Following the interim PK analyses, dose modifications may be considered if warranted for all patients on the basis of individual and population PK data to ensure patient safety and/or to match adult exposures. Recommendations will be based on evaluations of PK, safety, efficacy, and biomarker data as available and appropriate.

If patients must be tapered off corticosteroids used to treat adverse events, study treatment may be withheld for > 105 days. The acceptable length of interruption will depend on agreement between the investigator and the Medical Monitor.

Dose interruptions for reasons other than toxicity, such as surgical procedures, may be allowed with Medical Monitor approval. The acceptable length of interruption will depend on agreement between the investigator and the Medical Monitor.

5.1.1.2 Immune-Mediated Adverse Events

Toxicities associated or possibly associated with atezolizumab treatment should be managed according to management guidelines described in the Atezolizumab Investigator's Brochure in conjunction with standard medical practice. These guidelines outline the general management in adult patients; therefore, recommended dosing may need to be adjusted appropriately for pediatric patients. Additional tests, such as autoimmune serology or biopsies, should be used to determine a possible immunogenic etiology.

Although most immune-mediated adverse events 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 atezolizumab 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.

The investigator should consider the benefit-risk balance a given patient may be experiencing prior to further administration of atezolizumab. Atezolizumab should be permanently discontinued in patients with life-threatening immune-mediated adverse events and per management guidelines described in the Atezolizumab Investigator's Brochure.

Management of systemic immune activation is presented below. Refer to the Atezolizumab Investigator's Brochure for details on management of atezolizumab-specific adverse events, including pulmonary events, hepatic events, gastrointestinal events, endocrine events, ocular events, infusion-related reactions, pancreatic events, dermatologic events, neurologic disorders, and immune-related meningoencephalitis.

5.1.1.3 Systemic Immune Activation

Systemic immune activation is a rare condition characterized by an excessive immune response. Given the mechanism of action of atezolizumab, systemic immune activation is considered a potential risk when given in combination with other immunomodulating agents. Systemic immune activation should be included in the differential diagnosis for patients who, in the absence of an alternate etiology, develop a sepsis-like syndrome after administration of atezolizumab, and initial evaluation should include *assessing* the following:

- CBC with peripheral smear
- PT, PTT, fibrinogen, and D-dimer
- Ferritin

- Triglycerides
- AST, ALT, and total bilirubin
- LDH
- Complete neurologic and abdominal examination (assess for hepatosplenomegaly)

If systemic immune activation is still suspected after the initial evaluation, contact the Medical Monitor for additional recommendations.

5.1.1.4 *Central Nervous System Signs and Symptoms (ATRT Only)*

For the ATRT cohort only, signs and symptoms of disease progression and pseudoprogression of this CNS tumor should be assessed at each visit. Study treatment should be interrupted immediately and patients should be treated with steroids and/or other medications to reduce intracranial pressure as per institutional guidelines in the case of signs and symptoms of increased intracranial pressure considered to be related to atezolizumab, including but not limited to vomiting, headache, changes in mental status, and vision changes. The Medical Monitor should be contacted within 24 hours if CNS signs and symptoms considered to be related to atezolizumab occur. Patients should be treated with steroids and/or other medications to reduce intracranial pressure as per institutional guidelines.

5.2 SAFETY PARAMETERS AND DEFINITIONS

Safety assessments will consist of monitoring and recording adverse events, including serious adverse events and adverse events of special interest, performing protocol-specified safety laboratory assessments, measuring protocol-specified vital signs, and conducting other protocol-specified tests that are deemed critical to the safety evaluation of the study.

Certain types of events require immediate reporting to the Sponsor, as outlined in Section 5.4.

5.2.1 Adverse Events

According to the ICH guideline for Good Clinical Practice, an adverse event is any untoward medical occurrence in a clinical investigation subject administered a pharmaceutical product, regardless of causal attribution. An adverse event can therefore be any of the following:

- Any unfavorable and unintended sign (including an abnormal laboratory test finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product
- Any new disease or exacerbation of an existing disease (a worsening in the character, frequency, or severity of a known condition), except as described in Section 5.3.5.10
- Recurrence of an intermittent medical condition (e.g., headache) not present at baseline

- Any deterioration in a laboratory value 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 drug
- 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)

5.2.2 Serious Adverse Events (Immediately Reportable to the Sponsor)

A serious adverse event is any adverse event that meets any of the following criteria:

- Is fatal (i.e., the adverse event actually causes or leads to death)
- Is life threatening (i.e., the adverse event, in the view of the investigator, places the patient at immediate risk of death)

  This does not include any adverse event that, had it occurred in a more severe form or was allowed to continue, might have caused death.
- Requires or prolongs inpatient hospitalization (see Section 5.3.5.11)
- Results in persistent or significant disability/incapacity (i.e., the adverse event results in substantial disruption of the patient's ability to conduct normal life functions)
- Is a congenital anomaly and/or birth defect in a neonate or infant born to a mother exposed to study drug
- Is a significant medical event in the investigator's judgment (e.g., may jeopardize the patient or may require medical or surgical intervention to prevent one of the outcomes listed above)

The terms "severe" and "serious" are not synonymous. Severity refers to the intensity of an adverse event (e.g., rated as mild, moderate, or severe, or according to NCI CTCAE v4.0 criteria; see Section 5.3.3); 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; see Section 5.4.2 for reporting instructions).

5.2.3 Adverse Events of Special Interest (Immediately Reportable to the Sponsor)

Adverse events of special interest, regardless of seriousness, 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 Section 5.4.2 for reporting instructions). Adverse events of special interest for this study include the following:

- Pneumonitis
- Colitis
- Endocrinopathies
  - Diabetes mellitus
  - Pancreatitis
  - Adrenal insufficiency
  - Hyperthyroidism
  - Hypothyroidism
- Hepatitis
- Transaminitis Grade ≥ 2 (AST or ALT $> 3 \times$ ULN and bilirubin $> 2 \times$ ULN) or AST/ALT $> 10 \times$ ULN
- Systemic lupus erythematosus
- Neurological
  - Guillain-Barré syndrome
  - Myasthenia gravis
  - Meningoencephalitis
- Nephritis
- Events suggestive of hypersensitivity, cytokine release, influenza-like illness, systemic inflammatory response syndrome, systemic immune activation, or infusion reactions syndrome
- Cases of potential drug-induced liver injury that include an elevated ALT or AST level in combination with either an elevated bilirubin level or clinical jaundice, as defined by Hy's law (see Section 5.3.5.7)
- Suspected transmission of an infectious agent by the study drug, 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 patient exposed to a medicinal product. This term applies only when a contamination of the study drug is suspected

5.3 METHODS AND TIMING FOR CAPTURING AND ASSESSING SAFETY PARAMETERS

The investigator is responsible for ensuring that all adverse events (see Section 5.2.1 for definition) are recorded on the Adverse Event eCRF and reported to the Sponsor in accordance with instructions provided in this section and in Section 5.4 and Section 5.6.

For each adverse event recorded on the Adverse Event eCRF, the investigator will make an assessment of seriousness (see Section 5.2.2 for seriousness criteria), severity (see Section 5.3.3), and causality (see Section 5.3.4).

5.3.1 Adverse Event Reporting Period

Investigators will seek information on adverse events at each patient contact. All adverse events, whether reported by the patient or noted by study personnel, will be recorded in the patient's medical record and on the Adverse Event eCRF.

After informed consent has been obtained **but prior to initiation of study drug**, only serious adverse events caused by a protocol-mandated intervention (e.g., invasive procedures such as biopsies, discontinuation of medications) should be reported (see Section 5.4.2 for instructions for reporting serious adverse events).

After initiation of study drug, all *serious* adverse events *and adverse events of special interest, regardless of relationship to study drug,* will be reported until 90 days after the last dose of study drug *or initiation of new anti-cancer therapy, whichever occurs first. All other adverse events, regardless of relationship to study drug, will be reported until 30 days after the last dose of study drug or initiation of new anti-cancer therapy, whichever occurs first.* After this period, the investigator should report any serious adverse events that are believed to be related to prior study drug treatment (see Section 5.6).

5.3.2 Eliciting Adverse Event Information

A consistent methodology of non-directive questioning should be adopted for eliciting adverse event information at all patient evaluation timepoints. Examples of non-directive questions include the following:

"How have you felt since your last clinic visit?"

"Have you had any new or changed health problems since you were last here?"

5.3.3 Assessment of Severity of Adverse Events

The adverse event severity grading scale for the NCI CTCAE (v4.0) 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 for Events Not Specifically Listed in the NCI CTCAE

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 most recent version of NCI CTCAE (v4.0), which can be found at http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

[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 oneself, 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 5.4.2 for reporting instructions), per the definition of serious adverse event in Section 5.2.2.

[d] Grade 4 and 5 events must be reported as serious adverse events (see Section 5.4.2 for reporting instructions), per the definition of serious adverse event in Section 5.2.2.

5.3.4 Assessment of Causality of Adverse Events

Investigators should use their knowledge of the patient, the circumstances surrounding the event, and an evaluation of any potential alternative causes to determine whether or not an adverse event is considered to be related to the study drug, indicating "yes" or "no" accordingly. The following guidance should be taken into consideration (see also Table 2):

- Temporal relationship of event onset to the initiation of study drug
- Course of the event, considering especially the effects of dose reduction, discontinuation of study drug, or reintroduction of study drug (as applicable)
- Known association of the event with the study drug or with similar treatments
- Known association of the event with the disease under study
- Presence of risk factors in the patient 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

Table 2 Causal Attribution Guidance

Is the adverse event suspected to be caused by the study drug on the basis of facts, evidence, science-based rationales, and clinical judgment?	
YES	There is a plausible temporal relationship between the onset of the adverse event and administration of the study drug, and the adverse event cannot be readily explained by the patient's clinical state, intercurrent illness, or concomitant therapies; and/or the adverse event follows a known pattern of response to the study drug; and/or the adverse event abates or resolves upon discontinuation of the study drug or dose reduction and if applicable reappears upon re-challenge.
NO	An adverse event will be considered related, unless it fulfills the criteria specified below. Evidence exists that the adverse event has an etiology other than the study drug (e.g., preexisting medical condition, underlying disease, intercurrent illness, or concomitant medication); and/or the adverse event has no plausible temporal relationship to administration of the study drug (e.g., cancer diagnosed 2 days after first dose of study drug).

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

5.3.5 Procedures for Recording Adverse Events

When adverse event terms do not already exist in NCI CTCAE, investigators should use correct medical terminology and concepts when recording adverse events on the Adverse Event eCRF. Avoid colloquialisms and abbreviations.

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

5.3.5.1 Infusion-Related Reactions

Adverse events that occur during or within 24 hours after study drug administration should be captured as individual signs and symptoms on the Adverse Event eCRF rather than an overall diagnosis (e.g., record dyspnea and hypotension as separate events rather than a diagnosis of infusion-related reaction or anaphylactic reaction).

5.3.5.2 Diagnosis versus Signs and Symptoms

For adverse events other than infusion-related reactions (see Section 5.3.5.1), 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 adverse events based on signs and symptoms should be nullified and replaced by one adverse event

report based on the single diagnosis, with a starting date that corresponds to the starting date of the first symptom of the eventual diagnosis.

5.3.5.3 Adverse Events That Are Secondary to Other Events

In general, adverse events that are 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. A medically significant secondary adverse event that is separated in time from the initiating event should be recorded as an independent event 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 consequent fracture, all three events should be reported separately on the eCRF.
- If neutropenia is accompanied by an infection, both events should be reported separately on the eCRF.

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

5.3.5.4 Persistent or Recurrent Adverse Events

A persistent adverse event is one that extends continuously, without resolution, between patient evaluation timepoints. Such events should be recorded only once on the Adverse Event eCRF. The initial severity (grade) of the event will be recorded at the time the event is first reported. If a persistent adverse event becomes more severe, the most extreme severity (grade) should also be recorded on the Adverse Event eCRF. Details regarding any increases or decreases in severity will be captured on the Adverse Event Grade Changes eCRF. If the event becomes serious, it should be reported to the Sponsor immediately (i.e., no more than 24 hours after learning that the event became serious; see Section 5.4.2 for reporting instructions). The Adverse Event eCRF should be updated by changing the event from “non-serious” to “serious,” providing the date that the event became serious, and completing all data fields related to serious adverse events.

A recurrent adverse event is one that resolves between patient evaluation timepoints and subsequently recurs. Each recurrence of an adverse event should be recorded as a separate event on the Adverse Event eCRF.

5.3.5.5 Abnormal Laboratory Values

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

- Is 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
- Is clinically significant in the investigator's judgment

  Note: For oncology studies, certain abnormal test values may not qualify as adverse events.

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 levels 5 × ULN associated with cholestasis), only the diagnosis (i.e., cholestasis) 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 adverse event. 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 be recorded only once on the Adverse Event eCRF (see Section 5.3.5.4 for details on recording persistent adverse events).

5.3.5.6 Abnormal Vital Sign Values

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

- Is 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
- Is 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 be recorded only once on the Adverse Event eCRF (see Section 5.3.5.4 for details on recording persistent adverse events).

5.3.5.7 Abnormal Liver Function Tests

The finding of an elevated ALT or AST level ($>3\times$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 (as defined by Hy's law). Therefore, investigators must report as an adverse event the occurrence of either of the following:

- Treatment-emergent ALT or AST level $>3\times$ULN in combination with total bilirubin $>2\times$ULN
- Treatment-emergent ALT or AST level $>3\times$ULN 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 Section 5.3.5.2) and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event), either as a serious adverse event or an adverse event of special interest (see Section 5.4.2).

5.3.5.8 Deaths

For this protocol, mortality is an efficacy endpoint. Deaths that occur during the protocol-specified adverse event reporting period (see Section 5.3.1) that are attributed by the investigator solely to progression of cancer should be recorded only on the Study Discontinuation eCRF. All other on-study deaths, regardless of relationship to study drug, must be recorded on the Adverse Event eCRF and immediately reported to the Sponsor (see Section 5.4.2).

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. The term **"sudden death"** should be used only for the occurrence of an abrupt and unexpected death due to presumed cardiac causes in a patient with or without preexisting heart disease, within 1 hour after the onset of acute symptoms or in the case of an unwitnessed death within 24 hours after the patient was last seen alive

and stable. 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.

During survival follow-up, deaths attributed to progression of cancer should be recorded only on the Study Discontinuation eCRF.

5.3.5.9 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 adverse event 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").

5.3.5.10 Lack of Efficacy or Worsening of Cancer

Events that are clearly consistent with the expected pattern of disease evolution should not be recorded as adverse events. These data will be captured as efficacy assessment data only. In most cases, the expected pattern of progression will be based on *m*INRC, Revised Response Criteria for Malignant Lymphoma, RECIST v1.1*, or RANO criteria* as appropriate. In rare cases, the determination of clinical progression will be based on symptomatic deterioration. However, every effort should be made to document progression through use of objective criteria. If there is any uncertainty as to whether an event is a result of progressive disease, it should be reported as an adverse event.

5.3.5.11 Hospitalization or Prolonged Hospitalization

Any adverse event that results in hospitalization (i.e., in-patient admission to a hospital) or prolonged hospitalization should be documented and reported as a serious adverse event (per the definition of serious adverse event in Section 5.2.2), except as outlined below.

The following hospitalization scenarios are not considered to be adverse events:

- Hospitalization for respite care (temporary hospitalization of a dependent that provides a period of rest for the caregiver)

- 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 patient has not experienced an adverse event.

- Hospitalization due solely to progression of the underlying cancer

The following hospitalization scenarios are not considered to be serious adverse events but should be reported as adverse events instead:

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

5.3.5.12 Adverse Events Associated with an Overdose or Error in Drug Administration

An overdose is the accidental or intentional use of a drug in an amount higher than the dose being studied. An overdose or incorrect administration of study treatment is not itself an adverse event, but it may result in an adverse event. All adverse events associated with an overdose or incorrect administration of study drug should be recorded 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; see Section 5.4.2).

No safety data related to overdosing of atezolizumab are available.

5.4 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 drug:

- Serious adverse events (see Section 5.4.2 for further details)
- Adverse events of special interest, regardless of seriousness (see Sections 5.3.2 and 5.4.2 for further details)
- Pregnancies (see Section 5.4.3 for further details)

For these specific events, the investigator must report new significant follow-up information 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.

5.4.1 Emergency Medical Contacts

Medical Monitor Contact Information for United States and Canada

Medical Monitor: [redacted], M.D. (primary)
Mobile Telephone No.: [redacted]

Medical Monitor: [redacted], M.D. (secondary)
Mobile Telephone No.: [redacted]

Medical Monitor Contact Information for European Union and Israel

Medical Monitor: [redacted], M.D. (primary)
Telephone No.: [redacted]

To ensure the safety of study patients, an Emergency Medical Call Center Help Desk will access the Roche Medical Emergency List, escalate emergency medical calls, provide medical translation service (if necessary), connect the investigator with a Roche Medical Monitor, and track all calls. The Emergency Medical Call Center Help Desk will be available 24 hours per day, 7 days per week. Toll-free numbers for the Help Desk, as well as Medical Monitor contact information, will be distributed to all investigators.

5.4.2 Reporting Requirements for Serious Adverse Events and Adverse Events of Special Interest

5.4.2.1 Events That Occur prior to Study Drug Initiation

After informed consent has been obtained but prior to initiation of study drug, 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 Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the event), either by faxing or by scanning and e-mailing the form with the use of the fax number or e-mail address provided to investigators.

5.4.2.2 Events That Occur after Study Drug Initiation

After initiation of study drug, serious adverse events and adverse events of special interest*, regardless of relationship to study drug,* will be reported until 90 days after the last dose of study drug *or initiation of new anti-cancer therapy, whichever occurs first. All other adverse events, regardless of relationship to study drug, will be reported until*

30 days after the last dose of study drug or initiation of new anti-cancer therapy, whichever occurs first.

The investigator should also report any serious adverse events that are believed to be related to prior study drug treatment even if these occur after the abovementioned reporting periods. Investigators should record all case details that can be gathered immediately (i.e., within 24 hours after learning of the event) on the Adverse Event eCRF and submit the report via the electronic data capture (EDC) system. A report will be generated and sent to Roche Safety Risk Management by the EDC system.

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 Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the event), either by faxing or by scanning and emailing the form with the use of the fax number or email address provided to investigators. Once the EDC system is available, all information will need to be entered and submitted via the EDC system.

Instructions for reporting post-study adverse events are provided in Section 5.6.

5.4.3 Reporting Requirements for Pregnancies

5.4.3.1 Pregnancies in Patients

Patients of childbearing potential will be instructed to immediately inform the investigator if they become pregnant during the study or within *5 months* after the last dose of study drug. A Clinical Trial Pregnancy Reporting Form should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the pregnancy), either by faxing or scanning and emailing the form using the fax number or email address provided to investigators. Pregnancy should not be recorded on the Adverse Event eCRF. The investigator should discontinue study drug and counsel the patient, discussing the risks of the pregnancy and the possible effects on the fetus. Monitoring of the patient should continue until conclusion of the pregnancy. Any serious adverse events associated with the pregnancy (e.g., an event in the fetus, an event in the mother during or after the pregnancy, or a congenital anomaly or birth defect in the child) should be reported on the Adverse Event eCRF. In addition, the investigator will submit a Clinical Trial Pregnancy Reporting Form when updated information on the course and outcome of the pregnancy becomes available.

5.4.3.2 Pregnancies in Partners of Male Patients

Male patients will be instructed through the Informed Consent Form to immediately inform the investigator if their partner becomes pregnant during the study or after the last dose of study drug. A Clinical Trial Pregnancy Reporting Form should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the pregnancy), either by faxing or scanning and e-mailing the form using the fax number or e-mail address provided to the investigators. Attempts should be made to

collect and report details of the course and outcome of any pregnancy in the partner of a male patient exposed to study drug. The pregnant partner will need to sign an Authorization for Use and Disclosure of Pregnancy Health Information to allow for follow-up on her pregnancy. Once the authorization has been signed, the investigator will submit a Clinical Trial Pregnancy Reporting Form when updated information on the course and outcome of the pregnancy becomes available. An investigator who is contacted by the male patient 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 obstetrician.

5.4.3.3 Abortions

Any abortion should be classified as a serious adverse event (because the Sponsor considers abortions to be medically significant), 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 5.4.2).

5.4.3.4 Congenital Anomalies and Birth Defects

Any congenital anomaly or birth defect in a child born to a patient exposed to study drug or the partner of a male patient exposed to study drug 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; see Section 5.4.2).

5.5 FOLLOW-UP OF PATIENTS AFTER ADVERSE EVENTS

5.5.1 Investigator Follow-Up

The investigator should follow up each adverse event until the event has resolved to baseline grade or better, the event is assessed as stable by the investigator, the patient is lost to follow-up, or the patient withdraws consent. Every effort should be made to follow up all serious adverse events considered to be related to study drug or study-related procedures until a final outcome can be reported.

During the study period, resolution of adverse events (with dates) should be documented on the Adverse Event eCRF and in the patient's medical record to facilitate source data verification.

All pregnancies reported during the study should be followed up until pregnancy outcome.

5.5.2 Sponsor Follow-Up

For serious adverse events, adverse events of special interest, and pregnancies, the Sponsor or a designee may follow up by telephone, fax, e-mail, and/or a monitoring visit to obtain additional case 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 case.

5.6 POST-STUDY ADVERSE EVENTS

The Sponsor should be notified if the investigator becomes aware of any serious adverse event that occurs after the end of the adverse event reporting period (defined as 90 days after the last dose of study drug *or until initiation of new anti-cancer therapy for serious adverse events and adverse events of special interest and 30 days for all other adverse events*), if the event is believed to be related to prior study drug treatment.

These events should be reported through use of the Adverse Event eCRF. However, if the EDC system is not available, the investigator should report these events directly to the Sponsor or its designee, either by faxing or by scanning and emailing the Serious Adverse Event/Adverse Event of Special Interest Reporting Form using the fax number or email address provided to investigators.

5.7 EXPEDITED REPORTING TO HEALTH AUTHORITIES, INVESTIGATORS, INSTITUTIONAL REVIEW BOARDS, AND ETHICS COMMITTEES

The Sponsor will promptly evaluate all serious adverse events and adverse events of special interest against cumulative product experience to identify and expeditiously communicate possible new safety findings to investigators, IRBs, ECs, and applicable health authorities on the basis of applicable legislation.

To determine reporting requirements for single adverse event cases, the Sponsor will assess the expectedness of these events using the following reference document:

- Atezolizumab Investigator's Brochure

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.

6. STATISTICAL CONSIDERATIONS AND ANALYSIS PLAN

The study is an early-phase, multicenter, open-label, single-arm study designed to evaluate the safety, tolerability, pharmacokinetics, immunogenicity, and preliminary efficacy of atezolizumab in pediatric and young adult patients with solid tumors for which prior treatment has proven to be ineffective (i.e., relapsed or refractory disease) or intolerable and for whom there is no effective standard treatment available. The primary analysis will be conducted after the enrollment has been completed and all enrolled patients have been followed up for at least 6 months. A primary Clinical Study Report will be submitted to health authorities for information.

6.1 DETERMINATION OF SAMPLE SIZE

No formal hypothesis testing is planned in this study.

A minimum of 40 patients will be enrolled in this study across all tumor types. In addition, at least two tumor type cohorts must enroll a minimum of 10 patients. To make a preliminary assessment of the efficacy of the study drug, two response assessments are planned: an initial response assessment and an additional response assessment. Taking into account historical control ORRs for each pediatric tumor type, the minimum number of patients in the initial response assessment and the minimum number of responders needed for cohort expansion and advancement to the additional response assessment were calculated and are presented by tumor type in Table 3. Given the bony nature of osteosarcoma, responses in osteosarcomas do not always result in tumor shrinkage as the extracellular matrix produced by the tumor cells does not always disappear even when the cells die (Benjamin RS 2015). Thus, for osteosarcoma, CBR instead of objective response was considered in the response assessment. Patients with osteosarcoma are considered to have CBR if they have objective response or stable disease for at least 6 months, as determined by RECIST v1.1.

An initial response assessment will consider any available preclinical data in addition to any early efficacy or safety signals seen in the tumor type cohorts (enrollment may be closed while the response assessments are being conducted). The selection of expansion cohorts for additional response assessment, as well as the number of patients needed for the additional response assessment, will also take into account practical considerations (e.g., enrollment feasibility), biomarker analysis, safety profiles, and any other relevant information. The maximum number of patients per tumor type cohort will be 40. Similar consideration will be given to other rare pediatric tumor types that are enrolled in the study and not included in Table 3.

Table 3 Sample Size and Responder Requirements for Initial Response Assessment

Disease (Relapsed/Refractory)	Historical Control *Objective* Response Rate (%)	Initial Response Assessment	
		Minimum No. of Patients Enrolled	Minimum No. of Responders Needed for Tumor Type Cohort Expansion
Hepatoblastoma	10%	10	2
Hodgkin's disease	60 [a]	14	10
Wilms tumor	10	10	2
Neuroblastoma	18	10	3
Non-Hodgkin's lymphoma	40 [a]	12	6
High-grade osteosarcoma	20 [b]	10	3
Rhabdomyosarcoma	10	10	2
Non-rhabdomyosarcoma tissue sarcoma	10	10	2
Ewing sarcoma	10	10	2
Rhabdoid tumor	*5*	*6*	*1*
Atypical teratoid rhabdoid tumor	*5*	*6*	*1*

[a] Combination therapy.

[b] Clinical benefit response: objective response or stable disease for at least 6 months.

Overall, approximately *1*00 patients will be enrolled in the study.

6.2 SUMMARIES OF CONDUCT OF STUDY

Patient enrollment will be tabulated by study site. Patient disposition and reasons for discontinuations will be summarized for all enrolled patients. In addition, major protocol deviations will be summarized.

Patient demographics and baseline characteristics, including age, sex, race/ethnicity, medical history, and prior cancer treatment, will be summarized overall and by tumor type cohort. Descriptive statistics (mean, median, standard deviation, 25th percentile, 75th percentile, and range) will be presented for continuous variables, and proportions will be presented for categorical variables.

6.3 SAFETY ANALYSES

Safety analyses will be performed on the safety-evaluable population, which is defined as patients who receive any amount of study drug. Subgroup safety analyses by tumor type cohort will also be conducted as appropriate.

Study treatment exposure (such as treatment duration, total dose received, and number of cycles and dose modifications) will be summarized with descriptive statistics.

All adverse events, serious adverse events, adverse events leading to death, adverse events of special interest, and adverse events leading to study treatment discontinuation, occurring on or after the first dose of study treatment (i.e., treatment-emergent adverse events) will be summarized by mapped term, appropriate thesaurus level, and toxicity grade. For events of varying severity, the highest grade will be used in the summaries. Deaths and cause of death will be summarized.

Laboratory toxicities will be summarized by NCI CTCAE grade.

6.4 PHARMACOKINETIC ANALYSES

Individual and mean C_{max} of atezolizumab on Day 1 of Cycle 1 and Day 1 of Cycle 4 will be summarized. In addition, C_{min} of atezolizumab on Day 1 of Cycles 2, 3, 4, 8, 12, and 16 and every 8 cycles thereafter, at study drug discontinuation, and after washout will be summarized. Atezolizumab AUC for serum concentration-time profile in Cycle 1 will be estimated using a population PK model, as appropriate. Descriptive statistics will include mean, median, range, standard deviation, *coefficient of variation, geometric mean, and geometric mean coefficient of variation* as appropriate. After a minimum of 20 patients have completed Cycle 1, interim PK and safety analyses will be conducted. Relationships between PK and PD biomarkers may be explored using population PK and/or PD modeling approaches, as appropriate. Details regarding the modeling and simulations will be described in a separate Modeling and Simulations Data Analysis Plan prior to the modeling.

6.5 IMMUNOGENICITY ANALYSES

The immunogenicity analyses will include patients with at least one ATA assessment. The numbers and proportions of ATA-positive patients and ATA-negative patients during both the treatment and follow-up periods will be summarized. Patients are considered to be ATA positive if they are ATA negative *or missing* at baseline but develop an ATA response following study drug administration (treatment-induced ATA response), or if they are ATA positive at baseline and the titer of one or more post-baseline samples is at least 4-fold greater (i.e., $\geq$0.60 titer units) than the titer of the baseline sample (treatment-enhanced ATA response). Patients are considered to be ATA negative if they are ATA negative *or missing* at baseline and all post-baseline samples are negative, or if they are ATA positive at baseline but do not have any post-baseline samples with a titer that is at least 4-fold greater than the titer of the baseline sample (treatment unaffected).

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

6.6 EFFICACY ANALYSES

All efficacy analyses will be performed on the safety-evaluable population, which is defined as patients who receive any amount of study drug.

6.6.1 Primary Efficacy Endpoint

The primary endpoints for efficacy are ORR and PFS. For patients with measurable disease or patients with neuroblastoma who have evaluable disease at baseline, an objective response is defined as a complete or partial response on two consecutive occasions ≥4 weeks apart, as determined by the investigator using RECIST v1.1 for patients with solid tumors (see Appendix 6), *m*INRC for patients with neuroblastoma (see Appendix 3), Revised Response Criteria for Malignant Lymphoma for patients with Hodgkin's lymphoma or non-Hodgkin's lymphoma (see Appendix 4)*, and RANO criteria (see Appendix 11) for patients with ATRT.*

For patients with non-measurable but evaluable disease at baseline (except *patients with* neuroblastoma), an objective response is defined as a complete response on two consecutive occasions ≥ 4 weeks apart, as determined by the investigator using RECIST v1.1 for patients with solid tumors (see Appendix 6), Revised Response Criteria for Malignant Lymphoma for patients with Hodgkin's lymphoma or non-Hodgkin's lymphoma (see Appendix 4)*, and RANO criteria (see Appendix 11) for patients with ATRT.*

ORR is the percentage of patients who are determined to have an objective response. Patients with no post-baseline tumor assessments will be counted as non-responders. ORR and corresponding 95% exact CI using the Blyth–Still–Casella method will be summarized overall and by tumor type cohort (except for the osteosarcoma tumor type cohort).

CBR is defined as objective response or stable disease for at least 6 months, as determined by RECIST v1.1 for patients with osteosarcoma (see Appendix 6). CBRR is the percentage of patients who are determined to have a CBR. Patients with no post-baseline tumor assessments will be counted as not having CBR. CBRR and corresponding 95% CI will be summarized for the osteosarcoma tumor type cohort only.

PFS is defined as the time from initiation of study drug to the first documented occurrence of disease progression, as determined by the investigator using RECIST v1.1 for patients with solid tumors (see Appendix 6), *m*INRC for patients with neuroblastoma (see Appendix 3), Revised Response Criteria for Malignant Lymphoma for patients with Hodgkin's lymphoma or non-Hodgkin's lymphoma (see Appendix 4), *and RANO criteria (see Appendix 11) for patients with ATRT,* or death from any cause, whichever occurs first. Data for patients without progressive disease or death will be censored at the date of the last tumor assessment at which the patient was known to be progression-free or, if no tumor assessment is performed after the baseline visit, at the date of initiation of study drug. The Kaplan-Meier approach will be used to estimate median PFS. The 95% CI of the median PFS will be estimated using the Brookmeyer

and Crowley method. Subgroup analysis of PFS by tumor type cohort will be conducted as appropriate.

6.6.2 Secondary Efficacy Endpoints

The secondary efficacy endpoints include DOR and OS.

For patients who achieve an objective response, DOR is defined as the time from the first tumor assessment that supports the patient's objective response to the time of progressive disease, as determined by the investigator using *m*INRC for patients with neuroblastoma (see Appendix 3), Revised Response Criteria for Malignant Lymphoma for patients with Hodgkin's lymphoma or non-Hodgkin's lymphoma (see Appendix 4), *RANO criteria (see Appendix 11) for patients with ATRT,* and RECIST v1.1 for patients with other solid tumors (see Appendix 6), or death from any cause, whichever occurs first. The censoring method for DOR will be the same as that for PFS. The Kaplan-Meier approach will be used to estimate median DOR. The 95% CI of the median DOR will be estimated using the Brookmeyer and Crowley method. Subgroup analysis of DOR by tumor type cohort will be conducted as appropriate.

OS is defined as the time from initiation of study drug to death from any cause. Patients who are alive at the data cutoff date will be censored at the date the patient was last known to be alive. Patients with no post-baseline information will be censored at the date of initiation of study drug. The Kaplan-Meier approach will be used to estimate median OS. The 95% CI of the median OS will be estimated using the Brookmeyer and Crowley method. Subgroup analysis of OS by tumor type cohort will be conducted as appropriate.

In addition, analyses for ORR, PFS, and DOR using irRC for patients with neuroblastoma, Hodgkin's lymphoma or non-Hodgkin's lymphoma, and immune-modified RECIST v1.1 for patients with other solid tumors will be conducted with the same approaches as explained above.

6.7 EXPLORATORY ANALYSES

6.7.1 Biomarker Analyses

PD-L1 expression will be analyzed by IHC in tumor tissue samples collected at baseline.

Levels of potential PD biomarkers (including but not limited to cytokines, ctDNA concentration, and T-cell subpopulations) will be measured in plasma and whole blood collected at baseline; at Cycles 1, 2, 3, 8, 12, and 16 and every 8 cycles thereafter; and at the time of progressive disease. These samples will be analyzed for changes in biomarker levels in response to exposure to atezolizumab.

Plasma, whole blood, and archival tumor tissue samples will be collected at baseline and analyzed for non-inherited and inherited biomarkers (including but not limited to PD-L1, PD-1, CD4, CD8, FoxP3, cytokines [e.g., IL-2 and IFN-γ], ctDNA concentration, ctDNA

mutations [e.g., *KRAS*, *P53*, *PTEN*], and T-cell receptor sequencing) that may be correlated with severity of adverse effects, PK parameters, or response to atezolizumab.

Whole blood samples will be collected for TBNK cell enumeration. Changes in cell numbers during the study will be correlated with exposure to atezolizumab.

6.8 INTERIM ANALYSES

6.8.1 Planned Interim Analyses

Interim PK analyses will be conducted after the first 5 and 20 patients have completed Cycle 1, along with an ongoing evaluation of safety (see details in Section 6.3).
An additional interim PK analysis will be conducted after the first 5 patients who are $<$6 years old (if available) have completed Cycle 1.

Interim efficacy analyses will be conducted whenever a tumor type cohort has enrolled the number of patients required for initial or additional response assessment and patients have been followed up for approximately 6 months.

6.8.2 Optional Interim Analyses

Given the hypothesis-generating nature of this study, the Sponsor may choose to conduct additional interim efficacy and PK analyses. The decision to conduct an optional interim analysis and the timing of the analysis will be documented in the Sponsor's study master file prior to the conduct of the interim analysis. The interim analysis will be performed and interpreted by Sponsor study team personnel.

7. DATA COLLECTION AND MANAGEMENT

7.1 DATA QUALITY ASSURANCE

The Sponsor will be responsible for the data management of this study, including quality checking of the data. Data entered manually will be collected via EDC through use of eCRFs. Sites will be responsible for data entry into the EDC system. In the event of discrepant data, the Sponsor will request data clarification from the sites, which the sites will resolve electronically in the EDC system.

The Sponsor will produce an EDC Study Specification document that describes the quality checking to be performed on the data. Central laboratory data and IxRS data will be sent directly to the Sponsor with the use of the Sponsor's standard procedures to handle and process the electronic transfer of these data.

eCRFs and correction documentation will be maintained in the EDC system's audit trail. System backups for data stored by the Sponsor and records retention for the study data will be consistent with the Sponsor's standard procedures.

7.2 ELECTRONIC CASE REPORT FORMS

eCRFs are to be completed through use of a Sponsor-designated EDC system. Sites will receive training and have access to a manual for appropriate eCRF completion. eCRFs will be submitted electronically to the Sponsor and should be handled in accordance with instructions from the Sponsor.

All eCRFs should be completed by designated, trained site staff. eCRFs should be reviewed and electronically signed and dated by the investigator or a designee.

At the end of the study, the investigator will receive patient data for his or her site in a readable format on a compact disc that must be kept with the study records. Acknowledgment of receipt of the compact disc is required.

7.3 SOURCE DATA DOCUMENTATION

Study monitors will perform ongoing source data verification to confirm that critical protocol data (i.e., source data) entered into the eCRFs by authorized site personnel are accurate, complete, and verifiable from source documents.

Source documents (paper or electronic) are those in which patient 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, 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, patient files, and records kept at pharmacies, laboratories, and medico-technical departments involved in a clinical trial.

Before study initiation, the types of source documents that are to be generated will be clearly defined in the Trial Monitoring Plan. This includes any protocol data to be entered directly into the eCRFs (i.e., no prior written or electronic record of the data) and considered source data.

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 in Section 7.5.

To facilitate source data verification, the investigators and institutions must provide the Sponsor or its representative direct access to applicable source documents and reports for study-related monitoring, Sponsor audits, and IRB/EC review. The study site must also allow inspection by applicable health authorities.

7.4 USE OF COMPUTERIZED SYSTEMS

When clinical observations are entered directly into a study 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.

7.5 RETENTION OF RECORDS

Records and documents pertaining to the conduct of this study and the distribution of IMP, including eCRFs, electronic patient-reported outcome data (if applicable), Informed Consent Forms, laboratory test results, and medication inventory records, must be retained by the Principal Investigator for at least 15 years after 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 of time, the documents may be destroyed, subject to local regulations.

No records may be disposed of without the written approval of the Sponsor. Written notification should be provided to the Sponsor prior to transferring any records to another party or moving them to another location.

8. ETHICAL CONSIDERATIONS

8.1 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 European Union (E.U.) or European Economic Area will comply with the E.U. Clinical Trial Directive (2001/20/EC).

8.2 INFORMED CONSENT

The Sponsor's sample Informed Consent Form (and ancillary sample Informed Consent Forms such as a Child's Informed Assent Form 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. The Sponsor or its designee must review and approve any proposed deviations from the Sponsor's sample Informed Consent Forms 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.

If applicable, the Informed Consent Form will contain separate sections for any optional procedures. The investigator or authorized designee will explain to each patient the objectives, methods, and potential risks associated with each optional procedure. Patients will be told that they are free to refuse to participate and may withdraw their consent at any time for any reason. A separate, specific signature will be required to document a patient's agreement to participate in optional procedures. Patients who decline to participate will not provide a separate signature.

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

The Consent Forms should be revised whenever there are changes to study procedures or when new information becomes available that may affect the willingness of the patient to participate. The final revised IRB/EC-approved Consent Forms must be provided to the Sponsor for health authority submission purposes.

Patients must be re-consented to the most current version of the Consent Forms (or to a significant new information/findings addendum in accordance with applicable laws and IRB/EC policy) during their participation in the study. Young adult patients must re-consent to study when they reach age of adulthood in their home country. For any updated or revised Consent Forms, the case history or clinical records for each patient shall document the informed consent process and that written informed consent was obtained using the updated/revised Consent Forms for continued participation in the study.

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

For sites in the United States, each Consent Form may also include patient authorization to allow use and disclosure of personal health information in compliance with the U.S. Health Insurance Portability and Accountability Act of 1996 (HIPAA). If the site utilizes a separate Authorization Form for patient 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.

8.3 INSTITUTIONAL REVIEW BOARD OR ETHICS COMMITTEE

This protocol, the Informed Consent Forms, any information to be given to the patient, 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 patient 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 (see Section 9.6).

In addition to the requirements for reporting all adverse events to the Sponsor, investigators must comply with requirements for reporting serious adverse events to the local health authority and IRB/EC. 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.

8.4 CONFIDENTIALITY

The Sponsor maintains confidentiality standards by coding each patient enrolled in the study through assignment of a unique patient identification number. This means that patient names are not included in data sets that are transmitted to any Sponsor location.

Patient medical information obtained by this study is confidential and may be disclosed to third parties only as permitted by the Informed Consent Form (or separate authorization for use and disclosure of personal health information) signed by the patient, unless permitted or required by law.

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

Data generated by this study must be available for inspection upon request by representatives of the U.S. FDA and other national and local health authorities; Sponsor monitors, representatives, and collaborators; and the IRB/EC for each study site, as appropriate.

8.5 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 1 year after completion of the study (i.e., LPLV).

9. STUDY DOCUMENTATION, MONITORING, AND ADMINISTRATION

9.1 STUDY DOCUMENTATION

The investigator must maintain adequate and accurate records to enable the conduct of the study to be fully documented, including but not limited to the protocol, protocol amendments, Informed Consent Forms, and documentation of IRB/EC and governmental approval. In addition, at the end of the study, the investigator will receive the patient data, including an audit trail containing a complete record of all changes to data.

9.2 PROTOCOL DEVIATIONS

The investigator should document and explain any protocol deviations. The investigator should promptly report any deviations that might have an impact on patient safety and data integrity to the Sponsor and to the IRB/EC in accordance with established IRB/EC policies and procedures.

9.3 SITE INSPECTIONS

Site visits will be conducted by the Sponsor or an authorized representative for inspection of study data, patients' 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.

9.4 ADMINISTRATIVE STRUCTURE

This study will be sponsored by Roche and managed with the support of a contract research organization, which will provide clinical monitoring, sample management, and project management support. Approximately 100 patients are expected be enrolled in this study, at approximately 50 investigative sites in Europe and North America. Patients may be enrolled through the study groups Innovative Therapies for Children with Cancer and Pediatric Oncology Experimental Therapeutics Investigators' Consortium. Patients will be enrolled with the use of an IxRS.

EDC will be used for this study. Central facilities will be used for certain study assessments (e.g., specified biomarker tests, PK analyses). Accredited local laboratories will be used for routine monitoring; local laboratory ranges will be obtained.

An iDMC will monitor patient safety throughout the study.

9.5 PUBLICATION OF DATA AND PROTECTION OF TRADE SECRETS

Regardless of the outcome of a study, the Sponsor is dedicated to openly providing information on the study to health care professionals and to the public, both at scientific congresses and in peer-reviewed journals. The Sponsor will comply with all requirements for publication of study results.

The results of this study may be published or presented at scientific congresses. For all clinical trials in patients involving an IMP for which a marketing authorization application has been filed or approved in any country, the Sponsor aims to submit a journal manuscript reporting primary clinical trial results within 6 months after the availability of the respective Clinical Study Report. In addition, for all clinical trials in patients involving an IMP for which a marketing authorization application has been filed or approved in any country, the Sponsor aims to publish results from analyses of additional endpoints and exploratory data that are clinically meaningful and statistically sound.

The investigator must agree to submit all manuscripts or abstracts to the Sponsor prior to submission for publication or presentation. 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.

In accordance with standard editorial and ethical practice, the Sponsor will generally support publication of multicenter studies only in their entirety and not as individual center data. In this case, a coordinating investigator will be designated by mutual agreement.

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

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.

9.6 PROTOCOL AMENDMENTS

Any protocol amendments will be prepared by the Sponsor. 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 patients or changes that involve logistical or administrative aspects only (e.g., change in Medical Monitor or contact information).

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Appendix 1
Schedule of Assessments

	Screening Period [a]	Treatment Period																Follow-Up Period [b]		
		C1			C2			C3	C4	C5	C6	C7	C8	C9	C10	C11	C12+			
						ATRT Only														
Day	–28 to –1	1	8	15	1	*8*	*15*	1	1	1	1	1	1	1	1	1	1	Study Drug Discont. [c]	Day 90 Follow-Up [c]	Long-Term Follow-Up [d]
Informed consent [a]	x																			
Archival or fresh tumor tissue [e]	x																			
Medical history and demographics [f]	x																			
Echocardiogram or MUGA	x																			
Serum or urine pregnancy test [g]	x				x			x	x	x	x	x	x	x	x	x	x			
Vital signs [h]	x	x	x	x	x	*x*	*x*	x	x	x	x	x	x	x	x	x	x	x	x	
Physical examination [i]	x	x	x	x	x	*x*	*x*	x	x	x	x	x	x	x	x	x	x	x	x	
Weight [j]	x	x			x			x	x	x	x	x	x	x	x	x	x	x	x	x
Height, head circumference, Tanner staging [k]	x								x				x				x	x	x	x
Lansky or Karnofsky Performance Status [l]	x	x	x	x	x	*x*	*x*	x	x	x	x	x	x	x	x	x	x	x	x	
Hematology [m, n]	x	x	x	x	x			x	x	x	x	x	x		x		x	x	x	
Chemistry [n, o]	x	x	x	x	x			x	x	x	x	x	x		x		x	x	x	
Urinalysis [n, p]	x	x			x			x	x		x		x		x		x	x	x	

Appendix 1
Schedule of Assessments (cont.)

	Screening Period [a]	Treatment Period																Follow-Up Period [b]		
		C1			C2			C3	C4	C5	C6	C7	C8	C9	C10	C11	C12+			
						ATRT Only												Study Drug Discont. [c]	Day 90 Follow-up [c]	Long-Term Follow-Up [d]
Day	–28 to –1	1	8	15	1	*8*	*15*	1	1	1	1	1	1	1	1	1	1			
Coagulation (INR, aPTT, PT)	x																			
Amylase/lipase [q]	x				x				x		x		x		x		x	x	x	
Thyroid function testing [r]	x				x				x		x		x		x		x	x	x	
Virology testing [s]	x																			
PK/ATA blood samples [t]		x	x		x			x	x				x				x	x	x [u]	
Whole blood for TBNK		x						x										x	x [u]	
Whole blood for biomarkers [t]		x			x			x					x				x	x	x [u]	
Plasma for biomarkers [t]		x			x			x					x				x	x	x [u]	
Tumor assessments [v, w]	x				x				x		x		x				x	x [w]	x [w]	x [w]
Atezolizumab administration [x]		x			x			x	x	x	x	x	x	x	x	x	x			
Concomitant medications [y]	x	x	x	x	x	*x*	*x*	x	x	x	x	x	x	x	x	x	x	x	x	
Adverse events	x	x	x	x	x	*x*	*x*	x	x	x	x	x	x	x	x	x	x	x	x	

Appendix 1
Schedule of Assessments (cont.)

	Screening Period [a]	Treatment Period																Follow-Up Period [b]		
		C1			C2			C3	C4	C5	C6	C7	C8	C9	C10	C11	C12+			
						ATRT Only														
Day	–28 to –1	1	8	15	1	*8*	*15*	1	1	1	1	1	1	1	1	1	1	Study Drug Discont. [c]	Day 90 Follow-up [c]	Long-Term Follow-Up [d]
Tetanus toxoid antibody titer [z]		x																x		
Auto-antibody testing [aa]		x																		
Survival assessment																			x	x
Optional RCR tumor tissue sample and corresponding blood sample [bb, cc, dd]		x			x													x		

ATA = anti-therapeutic antibody; C = cycle; CT = computed tomography; discont. = discontinuation; eCRF = electronic Case Report Form; FDG-PET = fluorodeoxyglucose-positron emission tomography; HIV = human immunodeficiency virus; MIBG = metaiodobenzoguanine; MUGA = multigated acquisition scan; MRI = magnetic resonance imaging; PK = pharmacokinetic; RCR = Roche Clinical Repository; TBNK = T, B, and natural killer (cells).

Notes: All assessments should be performed within 3 days of the scheduled date (excluding Day 1 of Cycle 1), unless otherwise specified. On treatment days, all assessments should be performed prior to dosing, unless otherwise specified. Cycles are 3 weeks in length. Atezolizumab infusion may be delayed up to *5* days to accommodate holidays, weekends, and other patient obligations.

Assessments shaded in gray should be performed as scheduled, but the associated data do not need to be recorded on the eCRF (except in the case of *ATRT neurologic examinations,* an adverse event, or a pregnancy).

[a] Results of standard-of-care tests or examinations performed prior to obtaining informed consent and within 28 days prior to Day 1 of Cycle 1 may be used; such tests do not need to be repeated for screening. Informed consent must be documented before any study-specific assessments are performed.

[b] *In situations where it is either unsafe or not in the best interest of the patient to complete follow-up assessments after study drug discontinuation, survival data only may be submitted during the follow-up period with approval of the Medical Monitor.*

Appendix 1
Schedule of Assessments (cont.)

[c] Patients who discontinue study drug should return to the clinic for study drug discontinuation visits within 28 days of the last dose of atezolizumab. This may be done at the clinical visit where clinical or radiographic progression is first noted). A follow-up visit should also be done 90 (± 10) days after the last dose of study drug. If treatment with another anti-cancer treatment is scheduled to begin within 90 days after the last dose of study drug, this visit should be performed before the patient starts the other treatment, if possible. *If the day 90 visit is done after initiation of another anti-cancer treatment, only PK and/or ATA blood samples and those laboratory tests needed to monitor for the resolution of adverse events need to be drawn.*

[d] Long-term follow-up information will be collected every 3 months during the first two years (Years 1 and 2), every 6 months during Year 3, and yearly until study termination by Sponsor, death, loss to follow-up, or withdrawal of consent, whichever occurs first.

[e] A tumor specimen and associated pathology report must be confirmed to be available prior to patient participation in any study-specific screening procedures and must be shipped within 30 days of first dosing. See Section 4.5.6 for details on sample collection.

[f] Medical history includes clinically significant diseases, surgeries, cancer history (including prior cancer therapies, current cancer stage, and procedures), menstrual history, fertility history, and puberty history. Demographic data will include age, sex, and self-reported race/ethnicity as permitted by local regulatory authorities.

[g] All females of childbearing potential must undergo a serum pregnancy test within one week of the initial dose. Urine or serum pregnancy tests must be performed prior to the start of all subsequent cycles.

[h] Includes respiratory rate, pulse rate, systolic and diastolic blood pressures, oxygen saturation by pulse oximetry, and temperature. For the first infusion of atezolizumab, vital signs should be determined within 60 minutes before, every 15 (±5) minutes during, and 30 (±10) minutes after the infusion. For subsequent infusions, vital signs do not need to be obtained during the infusion if the prior infusion was tolerated without symptoms. Record abnormalities observed at baseline on the General Medical History and Baseline Conditions eCRF. At subsequent visits, record abnormalities on the Adverse Event eCRF.

[i] Includes evaluation of the head, eyes, ears, nose, and throat, and the cardiovascular, dermatological, musculoskeletal, respiratory, gastrointestinal, genitourinary, and neurological systems. *For patients with ATRT, a complete neurologic examination will be conducted at the time specified in the schedule of assessments, which includes two additional visits in Cycle 2, on Day 8 and Day 15.* Record abnormalities observed at baseline on the General Medical History and Baseline Conditions eCRF. At subsequent visits, changes from baseline abnormalities should be recorded in patient notes. Record new or worsened clinically significant abnormalities on the Adverse Event eCRF.

[j] *Weight should be measured within 7 days of Day 1 for each cycle.*

[k] During the treatment period, height, head circumference (until the age of 3), and Tanner stage should be measured every four cycles (approximately every 3 months). During the follow-up period, height, head circumference (until the age of 3), and Tanner stage should be measured every 3 months for the first 2 years, every 6 months during the third year, and yearly thereafter. Tanner staging and height should be performed until the patient has reached Tanner Stage V.

Appendix 1
Schedule of Assessments (cont.)

[l] Perform Lansky Performance Status for patients < 16 years old and Karnofsky Performance Status for patients ≥ 16 years old.

[m] Hematology includes WBC count, hemoglobin, platelet count, 3-cell differential count (absolute neutrophils, monocytes, and lymphocytes). Starting with Cycle 8, these assessments should take place every other cycle (e.g., Cycles 8, 10, 12, etc.).

[n] Laboratory tests should be performed ≤96 hours prior to Day 1 of each scheduled cycle. Screening labs may be used for Cycle 1, Day 1 hematology, chemistry, and urinalysis if drawn within two weeks of Cycle 1 Day 1.

[o] Chemistry includes sodium, potassium, magnesium, chloride, bicarbonate, glucose, BUN or urea, creatinine, total protein, albumin, phosphorus, calcium, total bilirubin (if abnormal, fractionate sample for direct and indirect), alkaline phosphatase, ALT, AST, LDH. Starting with Cycle 8, these assessments should take place every other cycle (e.g., Cycles 8, 10, 12, etc.).

[p] Urinalysis includes specific gravity, glucose, protein, and blood in patients > 3 years of age. Starting with Cycle 4, urinalyses should take place every other cycle (e.g., Cycles 4, 6, 8, etc.). Creatinine clearance should be done as clinically indicated. If radioisotope glomerular filtration rate is routinely performed at the institution to measure patients' creatinine clearance, this test can be used to assess renal function at screening, per the eligibility criteria. Otherwise, serum creatinine is sufficient to document renal function at screening.

[q] Amylase and lipase testing should be done at screening and then every two cycles (e.g., Cycles 2, 4, 6, etc.).

[r] Thyroid function testing includes thyroid-stimulating hormone, free T3, and free T4. Thyroid function testing should take place every two cycles (e.g., Cycles 2, 4, 6, etc.).

[s] Includes hepatitis B surface antigen, hepatitis B surface antibody, total hepatitis B core antibody, hepatitis C antibody, HIV-1, and HIV-2 antibody. If patient is positive for hepatitis B core antibody at screening, a test for hepatitis B virus DNA should be performed prior to Day 1 of Cycle 1. If patient is positive for hepatitis C antibody at screening, a test for hepatitis C virus RNA should be performed prior to Day 1 of Cycle 1.

[t] Blood samples will be obtained to characterize biomarkers, atezolizumab pharmacokinetics, and ATAs according to the schedule in Appendix 2.

[u] Collect sample between 90 to 150 days after last dose of study drug.

[v] The same *imaging technique(s) and* procedure*(s)* (CT, MRI, FDG-PET*, and/or MIBG* scan) used to assess disease sites at screening should be used throughout the study (e.g., the same contrast protocol for CT scans). To the extent that is feasible, assessments should be performed by the same evaluator to ensure internal consistency across visits. See Section 4.5.5 for detailed information on tumor and response evaluations.

[w] Tumor assessments must be performed during the last week of Cycles 2, 4, 6, and 8 and every 4th cycle thereafter (i.e., within 7 days prior to Day 1 of the next cycle). At the investigator's discretion, tumor assessments may be repeated at any time if progressive disease is suspected. An objective response should be confirmed by repeat assessments ≥4 weeks after initial documentation. Patients who discontinue study drug without progressive disease should continue follow up assessments, including tumor assessments, using the long-term follow up schedule (e.g., every three months for the first 2 years, every 6 months during year 3, etc.) until radiographic documentation of progressive disease, they start another treatment or consent is withdrawn. Patients who continue to receive study drug beyond radiographic progressive disease should continue follow-up assessments until they stop taking study drug.

Appendix 1
Schedule of Assessments (cont.)

[x] Atezolizumab will be administered by IV infusion every 3 weeks. Patients will be weighed at the beginning of each cycle, and the dose will be adjusted as needed.

[y] Includes any medication (e.g., prescription drugs, over-the-counter drugs, herbal or homeopathic remedies, nutritional supplements) used by a patient from 7 days prior to screening to the study drug discontinuation visit.

[z] Only required in children who have been vaccinated.

[aa] Samples should be obtained prior to infusion of the first dose and will be held for possible testing in patients who develop immune-related or inflammatory adverse events during the study. Auto-antibody testing to include at least anti-nuclear antibody, anti–double-stranded DNA, circulating anti-neutrophil cytoplasmic antibody, and perinuclear anti-neutrophil cytoplasmic antibody.

[bb] Patients who are willing to participate must provide separate informed consent for collection of tumor tissue samples for the RCR. Sample collection is not applicable if the site has not been granted approval for RCR sampling.

[cc] Optional RCR tumor tissue samples will be collected prior to drug initiation, 4 weeks after the first dose of drug, and at the time of progressive disease or treatment discontinuation.

[dd] Mandatory blood sample will be collected prior to drug initiation and is required as an experimental control ONLY if patients consent to optional tumor tissue samples.

Appendix 2
Schedule of Pharmacokinetic, Pharmacodynamic, and Immunogenicity Assessments

Visit	Timepoint	Sample Type
Cycle 1, Day 1	Prior to the infusion	Serum for atezolizumab PK and ATA [a] *EDTA* plasma and whole blood for PD
	30 (±10) min after the end of the infusion	Serum for atezolizumab PK
Cycle 1, Day 8	*Any time during visit*	Serum for atezolizumab PK
Cycle 2, Day 1	Prior to the infusion [b]	Serum for atezolizumab PK and ATA [a] Plasma and whole blood for PD
Cycle 3, Day 1	Prior to the infusion [b]	Serum for atezolizumab PK and ATA [a] Plasma and whole blood for PD
Cycle 4, Day 1	Prior to the infusion [b]	Serum for atezolizumab PK and ATA [a]
	30 (± 10) min after the end of the infusion	Serum for atezolizumab PK
Cycle 8, Day 1	Prior to the infusion [b]	Serum for atezolizumab PK and ATA [a] Plasma and whole blood for PD
Cycle 12, Day 1	Prior to the infusion [b]	Serum for atezolizumab PK and ATA [a] Plasma and whole blood for PD
Day 1 of Cycle 16 and every 8 cycles thereafter	Prior to the infusion [b]	Serum for atezolizumab PK and ATA [a] Plasma and whole blood for PD
Study drug discontinuation visit	*Any time during visit*	Serum for atezolizumab PK and ATA [a] Plasma and whole blood for PD
At least 90 days (but no more than 150 days) after last dose of study drug	*Any time during visit*	Serum for atezolizumab PK and ATA [a] Plasma and whole blood for PD

ATA = anti-therapeutic antibody; PD = pharmacodynamic; PK = pharmacokinetic.

[a] Serum samples will be split into 2 × 500 µL serum aliquots, one for PK and one for ATA.

[b] Blood draws can occur up to 2 days prior to infusion.

Appendix 3
Modified International Neuroblastoma Response Criteria

Below response assessment is modified from the original INRC publication in 1993.

DEFINITION OF MEASURABLE (EVALUABLE) DISEASE ON CT/MRI SCAN

The presence of at least one lesion that can be accurately measured in at least one dimension with the longest diameter at least 20 mm. With a spiral CT scan, lesions must be at least 10 mm. The investigator will identify up to 10 measurable target lesions to be followed for response. Note that bone lesions will be considered as non-target lesions for evaluation of CT/MRI response since they will be evaluated with MIBG scans.

Malignant Lymph Nodes. *To be considered pathologically enlarged and measurable, a lymph node must be ≥15 mm in the short axis when assessed by CT scan (CT scan slice thickness recommended to be ≤5 mm). At baseline and in follow-up, only the short axis will be measured and followed.* Serial measurements of lesions are to be done with CT or MRI. The same method of assessment used to characterize each identified and reported lesion at baseline should be used during follow-up.

RESPONSE CRITERIA FOR MEASURABLE DISEASE ON CT/MRI SCAN

The sum of the longest diameter (LD) for all target lesions will be calculated and reported as the disease measurement. The response of the CT/MRI lesions will be defined as outlined below:

- Complete response (CR): Disappearance of all target and non-target CT/MRI lesions
- Very good partial response (VGPR): Greater than 90% decrease of the disease measurement for CT/MRI lesions, taking as reference the disease measurement done to confirm measurable disease at study entry; non-target CT/MRI lesions stable to smaller in size
- Partial response (PR): At least a 30% decrease in the disease measurement for CT/MRI lesions, taking as reference the disease measurement done to confirm measurable disease at study entry; non-target CT/MRI lesions stable to smaller in size
- Progressive disease (PD): At least a 20% increase in the disease measurement, taking as reference the smallest disease measurement since the treatment started, or a new site of tumor; non-target CT/MRI lesions stable, smaller, or increased in size
- Stable disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD taking as reference the smallest disease measurement since the treatment started; no new sites of disease

Appendix 3
International Neuroblastoma Response Criteria (cont.)

RESPONSE CRITERIA FOR MORPHOLOGIC BONE MARROW DISEASE

Only those patients with morphologic evidence of neuroblastoma by routine H and E staining (NSE staining only is not evaluable) will be evaluable to assess bone marrow response.

- CR: No tumor cells detectable by routine morphology on two subsequent bilateral bone marrow aspirates and biopsies done at least three weeks apart after study entry.
- PD: Tumor seen on morphology on two consecutive bone marrows done at least 3 weeks apart in patients who had no tumor in bone marrow at study entry

  Patient may be declared to have PD in bone marrow after only one diagnostic bone marrow at the discretion of the treating physician

  Patients who enter study with bone marrow tumor by morphology will be considered to have PD if there is a minimum of 25% tumor in the marrow by morphology and a doubling in the amount of tumor in the marrow compared with the level present at study entry. For example, a patient entering with 5% tumor in marrow by morphology must increase to $>$25% tumor to have PD; a patient entering with 30% tumor must increase to $>$60% tumor.
- SD: Persistence of an amount of tumor in the bone marrow by morphology that does not meet criteria for either CR or PD

  Patients who clear morphologic tumor but have immunocytologic tumor will be called SD.

RESPONSE CRITERIA FOR MIBG-POSITIVE LESIONS

All patients with known MIBG-avid lesions will be evaluable for MIBG response following the first course of therapy. The following criteria will be used to report MIBG response:

- CR: Complete resolution of all MIBG-positive lesions
- PR: Resolution of at least one MIBG-positive lesion, with persistence of other MIBG positive lesions
- SD: No change in MIBG scan in number of positive lesions (includes patients who have same number of positive lesions but decreased intensity)
- PD: Development of new MIBG-positive lesions

Appendix 3
International Neuroblastoma Response Criteria (cont.)

DEFINITION OF OVERALL RESPONSE FOR EACH PATIENT WITH NEUROBLASTOMA

The International Neuroblastoma Response Criteria were developed to define responses in patients being treated with frontline therapy from diagnosis.[1] These criteria were utilized as a basis for the following response criteria, which integrate response at all sites defined as measurable in this study, including CT/MRI lesions that meet RECIST criteria, MIBG-positive lesions, and bone marrow disease. These criteria will be used to define the overall response for each patient.

- CR: Disappearance of all target lesions; no evidence of tumor at any site (chest, abdomen, liver, bone, bone marrow, nodes, etc.); homovanillic acid (HVA) and vanillylmandelic acid (VMA) normal
- VGPR: Greater than 90% decrease of the disease measurement for CT/MRI target lesions, taking as reference the disease measurement done to confirm measurable disease in target lesions at study entry; all preexisting bone lesions with CR by MIBG; MIBG scan can be ±or CR in soft tissue lesions corresponding to lesions on CT/MRI; CR in bone marrow; no new sites of tumor; HVA/VMA normal
- PR: At least a 30% decrease in the disease measurement for CT/MRI target lesions, taking as reference the disease measurement done to confirm measurable disease in target lesions at study entry; bone marrow with CR; MIBG with either PR or CR in bone lesions; MIBG may be SD or CR in soft tissue lesions corresponding to lesions on CT/MRI; HVA/VMA may still be elevated.
- PD: Any one of the following:

  At least a 20% increase in the disease measurement for CT/MRI target lesions, taking as reference the smallest disease measurement recorded since the start of treatment

  Appearance of one or more new lesions or new sites of tumor

  PD as defined above for either bone marrow or MIBG lesions
- SD: Stable disease by either CT/MRI lesion, bone marrow, or MIBG criteria; no new lesions; no new sites of disease

The overall response as assessed at any particular timepoint based on the various disease sites is summarized in the table below.

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[1] Brodeur GM, Pritchard J, Berthold F, et al. Revisions of the international criteria for neuroblastoma diagnosis, staging, and response to treatment. J Clin Oncol 1993;11:1466–77.

Appendix 3
International Neuroblastoma Response Criteria (cont.)

Table 1 Overall Response at Any Timepoint

CT/MRI Lesions	MIBG Lesions	Bone Marrow	Catechols	Overall Response
PD	Any	Any	Any	PD
Any	PD	Any	Any	PD
Any	Any	PD	Any	PD
CR	CR	CR	Normal	CR
VGPR	CR in bone lesions ; May have SD/CR in soft tissue sites corresponding to lesions on CT/MRI	CR	Normal	VGPR
PR	PR/CR in bone lesions; May have SD/CR in soft tissue sites corresponding to lesions on CT/MRI	CR	Any	PR
SD	SD	SD	Any	SD
SD/PR/VGPR/CR	SD	SD/CR	Any	SD
SD/PR/VGPR/CR	SD/PR/CR	SD	Any	SD

CR = complete response; CT = computed tomography; MRI = magnetic resonance imaging; PD = progressive disease; PR = partial response; SD = stable disease; VGPR = very good partial response.

Appendix 4
Revised Response Criteria for Malignant Lymphoma

SELECTION OF TARGET LESIONS

Up to six of the largest dominant nodes or tumor masses selected according to all of the following:

- Clearly measurable in at least two perpendicular dimensions

  All nodal lesions must measure:

  > 1.5 cm in greatest transverse diameter (GTD) regardless of short axis measurement, or

  > 1.0 cm in short axis regardless of the GTD measurement

  All extranodal lesions must measure ≥ 10 mm in the GTD and twice the reconstruction interval of the scan.

  Extranodal lesions within the liver or spleen must be at least 1.0 cm in two perpendicular dimensions
- If possible, they should be from disparate regions of the body
- Should include mediastinal and retroperitoneal areas of disease whenever these sites are involved

Measurable extranodal disease should be assessed in a manner similar to that used for nodal disease.

SELECTION OF NON-TARGET LESIONS

Non-target lesions will be qualitatively assessed at each subsequent timepoint. All of the sites of disease present at baseline and not classified as target lesions will be classified as non-target lesions, including any measurable lesions that were not chosen as target lesions. Examples of non-target lesions include:

- All bone lesions, irrespective of the modality used to assess them
- Lymphangitis of the skin or lung
- Cystic lesions
- Splenomegaly and hepatomegaly
- Irradiated lesions
- Measurable lesions beyond the maximum number of six
- Groups of lesions that are small and numerous
- Pleural/pericardial effusions and/or ascites

Appendix 4
Revised Response Criteria for Malignant Lymphoma (cont.)

For this study, a significant increase in existing pleural effusions, ascites, or other fluid collections will be considered sufficient evidence of progression and will not require cytological proof of malignancy. Effusions, ascites, or other fluid collections will be followed as non-target lesions.

- **Existing effusions/ascites:** Effusions, ascites, or other fluid collections will be followed as non-target lesions. At each timepoint, radiologists will check for the presence or absence of effusions/ascites. If there is a significant volume increase in the absence of a benign etiology, progression can be assessed.
- **New effusions/ascites:** Significant new effusions, ascites, or other fluid collections, which are radiographically suggestive of malignancy, should be recorded as new lesions.

REPORTING CONVENTIONS

UNABLE TO EVALUATE (UE) LESION CATEGORY

This category is reserved for target and non-target lesions that are deemed unevaluable because 1) subsequent (post-baseline) examinations had not been performed, 2) lesions could not be evaluated because of poor radiographic technique or poorly defined margins, or 3) lesions identified at baseline were not at a subsequent timepoint.

Examples of UE lesions are a lung lesion in the hilum obstructing the bronchus and causing atelectasis of the lobe or a hypodense liver lesion that becomes surrounded by fatty infiltration. In both examples the boundaries of the lesion can be difficult to distinguish. Every effort should be made to assign measurements to lesions that develop less distinct margins because they become much smaller. Another example is the instance when lesions identified at baseline were not imaged at a subsequent timepoint. Lesions that cannot be measured or evaluated will be classified for that timepoint as UE.

If a target lesion is classified as UE post-baseline, the sum of the product of the diameters (SPD)/area (whichever applies) of the target lesions cannot accurately be determined for that timepoint, a response of complete response (CR), partial remission (PR), or stable disease (SD) cannot be assigned for that timepoint, and the response assessment will be UE unless unequivocal progression is determined on the basis of non-target or new lesions or the evaluable target lesions.

Progressive disease (PD) can be determined without evaluation of all sites of disease based on the greatest transverse diameter (GTD), area or SPD for target lesions, evaluation of unequivocal progression in non-target lesions, or observation of a new lesion within the available radiographic or clinical assessments.

Appendix 4
Revised Response Criteria for Malignant Lymphoma (cont.)

TOO SMALL TO MEASURE (TSTM) LESION CATEGORY

Any target lesion findings identified on baseline images, which at a subsequent timepoint decreases in size to < 5 mm in any dimension, should be categorized as TSTM. The lesion, node, or mass should be assigned measurements of 5×5 mm (for the GTD and the short axis) on the source document for the purposes of calculating the area. If that lesion increases in size to ≥ 5 mm in any dimension afterwards, its true size (GTD and short axis) should be recorded. The purpose of the assigned value for the measurement is the acknowledgment that small findings are not accurately measured.

Appendix 4
Revised Response Criteria for Malignant Lymphoma (cont.)

Timepoint Response

Target Lesions	Non-Target Lesions	New Lesions [a]	Timepoint Response
CR	CR	No	CR
CR	SD	No	PR
CR	UE	No	UE
PR	UE	No	UE
PR	CR	No	PR
PR	SD	No	PR
SD	UE	No	UE
SD	CR	No	SD
SD	SD	No	SD
PD	Any	Yes/No	PD
Any	PD	Yes/No	PD
Any	Any	Yes	PD
UE	Non-PD	No	UE
UE	UE	No	UE
CR	NA [c]	No	CR
PR	NA [c]	No	PR
SD	NA [c]	No	SD
NA [b]	SD	No	SD
NA [b]	CR	No	CR
NA [b]	UE	No	UE
NA [b]	NA [c]	No	UE

CR = complete response; NA = not applicable; PD = progressive disease; PR = partial response; SD = stable disease; UE = unable to evaluate.

Note: Modified from Cheson BD, Pfistner B, Juweid ME, et al. Revised response criteria for malignant lymphoma. J Clin Oncol 2007;25:579–86.

[a] Identification of new lesions at a post-baseline time point will result in a response assessment of PD. If an identified new lesion subsequently becomes UE, the timepoint response will be recorded as PD unless the new lesion has proven to have resolved.

[b] No target lesions identified at baseline.

[c] No non-target lesions identified at baseline.

Appendix 4
Revised Response Criteria for Malignant Lymphoma (cont.)

Response should be determined on the basis of radiographic and clinical evidence of disease. For the end-of-treatment response assessment, an FDG-PET will be performed 6–8 weeks after the last study treatment. Assessment of PET should follow the criteria described by Juweid et al. 2007, which is presented in the table Response Definitions for Clinical Trials.

COMPLETE RESPONSE

- Complete disappearance of all detectable clinical evidence of disease and disease-related symptoms if present before therapy
- Typically ^{18}F-fleurodeoxyglucose (FDG)–avid lymphoma: in patients with no pre-treatment positron emission tomography (PET) scan or when the PET scan was positive before therapy, a post-treatment residual mass of any size is permitted as long as it is PET negative.
- Variably FDG-avid lymphomas/FDG avidity unknown: in patients without a pre-treatment PET scan, or if a pre-treatment PET scan was negative, all lymph nodes and nodal masses must have regressed on CT to normal size ($\leq$1.5 cm in their greatest transverse diameter for nodes $>$1.5 cm before therapy). Previously involved nodes that were 1.1 to 1.5 cm in their long axis and $>$1.0 cm in their short axis before treatment must have decreased to $\leq$1.0 cm in their short axis after treatment.
- The spleen and/or liver, if considered enlarged before therapy on the basis of a physical examination or CT scan, should not be palpable on physical examination and should be considered normal size by imaging studies, and nodules related to lymphoma should disappear. However, determination of splenic involvement is not always reliable because a spleen considered normal in size may still contain lymphoma, whereas an enlarged spleen may reflect variations in anatomy, blood volume, the use of hematopoietic growth factors, or causes other than lymphoma.
- If the bone marrow was involved by lymphoma before treatment, the infiltrate must have cleared on repeat bone marrow biopsy. The biopsy sample on which this determination is made must be adequate (with a goal of $>$20 mm unilateral core). If the sample is indeterminate by morphology, it should be negative by immunohistochemistry. A sample that is negative by immunohistochemistry but that demonstrates a small population of clonal lymphocytes by flow cytometry will be considered a CR until data become available demonstrating a clear difference in patient outcome.

Appendix 4
Revised Response Criteria for Malignant Lymphoma (cont.)

PARTIAL RESPONSE

- At least a 50% decrease in SPD of up to six of the largest dominant nodes or nodal masses. These nodes or masses should be selected according to all of the following: they should be clearly measurable in at least two perpendicular dimensions; if possible they should be from disparate regions of the body; and they should include mediastinal and retroperitoneal areas of disease whenever these sites are involved.
- No increase should be observed in the size of other nodes, liver, or spleen.
- Splenic and hepatic nodules must regress by ≥50% in their SPD or, for single nodules, in the GTD.
- With the exception of splenic and hepatic nodules, involvement of other organs is usually assessable and no measurable disease should be present.
- Bone marrow assessment is irrelevant for determination of a PR if the sample was positive before treatment. However, if positive, the cell type should be specified (e.g., large-cell lymphoma or small neoplastic B cells). Patients who achieve a CR by the above criteria but who have persistent morphologic bone marrow involvement will be considered partial responders. If the bone marrow was involved before therapy and a clinical CR is achieved, but with no bone marrow assessment after treatment, patients should be considered partial responders.
- No new sites of disease should be observed.
- Typically FDG-avid lymphoma: for patients with no pre-treatment PET scan or if the PET scan was positive before therapy, the post-treatment PET should be positive in at least one previously involved site.
- Variably FDG-avid lymphomas/FDG-avidity unknown: for patients without a pre-treatment PET scan, or if a pre-treatment PET scan was negative, CT criteria should be used.

In patients with follicular lymphoma or mantle-cell lymphoma, a PET scan is only indicated with one or at most two residual masses that have regressed by more than 50% on CT; those with more than two residual lesions are unlikely to be PET negative and should be considered partial responders.

Appendix 4
Revised Response Criteria for Malignant Lymphoma (cont.)

STABLE DISEASE

- A patient is considered to have SD when he or she fails to attain the criteria needed for a CR or PR but does not fulfill those for progressive disease (PD) (see Relapsed Disease [after Complete Response] or Progressive Disease [after Partial Response or Stable Disease]).
- Typically FDG-avid lymphomas: the PET should be positive at prior sites of disease with no new areas of involvement on the post-treatment CT or PET.
- Variably FDG-avid lymphomas/FDG-avidity unknown: for patients without a pre-treatment PET scan or if the pre-treatment PET was negative, there must be no change in the size of the previous lesions on the post-treatment CT scan.

RELAPSED DISEASE (AFTER COMPLETE RESPONSE) OR PROGRESSIVE DISEASE (AFTER PARTIAL RESPONSE OR STABLE DISEASE)

Lymph nodes should be considered abnormal if the long axis is more than 1.5 cm, regardless of the short axis. If a lymph node has a long axis of 1.1 to 1.5 cm, it should only be considered abnormal if its short axis is more than 1.0. Lymph nodes $\leq 1.0 \times \leq 1.0$ cm will not be considered as abnormal for relapse or progressive disease.

- Appearance of any new lesion > 1.5 cm in any axis during or at the end of therapy, even if other lesions are decreasing in size. Increased FDG uptake in a previously unaffected site should only be considered relapsed or progressive disease after confirmation with other modalities. In patients with no prior history of pulmonary lymphoma, new lung nodules identified by CT are mostly benign. Thus, a therapeutic decision should not be made solely on the basis of the PET without histologic confirmation.
- At least a 50% increase from nadir in the SPD of any previously involved nodes, or in a single involved node, or the size of other lesions (e.g., splenic or hepatic nodules). To be considered PD, a lymph node with a diameter of the short axis < 1.0 cm must increase by $\geq 50\%$ and to a size of 1.5×1.5 cm or > 1.5 cm in the long axis.
- At least a 50% increase in the longest diameter of any single previously identified node > 1 cm in its short axis.
- Lesions should be PET positive if observed in a typical FDG-avid lymphoma or the lesion was PET positive before therapy unless the lesion is too small to be detected with current PET systems (< 1.5 cm in its long axis by CT).

Measurable extranodal disease should be assessed in a manner similar to that for nodal disease. For these recommendations, the spleen is considered nodal disease. Disease that is only assessable (e.g., pleural effusions, bone lesions) will be recorded as present

or absent only, unless, while an abnormality is still noted by imaging studies or physical examination, it is found to be histologically negative.

In clinical trials where PET is unavailable to the vast majority of participants, or where PET is not deemed necessary or appropriate for use (e.g., a study involving patients with mucosa-associated lymphoid tissue lymphoma), response should be assessed as above but only using CT scans. However, residual masses should not be assigned unconfirmed complete response status but should be considered partial responses.

Appendix 4
Revised Response Criteria for Malignant Lymphoma (cont.)

Response Definitions for Clinical Trials (Revised International Working Group Criteria 2007)

Response	Definition	Nodal Masses	Spleen, Liver	Bone Marrow
CR	Disappearance of all evidence of disease	a) FDG-avid or PET positive prior to therapy; mass of any size permitted if PET negative b) Variably FDG-avid or PET negative; regression to normal size on CT	No palpable, nodules; nodules disappeared	Infiltrate cleared on repeat biopsy; if indeterminate on morphology and immunohistochemistry; bone marrow should be negative
PR	Regression of measurable disease and no new sites	A ≥ 50% decrease in SPD of up to six largest dominant masses; no increase in size of other nodes a) FDG-avid or PET positive prior to therapy; one or more PET positive at previously involved site b) Variably FDG-avid or PET negative; regression on CT	A ≥ 50% decrease in SPD of nodules (for single nodule in the greatest transverse diameter); no increase in size of liver or spleen	Irrelevant if positive prior to therapy; cell type should be specified
SD	Failure to attain CR/PR or PD	a) FDG-avid or PET positive prior to therapy; PET positive at prior sites of disease and no new sites on CT or PET b) Variably FDG-avid or PET negative; no change in size of previous lesions on CT		
Relapsed disease or PD	Any new lesion or increase by ≥ 50% of previously involved sites from nadir	Appearance of a new lesion(s) > 1.5 cm in any axis, ≥ 50% increase in SPD of more than one node, or ≥ 50% increase in longest diameter of previously identified node > 1 cm in short axis Lesions PET positive if FDG-avid lymphoma or PET positive prior to therapy	50% increase from nadir in the SPD of any previous lesions	New or recurrent involvement

CR = complete response; CT = computed tomography; FDG = ^{18}F-fluorodeoxyglucose; PD = progressive disease; PET = positron-emission tomography; PR = partial response; SPD = sum of the product of the diameters.

Excerpted from: Juweid ME, Stroobants S, Hoekstra OS, et al. Use of positron emission tomography for response assessment of lymphoma: consensus of the Imaging Subcommittee of International Harmonization Project in Lymphoma. J Clin Oncol 2007;25:571–8.

Appendix 5
Modified Response Evaluation Criteria in Solid Tumors

Conventional response criteria may not be adequate to characterize the anti-tumor activity of immunotherapeutic agents like atezolizumab, which can produce delayed responses that may be preceded by initial apparent radiological progression, including the appearance of new lesions. Therefore, modified response criteria have been developed that account for the possible appearance of new lesions and allow radiological progression to be confirmed at a subsequent assessment.

Modified Response Evaluation Criteria in Solid Tumors (RECIST) is derived from RECIST, Version 1.1 (v1.1) conventions[1] and immune-related response criteria[2] (irRC). When not otherwise specified, RECIST v1.1 conventions will apply.

Modified RECIST and RECIST v1.1: Summary of Changes

	RECIST v1.1	Modified RECIST
New lesions after baseline	Define progression	New measurable lesions are added into the total tumor burden and followed.
Non-target lesions	May contribute to the designation of overall progression	Contribute only in the assessment of a complete response
Radiographic progression	First instance of ≥20% increase in the sum of diameters or unequivocal progression in non-target disease	Determined only on the basis of measurable disease

RECIST = Response Evaluation Criteria in Solid Tumors.

A. DEFINITIONS OF MEASURABLE/NON-MEASURABLE LESIONS

All measurable and non-measurable lesions should be assessed at Screening and at the protocol-specified tumor assessment timepoints. Additional assessments may be performed, as clinically indicated for suspicion of progression.

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[1] Eisenhauer et al. Eur J Cancer 2009;45: 228–47; Topalian et al. N Engl J Med 2012;366:2443–54; and Wolchok et al., Clin Can Res 2009;15:7412–20.

[2] Wolchok et al. Clin Can Res 2009;15:7412–20; Nishino et al. J Immunother Can 2014;2:17; Nishino et al. Clin Can Res 2013;19:3936–43.

Appendix 5
Modified Response Evaluation Criteria in Solid Tumors (cont.)

A.1 MEASURABLE LESIONS

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 as follows:

- 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 examination (lesions that cannot be accurately measured with calipers should be recorded as non-measurable)

Malignant Lymph Nodes. To be considered pathologically enlarged and measurable, a lymph node must be ≥ 15 mm in the short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and follow-up, only the short axis will be measured and followed.

A.2 NON-MEASURABLE LESIONS

Non-measurable tumor lesions encompass small lesions (longest diameter < 10 mm or pathological lymph nodes with short axis ≥ 10 but < 15 mm), 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 mass/abdominal organomegaly identified by physical examination that is not measurable by reproducible imaging techniques.

A.3 SPECIAL CONSIDERATIONS REGARDING LESION MEASURABILITY

Bone lesions, cystic lesions, and lesions previously treated with local therapy require particular comment, as outlined below.

Bone Lesions

Bone scan, positron emission tomography (PET) scan, or plain films are not considered adequate imaging techniques for measuring 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.

Appendix 5
Modified Response Evaluation Criteria in Solid Tumors (cont.)

Cystic Lesions

Lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts.

Cystic lesions thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same patient, these are preferred for selection as target lesions.

Lesions with Prior Local Treatment

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. Study protocols should detail the conditions under which such lesions would be considered measurable.

B. TUMOR RESPONSE EVALUATION

B.1 DEFINITIONS OF TARGET/NON-TARGET LESIONS

Target Lesions

When more than one measurable lesion is present at baseline, all lesions up to a maximum of five lesions total (and a maximum of two lesions per organ) representative of all involved organs should be identified as target lesions and will be recorded and measured at baseline. This means that, for instances in which patients have only one or two organ sites involved, a maximum of two lesions (one site) and four lesions (two sites), respectively, will be recorded. Other lesions (albeit measurable) in those organs will be recorded as non-measurable lesions (even if the size is $>$10 mm by CT scan).

Target lesions should be selected on the basis of their size (lesions with the longest diameter) and be representative of all involved organs, but in addition, should lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement, in which circumstance, the next largest lesion that can be measured reproducibly should be selected.

Lymph nodes merit special mention since they are normal anatomical structures that may be visible by imaging even if not involved by tumor. As noted above,

pathological nodes that 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 two dimensions in the plane in which the image is obtained (for CT, 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 that is reported as being 20 mm × 30 mm has a short axis of 20 mm and qualifies as a malignant, measurable node. In this example, 20 mm should be recorded as the node measurement. 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 of <10 mm are considered non-pathological and should not be recorded or followed.

Lesions irradiated within 3 weeks prior to Cycle 1 Day 1 may not be counted as target lesions.

Non-Target Lesions

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.

It is possible to record multiple non-target lesions involving the same organ as a single item on the eCRF (e.g., “multiple enlarged pelvic lymph nodes” or “multiple liver metastases”).

After baseline, changes in non-target lesions will contribute only in the assessment of complete response (i.e., a complete response is attained only with the complete disappearance of all tumor lesions, including non-target lesions) and will not be used to assess progressive disease.

New Lesions

During the study, all new lesions identified and recorded after baseline must be assessed at all tumor assessment timepoints. New lesions will also be evaluated for measurability with use of the same criteria applied to prospective target lesions at baseline per RECIST, (e.g., non–lymph node lesions must be ≥10mm; see note for new lymph node lesions below). Up to a maximum of five new lesions total (and a maximum of two lesions per organ), all with measurements at all timepoints, can be included in the

tumor response evaluation. New lesion types that would not qualify as target lesions per RECIST cannot be included in the tumor response evaluation.

New lesions that are not measurable at first appearance but meet measurability criteria at a subsequent timepoint will be measured from that point on and contribute to the sum of longest diameters (SLD), if the maximum number of 5 measurable new lesions being followed has not been reached.

B.2 CALCULATION OF SUM OF THE DIAMETERS

A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated as a measure of tumor burden.

The sum of the diameters is calculated at baseline and at each tumor assessment for the purpose of classification of tumor responses.

Sum of the Diameters at Baseline: The sum of the diameters for all target lesions identified at baseline prior to treatment on Day 1.

Sum of the Diameters at Tumor Assessment: For every on-study tumor assessment collected per protocol or as clinically indicated the sum of the diameters at tumor assessment will be calculated using tumor imaging scans. All target lesions selected at baseline and up to five new measurable lesions (with a maximum of two new lesions per organ) that have emerged after baseline will contribute to the sum of the diameters at tumor assessment. Hence, each net percentage change in tumor burden per assessment with use of modified RECIST accounts for the size and growth kinetics of both old and new lesions as they appear.

Note: In the case of new lymph nodes, RECIST v1.1 criteria for measurability (equivalent to baseline target lesion selection) will be followed. That is, if at first appearance the short axis of a new lymph node lesion $\geq$15 mm, it will be considered a measureable new lesion and will be tracked and included in the SLD. Thereafter, the lymph node lesion will be measured at subsequent timepoints and measurements will be included in the SLD, even if the short axis diameter decreases to $<$15 mm (or even $<$10 mm). However, if it subsequently decreases to $<$10 mm, and all other lesions are no longer detectable (or have also decreased to a short axis diameter of $<$10 mm if lymph nodes), then a response assessment of CR may be assigned.

If at first appearance the short axis of a new lymph node is $\geq$10 mm and $<$15 mm, the lymph node will not be considered measurable but will still be considered a new lesion. It will not be included in the SLD unless it subsequently becomes measurable (short axis diameter $\geq$15 mm).

The appearance of new lymph nodes with diameter <10 mm should not be considered pathological and not considered a new lesion.

B.3 RESPONSE CRITERIA

Timepoint Response

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

Complete Response (CR): Disappearance of all target and non-target lesions. Lymph nodes that shrink to <10 mm short axis are considered normal.

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

Note: the appearance of new measurable lesions is factored into the overall tumor burden, but *does not automatically qualify as progressive disease* until the sum of the diameters increases by $\geq 20\%$ when compared with the sum of the diameters at nadir.

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

Progressive Disease (PD): At least a 20% increase in the sum of diameters of all target and selected new measurable lesions, taking as reference the smallest sum on study (nadir SLD; this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm.

Impact of New Lesions on Modified RECIST

New lesions alone do not qualify as progressive disease. However, their contribution to total tumor burden is included in the sum of the diameters, which is used to determine the overall modified RECIST tumor response.

Appendix 5
Modified Response Evaluation Criteria in Solid Tumors (cont.)

Missing Assessments and Not Evaluable Designation

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

Table 1 Modified RECIST Timepoint Response Definitions

% Change in Sum of the Diameters [a]	Non-Target Lesion Response Assessment	Overall Modified RECIST Timepoint Response
−100% from baseline [b]	CR	CR
−100% from baseline [b]	Non-CR or not all evaluated	PR
≤ −30% from baseline	Any	PR
> −30% to <+20%	Any	SD
Not all evaluated	Any	NE
≥ +20%from nadir SLD	Any	PD

CR = complete response; NE = not evaluable; PD = progressive disease; PR = partial response; RECIST = Response Evaluation Criteria in Solid Tumors; SD = stable disease; SLD = sum of the longest diameter.

[a] Percent change in sum of the diameters (including measurable new lesions when present).

[b] When lymph nodes are included as target lesions, the % change in the sum of the diameters may not be 100% even if complete response criteria are met, since a normal lymph node is defined as having a short axis of <10 mm. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm in order to meet the definition of CR.

Appendix 6
Response Evaluation Criteria in Solid Tumors: Modified Excerpt from Original Publication

Selected sections from the Response Evaluation Criteria in Solid Tumors (RECIST), Version 1.1[1] are presented below, with slight modifications and the addition of explanatory text as needed for clarity.[2]

MEASURABILITY OF TUMOR AT BASELINE

DEFINITIONS

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

a. Measurable Tumor Lesions

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 CT or MRI scan (CT/MRI scan slice thickness/interval no greater than 5 mm)
- 10-mm caliper measurement by clinical examination (lesions that cannot be accurately measured with calipers should be recorded as non-measurable)
- 20 mm by chest X-ray

Malignant Lymph Nodes. To be considered pathologically enlarged and measurable, a lymph node must be ≥ 15 mm in the short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed. See also notes below on "Baseline Documentation of Target and Non-Target Lesions" for information on lymph node measurement.

b. Non-Measurable Tumor Lesions

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

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[1] 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;45:228–47.

[2] For consistency within this document, the section numbers and cross-references to other sections within the article have been deleted and minor formatting changes have been made.

Appendix 6
Response Evaluation Criteria in Solid Tumors: Modified Excerpt from Original Publication (cont.)

c. Special Considerations Regarding Lesion Measurability

Bone lesions, cystic lesions, and lesions previously treated with local therapy require particular comment, as outlined below.

Bone lesions:

- Bone scan, positron emission tomography (PET) scan, or plain films are not considered adequate imaging techniques to measure bone lesions. However, these techniques can be used to confirm the presence or disappearance of bone lesions.
- Lytic bone lesions or mixed lytic-blastic lesions, with identifiable soft tissue components, that can be evaluated by cross-sectional imaging techniques such as CT or MRI can be considered 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 malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts.
- Cystic lesions thought to represent cystic metastases can be considered measurable lesions if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same patient, these are preferred for selection as target lesions.

Lesions with prior local treatment:

- 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. Study protocols should detail the conditions under which such lesions would be considered measurable.

TARGET LESIONS: SPECIFICATIONS BY METHODS OF MEASUREMENTS

a. 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.

Appendix 6
Response Evaluation Criteria in Solid Tumors: Modified Excerpt from Original Publication (cont.)

b. 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 be considered measurable only when they are superficial and ≥ 10 mm in 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, since CT is more sensitive than X-ray, particularly in identifying new lesions. However, lesions on chest X-ray may be considered measurable if they are clearly defined and surrounded by aerated lung.

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 prior to enrollment it is known that a patient is unable to undergo CT scans with intravenous (IV) contrast because of allergy or renal insufficiency, the decision as to whether a non-contrast CT or MRI (without IV contrast) will be used to evaluate the patient at baseline and during the study should be guided by the tumor type under investigation and the anatomic location of the disease. For patients who develop contraindications to contrast after baseline contrast CT is done, the decision as to whether non-contrast CT or MRI (enhanced or non-enhanced) will be performed should also be based on the tumor type and the anatomic location of the disease and should be optimized to allow for comparison with the prior studies if possible. Each case should be discussed with the radiologist to determine if substitution of these other approaches is possible and, if not, the patient should be considered not evaluable from that point forward. Care must be taken in measurement of target lesions on a different modality and interpretation of non-target disease or new lesions since the same lesion may appear to have a different size using a new modality.

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

Appendix 6
Response Evaluation Criteria in Solid Tumors: Modified Excerpt from Original Publication (cont.)

Endoscopy, Laparoscopy, Tumor Markers, Cytology, Histology. The utilization of these techniques for objective tumor evaluation cannot generally be advised.

TUMOR RESPONSE EVALUATION

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 to use this as a comparator for subsequent measurements. Measurable disease is defined by the presence of at least one measurable lesion, as detailed above.

BASELINE DOCUMENTATION OF TARGET AND NON-TARGET LESIONS

When more than one measurable lesion is present at baseline, all lesions up to a maximum of five lesions total (and a maximum of two lesions per organ) representative of all involved organs should be identified as target lesions and will be recorded and measured at baseline. This means in instances where patients have only one or two organ sites involved, a maximum of two lesions (one site) and four lesions (two sites), respectively, will be recorded. Other lesions (albeit measurable) in those organs will be recorded as non-measurable lesions (even if the size is >10 mm by CT scan).

Target lesions should be selected on the basis of their size (lesions with the longest diameter) and be representative of all involved organs but, additionally, should lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement, in which circumstance the next largest lesion that can be measured reproducibly should be selected.

Lymph nodes merit special mention since they are normal anatomical structures that may be visible by imaging even if not involved by tumor. As noted above, pathological nodes that 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 two dimensions in the plane in which the image is obtained (for CT scan, this is almost always the axial plane; for MRI the plane of acquisition may be axial, sagittal, or coronal). The smaller of these measures is the short axis. For example, an abdominal node that 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

Appendix 6
Response Evaluation Criteria in Solid Tumors: Modified Excerpt from Original Publication (cont.)

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.

Lesions irradiated within 3 weeks prior to Cycle 1 Day 1 may not be counted as target lesions.

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 of 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 of diameters will be used as a 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."

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

RESPONSE CRITERIA

a. Evaluation of Target Lesions

This section provides the definitions of the criteria used to determine objective tumor response for 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 of diameters
- Progressive disease (PD): at least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (nadir), including baseline

  In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm.

  The appearance of one or more new lesions is also considered progression.

- Stable disease (SD): neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum on study

Appendix 6
Response Evaluation Criteria in Solid Tumors: Modified Excerpt from Original Publication (cont.)

b. 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 < 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 CR criteria are met since a normal lymph node is defined as having a short axis < 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 that 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 eCRF as follows:

- If it is the opinion of the radiologist that the lesion has likely disappeared, the measurement should be recorded as 0 mm.
- If the lesion is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned and BML (below measurable limit) should be ticked. (Note: It is less likely that this rule will be used for lymph nodes since they usually have a definable size when normal and are frequently surrounded by fat such as in the retroperitoneum; however, if a lymph node is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned in this circumstance as well 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.

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.

Appendix 6
Response Evaluation Criteria in Solid Tumors: Modified Excerpt from Original Publication (cont.)

c. 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. Although some non-target lesions may actually be measurable, they need not be measured and, instead, should be assessed only qualitatively at the timepoints specified in the protocol.

- 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-PD: persistence of one or more non-target lesion(s) and/or (if applicable) maintenance of tumor marker level above the normal limits
- PD: unequivocal progression of existing non-target lesions

  The appearance of one or more new lesions is also considered progression.

d. Special Notes on Assessment of Progression of Non-Target Disease

When the Patient Also Has Measurable Disease. In this setting, to achieve unequivocal progression on the basis of the non-target disease, there must be an overall level of substantial worsening in non-target disease in a magnitude that, even in the 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 Patient Has Only Non-Measurable Disease. This circumstance arises in some Phase III trials when it is not a criterion of study entry to have measurable disease. The same general concepts apply here as noted above; however, in this instance, there is no measurable disease assessment to factor into the interpretation of an increase in non-measurable disease burden. Because worsening in non-target disease cannot be easily quantified (by definition: if all lesions are truly non-measurable), a useful test that can be applied when assessing patients for unequivocal progression is to consider if the increase in overall disease burden based on the change in non-measurable disease is comparable in magnitude to the increase that would be required to declare PD for measurable disease; that is, an increase in tumor burden representing an additional 73% increase in volume (which is equivalent to a 20% increase in diameter in a measurable lesion). Examples include an increase in a pleural effusion from “trace” to “large” or 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 patient should be considered to have had overall PD at that point. Although 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.

e. 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, that is, 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 patient's baseline lesions show PR or CR. 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.

EVALUATION OF RESPONSE

a. Timepoint Response (Overall Response)

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

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

Appendix 6
Response Evaluation Criteria in Solid Tumors: Modified Excerpt from Original Publication (cont.)

Table 1 Timepoint Response: Patients with Target Lesions (with or without 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; NE = not evaluable; PD = progressive disease; PR = partial response; SD = stable disease.

Table 2 Timepoint Response: Patients with 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; NE = not evaluable; PD = progressive disease.

[a] "Non-CR/non-PD" is preferred over "stable disease" for non-target disease since stable disease is increasingly used as an endpoint for assessment of efficacy in some studies; thus, assigning "stable disease" when no lesions can be measured is not advised.

b. Missing Assessments and Not-Evaluable Designation

When no imaging/measurement is done at all at a particular timepoint, the patient is not evaluable at that timepoint. If only a subset of lesion measurements are made at an assessment, usually the case is also considered not evaluable at that timepoint, unless a

convincing argument can be made that the contribution of the individual missing lesion(s) would not change the assigned timepoint response. This would be most likely to happen

in the case of PD. For example, if a patient had a baseline sum of 50 mm with three measured lesions and, during the study, only two lesions were assessed, but those gave a sum of 80 mm; the patient will have achieved PD status, regardless of the contribution of the missing lesion.

If one or more target lesions were not assessed either because the scan was not done or the scan could not be assessed because of poor image quality or obstructed view, the response for target lesions should be “unable to assess” since the patient is not evaluable. Similarly, if one or more non-target lesions are 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 timepoint.

Appendix 6
Response Evaluation Criteria in Solid Tumors: Modified Excerpt from Original Publication (cont.)

Table 3 Best Overall Response When Confirmation Is Required

Overall Response at First Timepoint	Overall Response at Subsequent Timepoint	Best Overall Response
CR	CR	CR
CR	PR	SD, PD, or PR [a]
CR	SD	SD, provided minimum duration for SD was met; otherwise, PD
CR	PD	SD, provided minimum duration for SD was met; otherwise, PD
CR	NE	SD, provided minimum duration for SD was met; otherwise, NE
PR	CR	PR
PR	PR	PR
PR	SD	SD
PR	PD	SD, provided minimum duration for SD was met; otherwise, PD
PR	NE	SD, provided minimum duration for SD was met; otherwise, NE
NE	NE	NE

CR = complete response; NE = not evaluable; PD = progressive disease; PR = partial response; SD = stable disease.

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

c. Special Notes on Response Assessment

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

Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as "symptomatic deterioration." Every effort should be made to document objective

progression even after discontinuation of treatment. Symptomatic deterioration is not a descriptor of an objective response; it is a reason for stopping study therapy. The objective response status of such patients is to be determined by evaluation of target and non-target disease as shown in Tables 1–3.

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.

If a patient undergoes an excisional biopsy or other appropriate approach (e.g., multiple passes with large core needle) of a new lesion or an existing solitary progressive lesion that following serial sectioning and pathological examination reveals no evidence of malignancy (e.g., inflammatory cells, fibrosis, etc.), then the new lesion or solitary progressive lesion will not constitute disease progression.

In studies for which patients with advanced disease are eligible (i.e., primary disease still or partially present), the primary tumor should also be captured as a target or non target lesion, as appropriate. This is to avoid an incorrect assessment of CR if the primary tumor is still present but not evaluated as a target or non-target lesion.

Appendix 7
Immune-Related Response Criteria

INTRODUCTION

Increasing clinical experience indicates that traditional response criteria (e.g., Response Evaluation Criteria in Solid Tumors [RECIST] and World Health Organization [WHO]) may not be sufficient to characterize fully activity in the new era of target therapies and/or biologics. In studies with cytokines, cancer vaccines, and monoclonal antibodies, complete response, partial response, or stable disease has been shown to occur after an increase in tumor burden as characterized by progressive disease by traditional response criteria. Therefore, conventional response criteria may not adequately assess the activity of immunotherapeutic agents because progressive disease (by initial radiographic evaluation) does not necessarily reflect therapeutic failure. Long-term effect on the target disease must also be captured. The immune-related response criteria[1] (irRC) are criteria that attempt to do that by enhancing characterization of new response patterns that have been observed with immunotherapeutic agents (i.e., ipilimumab). (Note: The irRC only index and measurable new lesions are taken into account.)

GLOSSARY

Term	Definition
SPD	Sum of the products of the two largest perpendicular diameters
Tumor burden	$SPD_{\text{index lesions}} + SPD_{\text{new, measurable lesions}}$
Nadir	Minimally recorded tumor burden
irCR	Immune-related complete response
irPR	Immune-related partial response
irSD	Immune-related stable disease
irPD	Immune-related progressive disease
irBOR	Immune-related best overall response

BASELINE ASSESSMENT USING irRC

Step 1. Identify the index lesions (five lesions per organ, up to ten visceral lesions and five cutaneous lesions).

[1] Wolchok JD, Hoos A, O'Day S, et al. Guidelines for the evaluation of immune therapy activity in solid tumors: immune-related response criteria. Clin Can Res 2009;15:7412–20.

Appendix 7
Immune-Related Response Criteria (cont.)

Step 2. Calculate the SPD of all of these index lesions:

$$\text{SPD} = \sum_{i} \text{(Largest diameter of lesion } i\text{)} \times \text{(Second largest diameter of lesion } i\text{)}.$$

POST-BASELINE ASSESSMENTS USING irRC

Step 1. Calculate the SPD of the index lesions.

Step 2. Identify new, measurable lesions ($\geq 5 \times 5$ mm; up to five new lesions per organ: five new cutaneous lesions and ten visceral lesions).

Step 3. Calculate the SPD of the new, measurable lesions.

Step 4. Calculate the tumor burden:

$$\text{Tumor burden} = \text{SPD}_{\text{index lesions}} + \text{SPD}_{\text{new, measurable lesions}}$$

Step 5. Calculate the change in tumor burden relative to baseline and the change in tumor burden relative to nadir.

Step 6. Derive the overall response using the table below.

Overall Response	Criterion
irCR	Complete disappearance of all lesions (whether measurable or not, and no new lesions) confirmed by a repeat, consecutive assessment ≥ 4 weeks from the date first documented
irPR	Decrease in tumor burden $\geq 50\%$ relative to baseline confirmed by a consecutive assessment ≥ 4 weeks from the date first documented
irSD	Criteria for irCR, irPR, and irPD are not met; does not require confirmation
irPD	Increase in tumor burden $\geq 25\%$ relative to nadir confirmed by a consecutive assessment ≥ 4 weeks from the date first documented

irCR = immune-related complete response; irPD = immune-related progressive disease; irPR = immune-related partial response; irSD = immune-related stable disease.

Appendix 7
Immune-Related Response Criteria (cont.)

DETERMINATION OF irBOR

Once a patient has completed all tumor assessments, his/her irBOR may be determined:

Condition	irBOR
At least one irCR	irCR
At least one irPR and no irCR	irPR
At least one irSD and no irCR and no irPR	irSD
At least one irPD and no irCR, no irPR, and no irSD	irPD

irBOR = immune-related best overall response; irCR = immune-related complete response; irPD = immune-related progressive disease; irPR = immune-related partial response; irSD = immune-related stable disease.

Appendix 8
Lansky Performance Status Scale

Score	Description
100	Fully active; normal
90	Minor restrictions in physically strenuous activity
80	Active but tires more quickly
70	Both greater restriction of and less time spent in play activity
60	Up and around, but minimal active play; keeps busy with quieter activities
50	Gets dressed, but lies around much of the day; no active play; able to participate in all quiet play and activities
40	Mostly in bed; participates in quiet activities
30	In bed; needs assistance even for quiet play
20	Often sleeping; play entirely limited to very passive activities
10	No play; does not get out of bed

Appendix 9
Karnofsky Performance Status Scale

Score	Description
100	Normal; no complaints; no evidence of disease
90	Able to carry on normal activity; minor signs or symptoms of disease
80	Normal activity with effort; some signs or symptoms of disease
70	Cares for self; unable to carry on normal activity or do active work
60	Requires occasional assistance, but is able to care for most of his/her needs
50	Requires considerable assistance and frequent medical care
40	Disabled; requires special care and assistance
30	Severely disabled; hospitalization indicated; death not imminent
20	Very sick; hospitalization indicated; death not imminent
10	Moribund; fatal processes progressing rapidly

Appendix 10
Recommended Anaphylaxis Management

The following equipment is needed in the event of a suspected anaphylactic reaction during study drug infusion. All equipment and medication must be in the appropriate sizes and doses for the pediatric patients being treated.

- Appropriate monitors (electrocardiogram, blood pressure, pulse oximetry)
- Oxygen and masks for oxygen delivery
- Airway management devices per standard of care
- Epinephrine for intravenous, intramuscular, and/or endotracheal administration in accordance with institutional guidelines
- Antihistamines (oral/IV H1 and H2 antagonists)
- Corticosteroids (IV)
- Albuterol (Salbutamol or equivalent) for bronchospasm
- Intravenous infusion solutions, tubing, catheters, and tape

The following are the procedures to follow in the event of a suspected anaphylactic reaction during study drug infusion:

- Stop the study drug infusion.
- Call for additional assistance!
- Maintain an adequate airway.
- Provide oxygen.
- Ensure IV access $\times 2$ if possible.
- Ensure that appropriate monitoring is in place, with continuous electrocardiogram and pulse oximetry monitoring, if possible.
- Administer epinephrine (1:1000, 0.01 mg/kg intramuscularly [IM]) into lateral thigh, or via route and dose as directed by physician-in-charge). May repeat every 5–15 minutes.
- Administer antihistamines and other medications as required by patient status and directed by the physician in charge.
- Continue to observe the patient and document observations until the patient is transferred to higher-level care.

Appendix 11
Response Assessment in Neuro-Oncology Criteria

Response	*Criteria*
Complete response	*Requires **all** of the following:* • *Complete disappearance of all enhancing measurable and non-measurable disease sustained for at least 4 weeks* • *No new lesions* • *Stable or improved non-enhancing (T2/FLAIR) lesions* • *Patients must be off corticosteroids (or on physiological replacement doses only)* • *Clinical status is stable or improved*
Partial response	*Requires **all** of the following:* • *≥50% decrease compared with baseline in the sum of products of perpendicular diameters of all measurable enhancing lesions sustained for at least 4 weeks* • *No progression of non-measurable T1 enhancing disease* • *No new lesions* • *Stable or improved non-enhancing (T2/FLAIR) lesions on the same or lower dose of corticosteroids compared to baseline* • *Clinical status is stable or improved* *Note: Patients with non-measurable disease only cannot have a partial response; the best response possible is stable disease*
Stable disease	*Requires **all** of the following:* • *Patient does not qualify for complete response, partial response, or progression* • *Stable non-enhancing (T2/FLAIR) lesions on same or lower dose of corticosteroids compared to baseline* • *Clinical status is stable or improved* *Note: In the event that the corticosteroid dose was increased for new symptoms and signs without confirmation of disease progression on neuroimaging, and subsequent follow-up imaging shows that this increase in corticosteroids was required because of disease progression, the last scan considered to show stable disease will be the scan obtained when the corticosteroid dose was equivalent to the baseline dose.*

FLAIR =fluid-attenuated inversion recovery.

Note: Adapted from Wen PY, Macdonald DR, Reardon DA, et al. Updated response assessment criteria for high-grade gliomas: response assessment in neuro-oncology working group. J Clin Oncol 2012;28:1963–72.

Appendix 11
Response Assessment in Neuro-Oncology Criteria (cont.)

Response	*Criteria*
Progression	*Defined by **any** of the following:* • *≥25% increase in sum of the products of perpendicular diameters of enhancing lesions compared with the smallest tumor measurement obtained either at baseline (of no decrease) or best response, on a stable or increasing dose of corticosteroids* • *Significant increase in T2/FLAIR non-enhancing lesions while taking stable or increasing doses of steroids compared with baseline scan or best response after initiation of therapy, not caused by comorbid events (e.g., radiation therapy, demyelination, ischemic injury, seizures, postoperative changes, or other treatment effects)* • *Presence of any new lesions* • *Clear clinical deterioration not attributable to other causes apart from the tumor (e.g., seizures, medication adverse effects, complications of therapy, cerebrovascular events, infection, and so on) or decreases in corticosteroid dose* • *Failure to return for evaluation due to death or deteriorating condition* • *Clear progression of nonmeasurable disease*

FLAIR =fluid-attenuated inversion recovery.

Note: Adapted from Wen PY, Macdonald DR, Reardon DA, et al. Updated response assessment criteria for high-grade gliomas: response assessment in neuro-oncology working group. J Clin Oncol 2012;28:1963–72.